Birth Order and Pediatric Allergic Disease: A Nationwide Longitudinal Survey

Condensed title: Birth Order and Pediatric Allergic Disease

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Abstract

Background Environmental factors seem to be related to the incidence of allergic disease. Children with a later birth order are often exposed to environments where pathogens and endotoxins can be found, and thus have a higher risk of developing infectious diseases. Therefore, birth order is regarded as an indicator that reflects postnatal environment. However, longitudinal studies are limited on this subject. This study sought to elucidate the relationships between birth order and allergic disease.

Methods From a nationwide longitudinal study that followed children born in 2001 (n=47,015), we selected doctors' visits for three types of allergic disease—bronchial asthma, food allergy, and atopic dermatitis—from infancy to 12 years of age and conducted binomial log-linear regression analysis to evaluate the associations between birth order and these diseases. We adjusted for child and parental factors and estimated risk ratio (RR) and 95% confidence interval (CI) for each outcome.

Results The associations between birth order and bronchial asthma were diverse; later birth order increased the risk in early childhood, but decreased the risks during school age. For example, the adjusted RR comparing third-born or higher and first-born children was 1.19 (95% CI, 1.05 to 1.35) between 30 and 42 months of age, but was 0.76 (95% CI, 0.65 to 0.89) between 10 and 11 years. Later birth order was generally protective for food allergy but increased the risk of atopic dermatitis.

Conclusion The influence of birth order depended on the type of allergic disease and the childhood period. Childhood is unique in terms of physical and immunological development, and the immune response to the postnatal environment in childhood appears to be heterogeneous.

Introduction

The incidence of allergic disease is on the rise, and environmental change is a possible contributor [1]. From examining the relationship between allergic rhinitis and birth order, Strachan et al. proposed the hygiene hypothesis, which suggests that sanitary environments in childhood play a role in increasing susceptibility to allergic disease [2]. Since then, many studies have investigated the relationship between allergy and postnatal environment such as birth order, older siblings, younger siblings, number of siblings, and daycare attendance [3]. Although the effect of each postnatal environment may depend on the lifestyle of the study population [4-7], previous studies demonstrated that compared with other factors, birth order has a more important role as a postnatal environmental factor [6].

Birth order reflects the number of older siblings, and children with a later birth order are often exposed to environments containing pathogens and endotoxins and have a higher risk of developing infectious diseases [8-10]. Previous studies examined the association between birth order and allergic disease, but the results were inconsistent [8-16]. This inconsistency may be because these studies were conducted with different age groups, study designs, and study populations. Indeed, cross-sectional studies have shown an association between later birth orders and a higher incidence of bronchial asthma in early childhood [11,12]. By contrast, studies of school-age children have reported an association between later birth orders and a lower risk of bronchial asthma or no association with bronchial asthma [7,13-15]. A population-based longitudinal study with a long follow-up period is therefore needed.

In this study, we evaluated the association between birth order and allergic disease—specifically, bronchial asthma, food allergy, and atopic dermatitis—from infancy to 12

years of age using data collected in a large nationwide longitudinal study conducted in Japan.

Methods

Participants

Since 2001, the Ministry of Health, Labour and Welfare (MHLW) Japan has implemented a nationally representative longitudinal study, the Longitudinal Survey of Babies in the 21st Century, to investigate medical conditions in children, including bronchial asthma, food allergy, and atopic dermatitis [16-17]. The study followed babies born between January 10 and 17 or July 10 and 17, 2001. Baseline questionnaires were sent to all families when the surveyed infants were 6 months old. Of the 53,575 questionnaires delivered, 47,015 were completed and returned (88% response rate). Follow-up questionnaires were sent to all participants who initially responded at 1-year intervals, except for a 1.5-year interval between 66 months and 7 years of age (i.e., at 18, 30, 42, 54, 66 months, 7 years, 8 years, 9 years, and so on). The 14th survey was completed in 2015. Birth record data from Japanese vital statistics (weight; gestational age; singleton, twin, or other multiple birth; sex; maternal parity; and parental age) were documented for each child in the study.

In this study, we used maternal parity as an indicator of birth order to examine the associations between birth order and allergic disease. We included all 47,015 participants in the analysis because information on parity was available for all.

Birth Order

Birth record data included maternal parity, which we used as an indicator of birth order. Parity information on the birth record included both live births and stillbirths (pregnancy loss after 12 weeks of gestational age). This indicator shows the biological order for full-term pregnancy and may not represent true birth order for some children

of mothers with a parity of two or more. Nonetheless, this misclassification is not substantial because the number of stillbirths in Japan is low, at 31.2 stillbirths per 1,000 live births in 2000 [18]. Here, we categorized birth order as follows: first-born, second-born, and third-born or higher.

Allergic Disease

The second to twelfth surveys asked whether the child had been seen by a doctor at least once for several common diseases during the previous 1 year or during the previous 1.5 years (only at the seventh survey). We selected three types of allergic disease to analyze—bronchial asthma, food allergy, and atopic dermatitis—and used doctor's visits for these three diseases as main outcomes in this study. Atopic dermatitis was combined with eczema into one category in the second and third surveys only, but each had its own category in subsequent surveys. Consequently, between the age of 6 and 30 months, doctor's visits for atopic dermatitis included eczema. We included disease status up to elementary school graduation in Japan (12 years of age and the twelfth survey). Thus, we examined whether there was at least one visit for each disease during the following age intervals: 6 to 18 months, 18 to 30 months, 30 to 42 months, 42 to 54 months, 54 to 66 months, 66 months to 7 years, 7 to 8 years, 8 to 9 years, 9 to 10 years, 10 to 11 years, and 11 to 12 years.

Statistical Analysis

First, we examined demographic characteristics distinguished by the birth order categories. Some participants were lost to follow-up at the second or later surveys. To evaluate the impact of loss to follow-up, we examined which children in each birth

order category tended to be lost at each survey and compared baseline characteristics between children who were included in the analysis and children who were lost to follow-up at each survey.

Binomial log-linear regression analysis was used to evaluate the relationships between birth order category—first, second, and third born or higher—and each disease status in each interval from 6 months to 12 years of age. We did not apply survival analysis for this study because each allergic disease status has heterogeneous pathologic conditions depending on age, and so we wanted to evaluate the impact of birth order on disease risk in each age period. The crude risk ratio (RR) and 95% confidence interval (CI) was estimated for each outcome. We then adjusted for potential confounders including child and parental factors as well as residential information. The first-born category was the reference group throughout the analysis.

Child factors included sex (dichotomous), singleton or multiple birth (dichotomous), term or preterm birth (<37 weeks of gestation; dichotomous), and daycare attendance (dichotomous). Parental factors included maternal age at delivery (<25, 25 to 29, 30 to 34, and ≥35 years; categorical), maternal smoking habits (non-smoker; smoker, ≤10 cigarettes per day; and smoker, >10 cigarettes per day; categorical), maternal educational level (categorical), and paternal educational level (categorical). Residential information included the type of residential area where the participant was born (ward, city, and town or village; categorical). The birth record for each child contained data on sex, singleton birth or not, gestational age, and maternal age at delivery. Maternal smoking status was ascertained at the first survey. In the second survey, respondents were asked who usually took care of the children, and we assumed that children reported as being taken care of by nursery school teachers were

attending a daycare center. Maternal and paternal educational level were used an indicator of socioeconomic status and obtained from the second survey (age 18 months). We reclassified the original eight educational categories into four, as follows: university (4 years) or higher, junior college (2 years) or vocational school, high school, and junior high school and other. Residential information was obtained from the national census conducted in 2000. These potential confounders were selected based on previous studies or prior knowledge of the association between birth order and allergic disease [7, 14, 19]. Cases with missing data were excluded and we conducted our analysis with complete cases only.

Subsequent birth of younger siblings may also affect disease risk [15, 20], so we also adjusted for increase in number of siblings as a dichotomy in the sensitivity analysis. We calculated the increase in number of siblings from 6 months of age (i.e., 1st survey) to each interval and dichotomized the information (i.e., increase or not). Because the number of siblings in the eleventh and twelfth surveys was not available, we used the increase up to the 10th survey (i.e., 10 years of age) for the analysis in the periods (i.e., 10 to 11 years, and 11 to 12 years).

All CI were calculated at the 95% level. Stata SE version 14 statistical software (StataCorp., College Station, TX) 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).

Results

The first-born category had the largest number of children, followed by the second- and third-born or higher categories (Table 1). With increasing birth order, children were more likely to be a multiple birth, preterm birth, cared for by nursery school teachers, and to have older mothers. Children in the third-born or higher category were more likely to have mothers who smoked, parents with lower educational levels, and mothers who lived in rural areas (towns or villages) in comparison with children in the first- and second-born categories.

Several children were lost to follow-up and the number increased as the participants got older (Supplemental Table 1). Children in the third-born or higher category were more likely to be lost. Those who were lost to follow-up tended to have young mothers and mothers who smoked. Supplemental Table 2 shows the demographic characteristics of children included in the analysis and those lost to follow-up only at the second survey, but the trends remained the same at each survey.

The associations between birth order and hospital visits for bronchial asthma were diverse (Table 2). Later birth order increased the risk at an earlier age, but became protective as the children got older. The adjusted RR for the third-born or higher category compared with the first-born category was 1.19 (95% CI, 1.05 to 1.35) between 30 and 42 months of age, but was 0.76 (95% CI, 0.65 to 0.89) between 10 and 11 years.

For food allergy, later birth order was generally protective (Table 3), particularly before 66 months of age. The adjusted RR for a visit between 54 and 66 months was 0.71 (95% CI, 0.58 to 0.86) for the second-born category and 0.68 (95% CI, 0.51 to 0.91) for the third-born or higher category compared with the first-born category. The

RR became unstable after that age due to the small number of cases.

By contrast, later birth order generally increased the risk of hospital visits for atopic dermatitis, especially after 30 months of age (Table 4). The adjusted RR for the visit between 11 and 12 years was 1.11 (95% CI, 1.00 to 1.24) for the second-born category and 1.18 (95% CI, 1.02 to 1.37) for the third-born or higher category, compared with the first-born category.

Although we also adjusted for the increase in number of siblings in the sensitivity analysis, the results did not change substantially (Supplemental Table 3).

Discussion

Main Findings

This study examined the relationships between birth order and hospital visits for allergic disease in a large nationwide longitudinal study in Japan. The associations between birth order and bronchial asthma were varied, with later birth order increasing the risk in early childhood, but decreasing the risk during school age. Later birth order was generally protective for food allergy but increased the risk of atopic dermatitis. To our knowledge, this is the first study to examine this subject in a large nationwide longitudinal study and to analyze three types of allergic disease simultaneously.

Possible Mechanisms

There are several reasons why birth order as an indicator of postnatal environment had varying effects on these three types of allergic disease. Children with a late birth order, such as second- and third-born children, are frequently and directly exposed to pathogens and endotoxins, which shifts the balance between type 1 T helper (Th1) and type 2 T helper (Th2) toward Th1 cells, and induces regulatory T cells (Tregs) [21-23], possibly reducing the incidence of allergic disease. In contrast, allergens present in dust induce a Th2 cell response, resulting in hypersecretion of cytokines (i.e., interleukin-4 and interleukin-13) that stimulate the production of IgE, and thus increase the incidence of allergic reactions. The subtle balance between these two opposing mechanisms as well as the drastic change in immune function during childhood are likely to influence the development of allergic disease in specific organs.

Bronchial Asthma

The associations between birth order and bronchial asthma were diverse. Later birth order increased the risk in early childhood but decreased the risk during school age. These findings are consistent with previous cross-sectional studies at each childhood period and our longitudinal study provides further insight into the periods during which associations between birth order and bronchial asthma can change [3,6,11-15]. A birth cohort study in Germany reported that daycare attendance but not birth order increased the prevalence of bronchial asthma during the first 3 years of life [4,5], however, the possible effect of unsanitary postnatal environments such as birth order and daycare attendance may depend on the background of the study population (such as the frequency of daycare attendance) [6]. Bronchial asthma, which is diagnosed mainly based on clinical symptoms such as recurrent episodes of wheezing and cough, is a heterogeneous condition. About 80% of bronchial asthma cases during early childhood, which are characterized by a narrow airway [24], are reported to manifest transient wheezing from respiratory infections [25, 26]. IgE-mediated atopic asthma, caused by airway hyperresponsiveness and airway remodeling [24], is more frequently observed among children aged ≥6 years [27]. Later-born children have a higher incidence of respiratory tract infections in early childhood [9], which could explain the higher incidence of asthma among later-born children in early childhood observed in the present study. However, later-born children frequently encounter stimuli that induce Th1 cells during early childhood, and this has the potential to shift the balance between Th1/Th2 toward Th1 [22]. This could have reduced the incidence of asthma, such as IgE-mediated atopic asthma, among later-born children in the school-age years as seen in this study.

Food Allergy

Consistent with previous studies [14,28], later birth order was generally protective for food allergy before, but not after, 66 months of age and particularly in early childhood. This finding is line with the previous cross-sectional study, which reported that later birth order decreased the prevalence of food allergy during infancy [14]. The reduced risk of food allergy among later-born children may be because second- and third-born children are more frequently exposed than first-born children to infectious agents, which shifts the balance between Th1/Th2 toward Th1 cells. Also, endotoxins activate and increase Tregs [23], which probably suppress the symptoms of food allergy [29]. Furthermore, Tregs play an important role in acquired resistance and the number of Tregs was significantly low in patients with food allergy before, but not after [30], the age of 6 years [31]. Unsanitary environments might contribute to a low incidence of food allergy.

Atopic Dermatitis

Our findings show that later birth order increased the risk of atopic dermatitis, especially after 30 months of age, and the lack of an association before 30 months of age in this study could be due to non-differential outcome misclassification because hospital visits for atopic dermatitis included eczema from 6 to 30 months. However, findings from previous studies are inconsistent. For example, some studies observed no association [9, 11, 15] or positive associations between birth order and atopic dermatitis [32], while others reported negative associations [15]. Moreover, one study reported that later birth order decreased prevalence of atopic dermatitis but increased prevalence of severe atopic dermatitis [33]. These inconsistent findings could be explained by the fact

that the etiology of atopic dermatitis is not well understood and IgE-mediated allergic factors, skin barrier dysfunction [34, 35], and non-allergic factors such as the postnatal environment could determine the symptoms. Unsanitary environments might increase the likelihood of atopic dermatitis, and thus further research is needed.

Influence of Younger Siblings

We used birth order as an indicator of postnatal environment, but some studies used the presence of younger siblings as another feature of the postnatal environment that can affect the prevalence of allergic disease [6, 36]. Although we adjusted for increase in the number of siblings (i.e., presence of younger siblings) in sensitivity analysis, the effect estimates for birth order did not change substantially (Supplemental Table 3) and those for increase in number of siblings were not consistent (data not shown). Older siblings generally are more likely to have contact with other children and contract infectious diseases than younger siblings, which may explain why the effect estimates for birth order were stable despite the adjustment and were more consistent than those for increase in number of siblings.

Strengths and Limitations

The strength of our study is the large, nationally representative sample. Approximately one-twentieth of children born in Japan in 2001 were included in this study and there was a high response rate at baseline (88%) and relatively high follow-up rates (>80% at age 5 and >70% at age 10), but we cannot rule out some selection bias. We also collected individual covariates, such as maternal smoking status and educational level.

This study has several limitations. First, the disease outcomes were obtained from questionnaire responses and then reported retrospectively. We were thus unable to determine the diagnostic accuracy of diseases. However, Japanese children have good access to pediatric medical care because of national health insurance coverage; in practice, the number of physician visits in Japan is twice the average in other developed countries [37]. Furthermore, in Japan, most children are seen by pediatric specialists who frequently see cases of pediatric allergic diseases in private practice or in hospital as outpatients. Therefore, we believe that the name of the disease in the survey response was based on a diagnosis made by a physician and was thus accurate. Second, we adjusted for several potential confounding factors in the model but not for other factors like parental history of allergic disease and differences in consultation behavior and socioeconomic factors depending on birth order. We adjusted with maternal and paternal educational level as the indicator of socioeconomic status, so additional residual confounding would not be a serious concern. Third, we did not consider the age difference between siblings, but we adjusted for the increase in number of siblings in each age period. Finally, almost 30% of children were lost to follow-up and this percentage increased as the participants got older (Supplemental Table 1). Children in the third-born or higher category were more likely to be lost to follow-up and those who were lost tended to have young mothers and mothers who smoked. The effect of cases lost to follow-up may change depending on the disease and may complicate the results. However, follow-up rates in our study were relatively high, so lost cases likely did not substantially affect our findings.

Conclusions

The influence of birth order on pediatric allergic disease depended on the type of allergic disease and childhood period. The hygiene hypothesis might be relevant, but the theory is complex and sanitary environments have advantages and disadvantages for allergic disease in childhood. Immune response to the postnatal environment in childhood might be heterogeneous. Because immune status in early childhood is related to allergic disease in adulthood, long-term follow-up is needed to provide further insight.

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Conflict of interest

The authors declare no conflict of interest.

Abbreviations: Th1: type 1 T helper, Th2: type 2 T helper, Tregs: regulatory T cells

Key words: atopic dermatitis, bronchial asthma, birth order, child, food allergy

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Table 1. Demographic characteristics of eligible children (n=47,015)

	Birth number		
	First (N=22,967)	Second (N=17,119)	Third (N=6,929)
Characteristics of children			
Sex, n (%)*			
Boys	11800 (51.4)	8976 (52.4)	3649 (52.7)
Girls	11167 (48.6)	8143 (47.6)	3280 (47.3)
Singleton birth, n (%)*	22699 (98.8)	16681 (97.4)	6659 (96.1)
Multiple birth, n (%)*	268 (1.2)	438 (2.6)	270 (3.9)
Mean gestational age, weeks (SD)*	39.1 (1.6)	38.7 (1.6)	38.6 (1.7)
Term birth, n (%)*	21952 (95.6)	16216 (94.7)	6465 (93.3)
Preterm birth, n (%)*	1015 (4.4)	903 (5.3)	464 (6.7)
Daycare attendance, n (%)†			
Not attend	18172 (84.8)	13301 (83.1)	5233 (81.5)
Attend	3249 (15.2)	2713 (16.9)	1186 (18.5)
Parental characteristics			
Mean maternal age at delivery, years (SD)*	28.5 (4.4)	30.7 (4)	33 (3.9)
Maternal smoking status, n (%)†			
Non-smoker	18975 (83)	14041 (82.6)	5549 (80.7)
Smoker (Less than or equal to 10 cigarettes per day)	2617 (11.5)	1863 (11)	721 (10.5)
Smoker (More than 10 cigarettes per day)	1259 (5.5)	1104 (6.5)	608 (8.8)
Maternal educational attainment, n (%)‡			
University or higher	3307 (15.5)	2123 (13.3)	601 (9.4)
Junior college or vocational school	9179 (43)	6516 (40.9)	2339 (36.6)
High school	7732 (36.2)	6491 (40.7)	2934 (45.9)
Junior high school and others	1128 (5.3)	813 (5.1)	512 (8)
Paternal educational attainment, n (%)‡			
University or higher	7787 (37)	5860 (37)	1978 (31.3)
Junior college or vocational school	3471 (16.5)	2405 (15.2)	882 (14)
High school	8118 (38.6)	6289 (39.7)	2761 (43.7)
Junior high school and others	1665 (7.9)	1274 (8.1)	694 (11)
Residential area, n (%)			
Wards	5363 (23.4)	3705 (21.6)	1229 (17.7)
Cities	13454 (58.6)	10221 (59.7)	4032 (58.2)
Towns or villages	4150 (18.1)	3193 (18.7)	1668 (24.1)

* Obtained from the birth record

† Obtained from the first survey (at the age of 6 months)

‡ Obtained from the second survey (at the age of 18 months)

Table 2. Crude and adjusted* RRs for associations between birth number and bronchial asthma from 0.5 to 12 years of age

	N*case*/N	% of cases	Crude RRs (95% CI)	Adjusted* RRs (95% CI)
Bronchial asthma				
Between 6 and 18 months (n=43,925)				
First	454 / 21462	2.1	1 (ref.)	1 (ref.)
Second	686 / 16037	4.3	2.02 (1.8 - 2.27)	2.1 (1.86 - 2.38)
Third	335 / 6426	5.2	2.46 (2.15 - 2.83)	2.61 (2.24 - 3.05)
Between 18 and 30 months (n=42,812)				
First	860 / 20926	4.1	1 (ref.)	1 (ref.)
Second	996 / 15630	6.4	1.55 (1.42 - 1.69)	1.62 (1.48 - 1.78)
Third	406 / 6256	6.5	1.58 (1.41 - 1.77)	1.69 (1.49 - 1.92)
Between 30 and 42 months (n=41,559)				
First	1105 / 20258	5.5	1 (ref.)	1 (ref.)
Second	1057 / 15225	6.9	1.27 (1.17 - 1.38)	1.29 (1.19 - 1.41)
Third	387 / 6076	6.4	1.17 (1.04 - 1.31)	1.19 (1.05 - 1.35)
Between 42 and 54 months (n=39,817)				
First	1357 / 19426	7.0	1 (ref.)	1 (ref.)
Second	1061 / 14596	7.3	1.04 (0.96 - 1.12)	1.06 (0.98 - 1.15)
Third	387 / 5795	6.7	0.96 (0.86 - 1.07)	0.98 (0.87 - 1.1)
Between 54 and 66 months (n=38,540)				
First	1605 / 18746	8.6	1 (ref.)	1 (ref.)
Second	1228 / 14217	8.6	1.01 (0.94 - 1.08)	1.01 (0.93 - 1.08)
Third	465 / 5577	8.3	0.97 (0.88 - 1.07)	0.94 (0.85 - 1.05)
Between 66 months and 7 years (n=36,798)				
First	1272 / 17911	7.1	1 (ref.)	1 (ref.)
Second	995 / 13581	7.3	1.03 (0.95 - 1.12)	1.03 (0.94 - 1.12)
Third	359 / 5306	6.8	0.95 (0.85 - 1.07)	0.93 (0.82 - 1.05)
Between 7 and 8 years (n=36,151)				
First	1115 / 17609	6.3	1 (ref.)	1 (ref.)
Second	852 / 13363	6.4	1.01 (0.92 - 1.1)	1.02 (0.93 - 1.12)
Third	296 / 5179	5.7	0.9 (0.8 - 1.02)	0.9 (0.78 - 1.03)
Between 8 and 9 years (n=35,275)				
First	1080 / 17201	6.3	1 (ref.)	1 (ref.)
Second	777 / 13021	6.0	0.95 (0.87 - 1.04)	0.95 (0.87 - 1.05)
Third	276 / 5053	5.5	0.87 (0.77 - 0.99)	0.83 (0.72 - 0.96)
Between 9 and 10 years (n=34,124)				
First	978 / 16700	5.9	1 (ref.)	1 (ref.)
Second	705 / 12568	5.6	0.96 (0.87 - 1.05)	0.93 (0.84 - 1.03)
Third	250 / 4856	5.2	0.88 (0.77 - 1.01)	0.83 (0.71 - 0.96)
Between 10 and 11 years (n=32,913)				
First	900 / 16082	5.6	1 (ref.)	1 (ref.)
Second	671 / 12152	5.5	0.99 (0.9 - 1.09)	0.97 (0.87 - 1.07)
Third	212 / 4679	4.5	0.81 (0.7 - 0.94)	0.76 (0.65 - 0.89)
Between 11 and 12 years (n=32,065)				
First	700 / 15653	4.5	1 (ref.)	1 (ref.)
Second	522 / 11878	4.4	0.98 (0.88 - 1.1)	0.97 (0.86 - 1.09)
Third	183 / 4534	4.0	0.9 (0.77 - 1.06)	0.86 (0.72 - 1.03)

CI, confidence interval; RR, risk ratio

* Adjusted for child factors (sex, singleton or not, preterm birth, and daycare attendance), parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment), and residential area.

Table 3. Crude and adjusted* RRs for associations between birth number and food allergy from 0.5 to 12 years of age

	N*case*/N	% of cases	Crude RRs (95% CI)	Adjusted* RRs (95% CI)
Food allergy				
Between 6 and 18 months (n=43,925)				
First	1152 / 21462	5.4	1 (ref.)	1 (ref.)
Second	705 / 16037	4.4	0.82 (0.75 - 0.9)	0.87 (0.79 - 0.95)
Third	205 / 6426	3.2	0.59 (0.51 - 0.69)	0.66 (0.57 - 0.78)
Between 18 and 30 months (n=42,812)				
First	614 / 20926	2.9	1 (ref.)	1 (ref.)
Second	342 / 15630	2.2	0.75 (0.65 - 0.85)	0.78 (0.68 - 0.9)
Third	87 / 6256	1.4	0.47 (0.38 - 0.59)	0.51 (0.4 - 0.65)
Between 30 and 42 months (n=41,559)				
First	361 / 20258	1.8	1 (ref.)	1 (ref.)
Second	236 / 15225	1.6	0.87 (0.74 - 1.02)	0.87 (0.73 - 1.04)
Third	63 / 6076	1.0	0.58 (0.45 - 0.76)	0.59 (0.44 - 0.78)
Between 42 and 54 months (n=39,817)				
First	308 / 19426	1.6	1 (ref.)	1 (ref.)
Second	188 / 14596	1.3	0.81 (0.68 - 0.97)	0.79 (0.65 - 0.96)
Third	54 / 5795	0.9	0.59 (0.44 - 0.78)	0.56 (0.41 - 0.77)
Between 54 and 66 months (n=38,540)				
First	304 / 18746	1.6	1 (ref.)	1 (ref.)
Second	174 / 14217	1.2	0.75 (0.63 - 0.91)	0.71 (0.58 - 0.86)
Third	66 / 5577	1.2	0.73 (0.56 - 0.95)	0.68 (0.51 - 0.91)
Between 66 months and 7 years (n=36,798)				
First	199 / 17911	1.1	1 (ref.)	1 (ref.)
Second	146 / 13581	1.1	0.97 (0.78 - 1.2)	1.02 (0.82 - 1.28)
Third	49 / 5306	0.9	0.83 (0.61 - 1.13)	0.96 (0.69 - 1.36)
Between 7 and 8 years (n=36,151)				
First	153 / 17609	0.9	1 (ref.)	1 (ref.)
Second	112 / 13363	0.8	0.96 (0.76 - 1.23)	0.96 (0.75 - 1.24)
Third	40 / 5179	0.8	0.89 (0.63 - 1.26)	0.91 (0.62 - 1.32)
Between 8 and 9 years (n=35,275)				
First	147 / 17201	0.9	1 (ref.)	1 (ref.)
Second	103 / 13021	0.8	0.93 (0.72 - 1.19)	0.94 (0.72 - 1.23)
Third	46 / 5053	0.9	1.07 (0.77 - 1.48)	1.12 (0.78 - 1.61)
Between 9 and 10 years (n=34,124)				
First	123 / 16700	0.7	1 (ref.)	1 (ref.)
Second	89 / 12568	0.7	0.96 (0.73 - 1.26)	0.94 (0.7 - 1.25)
Third	42 / 4856	0.9	1.17 (0.83 - 1.66)	1.2 (0.82 - 1.76)
Between 10 and 11 years (n=32,913)				
First	169 / 16082	1.1	1 (ref.)	1 (ref.)
Second	92 / 12152	0.8	0.72 (0.56 - 0.93)	0.69 (0.53 - 0.91)
Third	47 / 4679	1.0	0.96 (0.69 - 1.32)	0.95 (0.67 - 1.35)
Between 11 and 12 years (n=32,065)				
First	126 / 15653	0.8	1 (ref.)	1 (ref.)
Second	94 / 11878	0.8	0.98 (0.75 - 1.28)	0.93 (0.7 - 1.23)
Third	28 / 4534	0.6	0.77 (0.51 - 1.15)	0.72 (0.46 - 1.12)

CI, confidence interval; RR, risk ratio

* Adjusted for child factors (sex, singleton or not, preterm birth, and daycare attendance), parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment), and residential area.

Table 4. Crude and adjusted* RRs for associations between birth number and atopic dermatitis from 0.5 to 12 years of age

	N*case*/N	% of cases	Crude RRs (95% CI)	Adjusted* RRs (95% CI)
Atopic dermatitis				
Between 6 and 18 months (n=43,925)				
First	3713 / 21462	17.3	1 (ref.)	1 (ref.)
Second	2620 / 16037	16.3	0.94 (0.9 - 0.99)	0.95 (0.9 - 0.99)
Third	992 / 6426	15.4	0.89 (0.84 - 0.95)	0.9 (0.84 - 0.97)
Between 18 and 30 months (n=42,812)				
First	3186 / 20926	15.2	1 (ref.)	1 (ref.)
Second	2623 / 15630	16.8	1.1 (1.05 - 1.16)	1.1 (1.05 - 1.16)
Third	975 / 6256	15.6	1.02 (0.96 - 1.09)	1.03 (0.96 - 1.11)
Between 30 and 42 months (n=41,559)				
First	1347 / 20258	6.7	1 (ref.)	1 (ref.)
Second	1221 / 15225	8.0	1.21 (1.12 - 1.3)	1.25 (1.16 - 1.35)
Third	448 / 6076	7.4	1.11 (1 - 1.23)	1.17 (1.05 - 1.31)
Between 42 and 54 months (n=39,817)				
First	1324 / 19426	6.8	1 (ref.)	1 (ref.)
Second	1130 / 14596	7.7	1.14 (1.05 - 1.23)	1.18 (1.09 - 1.28)
Third	414 / 5795	7.1	1.05 (0.94 - 1.17)	1.15 (1.02 - 1.29)
Between 54 and 66 months (n=38,540)				
First	1397 / 18746	7.5	1 (ref.)	1 (ref.)
Second	1178 / 14217	8.3	1.11 (1.03 - 1.2)	1.15 (1.06 - 1.24)
Third	447 / 5577	8.0	1.08 (0.97 - 1.19)	1.15 (1.03 - 1.29)
Between 66 months and 7 years (n=36,798)				
First	1188 / 17911	6.6	1 (ref.)	1 (ref.)
Second	1024 / 13581	7.5	1.14 (1.05 - 1.23)	1.17 (1.07 - 1.27)
Third	372 / 5306	7.0	1.06 (0.94 - 1.18)	1.11 (0.98 - 1.26)
Between 7 and 8 years (n=36,151)				
First	1133 / 17609	6.4	1 (ref.)	1 (ref.)
Second	941 / 13363	7.0	1.09 (1.01 - 1.19)	1.13 (1.04 - 1.24)
Third	316 / 5179	6.1	0.95 (0.84 - 1.07)	1.02 (0.9 - 1.17)
Between 8 and 9 years (n=35,275)				
First	1001 / 17201	5.8	1 (ref.)	1 (ref.)
Second	851 / 13021	6.5	1.12 (1.03 - 1.23)	1.14 (1.04 - 1.25)
Third	322 / 5053	6.4	1.1 (0.97 - 1.24)	1.15 (1 - 1.31)
Between 9 and 10 years (n=34,124)				
First	894 / 16700	5.4	1 (ref.)	1 (ref.)
Second	763 / 12568	6.1	1.13 (1.03 - 1.25)	1.13 (1.02 - 1.25)
Third	284 / 4856	5.9	1.09 (0.96 - 1.24)	1.12 (0.97 - 1.29)
Between 10 and 11 years (n=32,913)				
First	912 / 16082	5.7	1 (ref.)	1 (ref.)
Second	729 / 12152	6.0	1.06 (0.96 - 1.16)	1.06 (0.96 - 1.17)
Third	303 / 4679	6.5	1.14 (1.01 - 1.3)	1.19 (1.03 - 1.36)
Between 11 and 12 years (n=32,065)				
First	774 / 15653	4.9	1 (ref.)	1 (ref.)
Second	653 / 11878	5.5	1.11 (1 - 1.23)	1.11 (1 - 1.24)
Third	263 / 4534	5.8	1.17 (1.02 - 1.34)	1.18 (1.02 - 1.37)

CI, confidence interval; RR, risk ratio

* Adjusted for child factors (sex, singleton or not, preterm birth, and daycare attendance), parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment), and residential area.

Supplemental Table 1. Distributions of the birth number, separated by included or loss to follow-up at eath survey

	Included in the analysis	Lost to follow-up
Second survey (at 18 months)		
First	21462 (93.5)	1505 (6.6)
Second	16037 (93.7)	1082 (6.3)
Third	6426 (92.7)	503 (7.3)
Third survey (at 30 months)		
First	20926 (91.1)	2041 (8.9)
Second	15630 (91.3)	1489 (8.7)
Third	6256 (90.3)	673 (9.7)
Fourth survey (at 42 months)		
First	20258 (88.2)	2709 (11.8)
Second	15225 (88.9)	1894 (11.1)
Third	6076 (87.7)	853 (12.3)
Fifth survey (at 54 months)		
First	19426 (84.6)	3541 (15.4)
Second	14596 (85.3)	2523 (14.7)
Third	5795 (83.6)	1134 (16.4)
Sixth survey (at 66 months)		
First	18746 (81.6)	4221 (18.4)
Second	14217 (83.1)	2902 (17.0)
Third	5577 (80.5)	1352 (19.5)
Seventh survey (at 7 years)		
First	17911 (78.0)	5056 (22.0)
Second	13581 (79.3)	3538 (20.7)
Third	5306 (76.6)	1623 (23.4)
Eighth survey (at 8 years)		
First	17609 (76.7)	5358 (23.3)
Second	13363 (78.1)	3756 (21.9)
Third	5179 (74.7)	1750 (25.3)
Ninth survey (at 9 years)		
First	17201 (74.9)	5766 (25.1)
Second	13021 (76.1)	4098 (23.9)
Third	5053 (72.9)	1876 (27.1)
10th survey (at 10 years)		
First	16700 (72.7)	6267 (27.3)
Second	12568 (73.4)	4551 (26.6)
Third	4856 (70.1)	2073 (29.9)
11th survey (at 11 years)		
First	16082 (70.0)	6885 (30.0)
Second	12152 (71.0)	4967 (29.0)
Third	4679 (67.5)	2250 (32.5)
12th survey (at 12 years)		
First	15653 (68.2)	7314 (31.9)
Second	11878 (69.4)	5241 (30.6)
Third	4534 (65.4)	2395 (34.6)

Supplemental Table 2. Demographic characteristics, separated by included or loss to follow-up at 2nd survey

	At second survey	
	Included in the analysis (N=43,925)	Lost to follow-up (N=3,090)
Characteristics of children		
Birth number, n (%)*		
First	21462 (48.9)	1505 (48.7)
Second	16037 (36.5)	1082 (35.0)
Third	6426 (14.6)	503 (16.3)
Sex, n (%)*		
Boys	22825 (52.0)	1600 (51.8)
Girls	21100 (48.0)	1490 (48.2)
Singleton birth, n (%)*	43033 (98.0)	3006 (97.3)
Multiple birth, n (%)*	892 (2.0)	84 (2.7)
Mean gestational age, weeks (SD)*	38.9 (1.6)	38.8 (1.7)
Term birth, n (%)*	41747 (95.0)	2886 (93.4)
Preterm birth, n (%)*	2178 (5.0)	204 (6.6)
Parental characteristics		
Mean maternal age at delivery, years (SD)*	30.1 (4.4)	28.2 (5.1)
Maternal smoking status, n (%)†		
Non-smoker	36574 (83.7)	1991 (65.4)
Smoker (Less than or equal to 10 cigarettes per day)	4644 (10.6)	557 (18.3)
Smoker (More than 10 cigarettes per day)	2474 (5.7)	497 (16.3)
Residential area, n (%)		
Wards	9645 (22.0)	652 (21.1)
Cities	25891 (58.9)	1816 (58.8)
Towns or villages	8389 (19.1)	622 (20.1)

* Obtained from the birth record

† Obtained from the first survey (at the age of 6 months)

Supplemental Table 3. Sensitivity analysis: additional adjustment for increase in number of siblings. Adjusted* RRs with their 95% CI for associations between birth number and each outcome from 0.5 to 12 years of age are shown.

	Bronchial asthma	Food allergy	Atopic dermatitis
Bronchial asthma			
Between 6 and 18 months (n=43,925)			
First	1 (ref.)	1 (ref.)	1 (ref.)
Second	2.1 (1.85 - 2.37)	0.86 (0.78 - 0.95)	0.95 (0.9 - 0.99)
Third	2.6 (2.23 - 3.04)	0.66 (0.56 - 0.77)	0.9 (0.84 - 0.97)
Between 18 and 30 months (n=42,812)			
First	1 (ref.)	1 (ref.)	1 (ref.)
Second	1.58 (1.43 - 1.74)	0.75 (0.65 - 0.86)	1.09 (1.03 - 1.14)
Third	1.64 (1.44 - 1.87)	0.48 (0.38 - 0.62)	1.01 (0.94 - 1.09)
Between 30 and 42 months (n=41,559)			
First	1 (ref.)	1 (ref.)	1 (ref.)
Second	1.22 (1.11 - 1.33)	0.81 (0.68 - 0.97)	1.27 (1.16 - 1.37)
Third	1.11 (0.97 - 1.26)	0.54 (0.4 - 0.72)	1.19 (1.06 - 1.34)
Between 42 and 54 months (n=39,817)			
First	1 (ref.)	1 (ref.)	1 (ref.)
Second	1 (0.92 - 1.09)	0.73 (0.59 - 0.89)	1.16 (1.06 - 1.26)
Third	0.91 (0.81 - 1.04)	0.51 (0.37 - 0.71)	1.13 (1 - 1.27)
Between 54 and 66 months (n=38,540)			
First	1 (ref.)	1 (ref.)	1 (ref.)
Second	0.96 (0.88 - 1.04)	0.6 (0.49 - 0.74)	1.15 (1.06 - 1.25)
Third	0.89 (0.79 - 1)	0.57 (0.42 - 0.76)	1.16 (1.03 - 1.3)
Between 66 months and 7 years (n=36,798)			
First	1 (ref.)	1 (ref.)	1 (ref.)
Second	0.98 (0.89 - 1.07)	0.97 (0.75 - 1.23)	1.17 (1.07 - 1.29)
Third	0.87 (0.77 - 1)	0.9 (0.63 - 1.29)	1.12 (0.98 - 1.27)
Between 7 and 8 years (n=36,151)			
First	1 (ref.)	1 (ref.)	1 (ref.)
Second	0.99 (0.9 - 1.1)	0.77 (0.58 - 1.02)	1.11 (1.01 - 1.23)
Third	0.87 (0.75 - 1.01)	0.7 (0.47 - 1.04)	1 (0.87 - 1.15)
Between 8 and 9 years (n=35,275)			
First	1 (ref.)	1 (ref.)	1 (ref.)
Second	0.92 (0.83 - 1.02)	0.83 (0.62 - 1.1)	1.13 (1.02 - 1.26)
Third	0.8 (0.69 - 0.93)	0.96 (0.65 - 1.41)	1.14 (0.99 - 1.31)
Between 9 and 10 years (n=34,124)			
First	1 (ref.)	1 (ref.)	1 (ref.)
Second	0.9 (0.81 - 1.01)	0.88 (0.64 - 1.2)	1.12 (1 - 1.24)
Third	0.8 (0.68 - 0.93)	1.1 (0.73 - 1.66)	1.11 (0.95 - 1.29)
Between 10 and 11 years (n=32,913)			
First	1 (ref.)	1 (ref.)	1 (ref.)
Second	0.93 (0.83 - 1.04)	0.57 (0.42 - 0.77)	1.03 (0.92 - 1.15)
Third	0.71 (0.6 - 0.84)	0.78 (0.53 - 1.14)	1.15 (0.99 - 1.33)
Between 11 and 12 years (n=32,065)			
First	1 (ref.)	1 (ref.)	1 (ref.)
Second	0.95 (0.83 - 1.08)	0.81 (0.59 - 1.12)	1.06 (0.94 - 1.19)
Third	0.84 (0.69 - 1.01)	0.63 (0.39 - 1.02)	1.12 (0.96 - 1.32)

CI, confidence interval; RR, risk ratio

* Adjusted for child factors (sex, singleton or not, preterm birth, daycare attendance, and change in number of siblings), parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment), and residential area.