

D. K. Yon¹
 S. W. Lee¹
 E. K. Ha¹
 K. S. Lee¹ 
 Y.-H. Jung¹
 H. M. Jee¹
 M. A. Kim²
 J.-C. Ahn³
 Y. H. Sheen⁴
 M. Y. Han¹ 

¹Department of Pediatrics, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

²Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

³Department of Otorhinolaryngology–Head and Neck Surgery, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

⁴Department of Pediatrics, CHA Gangnam Medical Center, CHA University School of Medicine, Seoul, Korea

Email: drmesh@gmail.com

Yon and Lee equally contributed to this study.

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Having small-for-gestational-age infants was associated with maternal allergic features in the JECS birth cohort

To the Editor,

Being small for gestational age (SGA) is associated with significant perinatal outcomes, such as foetal and neonatal distress, and long-term complications, such as insulin resistance and cardiovascular disease.^{1,2} Maternal history of chronic diseases such as hypertension can be a risk factor for being SGA.³ Asthma is one of the most frequent chronic diseases encountered during pregnancy, and Murphy et al⁴ reported that maternal asthma was associated with an increased risk of SGA in their systematic review. Based on those results, we hypothesized that inflammatory reactions caused by allergic diseases might increase the risk of intrauterine growth retardation (IUGR). To our knowledge, the association of SGA with maternal IgE sensitization and allergic diseases other than asthma has not been reported. The aim of this study was to

investigate the association between SGA and allergic diseases during pregnancy.

The Japan Environment and Children's Study (JECS) is a nationwide, multicentre, prospective birth cohort study described elsewhere.^{5,6} The physician's diagnosis of an allergic disease was verified by a questionnaire, and the lifetime prevalence of these conditions was assessed. The total serum and allergen-specific IgE titres of the mothers during pregnancy, assayed by ImmunoCAP (Thermo Fisher Scientific, Inc., Sweden), were analysed by an independent clinical laboratory. The present study is based on the data set "jecs-ag-20160424", which was released in June 2016. SGA was defined as a birthweight and length below the 10th percentile for gestational age [ICD-10 P05.1] based on the new, age-specific Japanese standards for birth size.⁷

For this analysis, we included mothers who delivered a full-term singleton ($n = 91\,557$). Mothers with unclear data for gestational age ($n = 1$); infant body weight < 1000 g, 6000 g $< (n = 4)$; body height < 30 cm, 60 cm $< (n = 2)$; or missing relevant data ($n = 1344$) were excluded. In total, 90 206 mothers/newborns were enrolled. We set the presence of SGA delivery as the primary outcome measure and the standard deviation (SD) score for birth height/weight as the secondary outcome measure. Maternal allergic features included the history of asthma, allergic rhinitis, atopic dermatitis (AD), food allergy (FA), drug allergy, and contact dermatitis. "Any allergic disease" (defined as any one of the allergic diseases listed above) was used as an explanatory variable. Natural, log-transformed total IgE level, high levels of total IgE (>170 IU/mL), and "sensitization to any specific IgE (IgEs ≥ 0.35 UA/mL)," including *Dermatophagoides pteronyssinus* (*Der p* 1), animal dander, Japanese cedar, birch, moth, and egg whites, were also used as explanatory variables. A logistic regression model and linear regression model were used to examine the association of maternal allergic features with SGA delivery and SD score with birth height/weight. Potential confounders, including maternal age, primiparity, marital state, past history of hypertension, type 1 or 2 diabetes, abnormal pregnancy (at least one of the following: pregnancy-induced hypertension, gestational diabetes mellitus, placenta abruption, ectopic pregnancy, placenta previa, hydatidiform mole or other abnormal pregnancy), body mass index (BMI) at early pregnancy, maternal weight gain during pregnancy, smoking and alcohol use during pregnancy, maternal education, annual family income, and place of recruitment, were used to estimate the adjusted odds ratio (aOR), regression coefficient (B), and 95% confidence interval (CI) in the multivariable analysis. Additionally, a subgroup analysis was carried out for mothers with asthma to test the

association of SGA with nonatopic asthma, which was defined as asthma without sensitization to any specific allergens. The association between SGA and nonatopic status among nonasthmatic mothers was also evaluated. Potential interactions between asthma and primiparity, history of abnormal pregnancy, and maternal weight gain were also tested in additional logistic regression models, which included each interaction term. This study was exploratory and aimed to assess the magnitude of the association between maternal allergy status and SGA delivery. Therefore, we did not define the statistical significance for P at the outset. The figures below show the estimates of the coefficients adjusted or not adjusted for the confounders and the 95% CI. We also give the P -value for the estimates in the figures for reference.

Table S1 shows the other maternal and infant characteristics. In this study, we found that 2870 (3.2%) mothers had an SGA birth. IgE sensitization to specific allergens was found in 74% of the mothers. The maternal prevalence of asthma and AD was 10.9% and 15.8%. Figure 1 shows the associations among SGA and maternal allergic features. Although there was no significant association of sensitization with any allergen-specific IgE or high levels of total IgE with SGA birth in either univariate or multivariable logistic regression analysis, a positive association was found between natural, log-transformed total IgE level and SGA (aOR 1.04, 95% CI: 1.02–1.07). Furthermore, there was a statistically inverse relationship between the SD scores for weight and height and the log-transformed total IgE level in the multivariable linear model ($B = -0.01$, 95% CI: -0.01 to -0.00 and $B = -0.01$, 95% CI: -0.01 to -0.00 , respectively) (Figure 2). Although contact dermatitis increased the odds of SGA in the univariate analysis (OR 1.29, 95% CI: 1.02–1.65), the tendency was not found after adjusting for confounding factors (aOR 1.25,

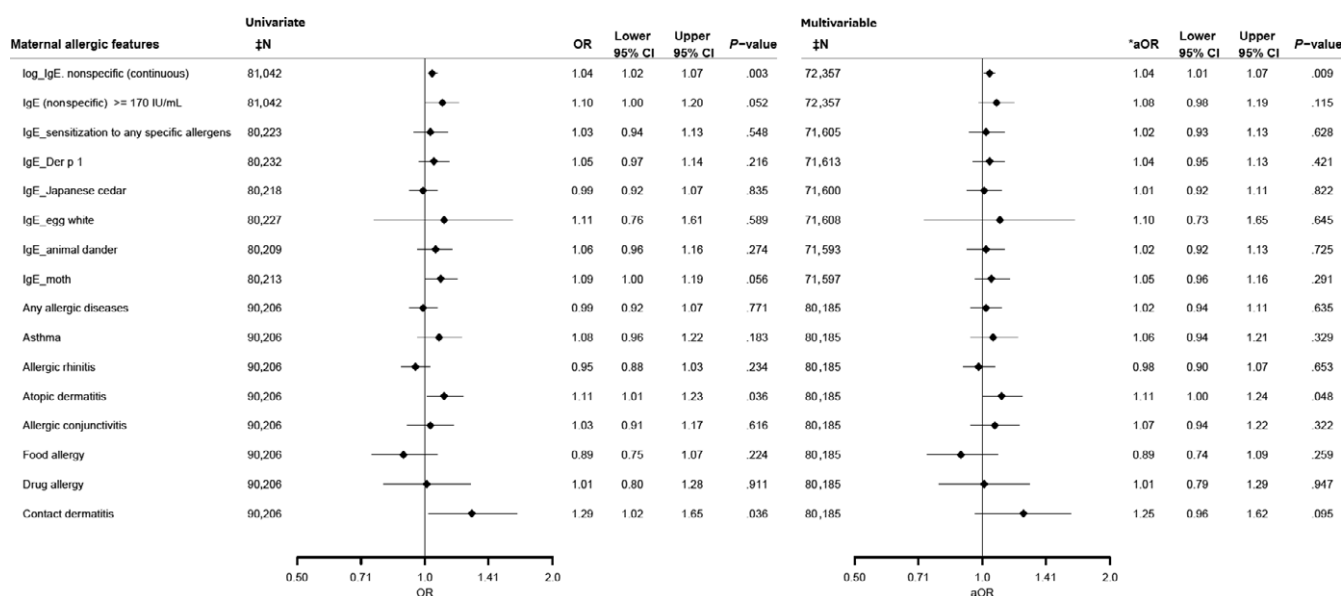


FIGURE 1 SGA: small for gestational age; OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval; IgE: immunoglobulin E; *Der p* 1: *Dermatophagoides pteronyssinus*. *aOR and 95% CIs were estimated with potential confounders including maternal age, primiparity, marital state, past history of hypertension, type I or II diabetes, abnormal pregnancy, body mass index (BMI) at beginning of pregnancy, maternal weight gain during pregnancy, smoking and alcohol during pregnancy, maternal education level, annual family income and place of recruitment. ‡Number of mothers without missing value

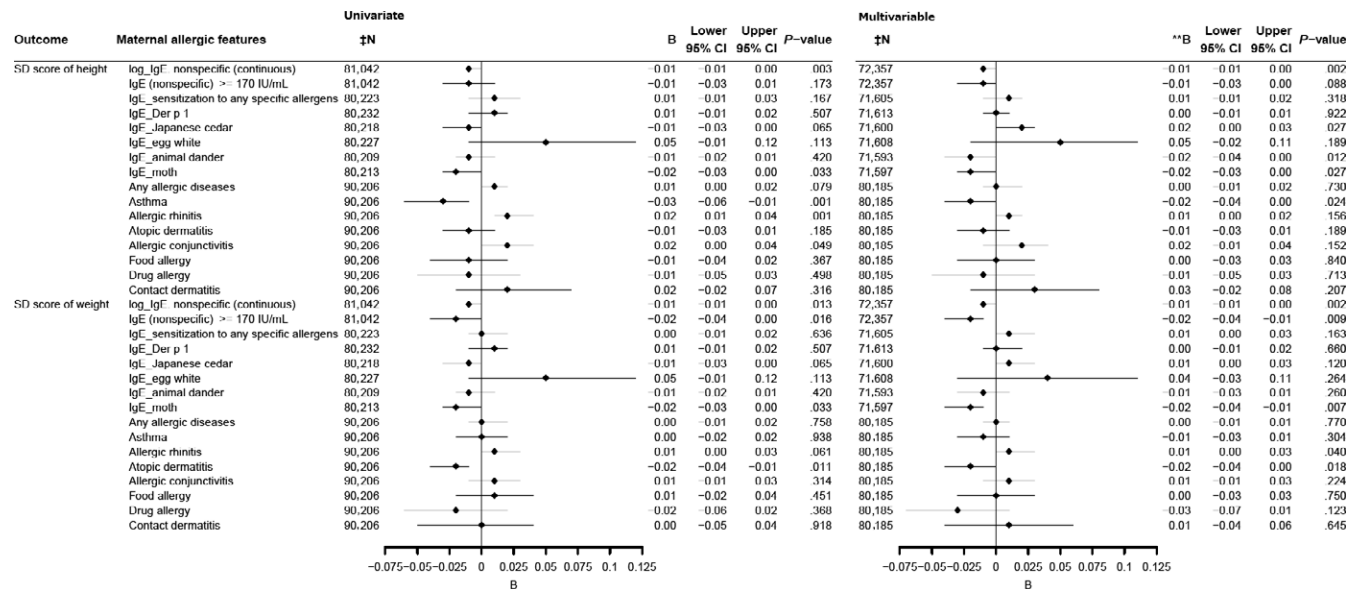


FIGURE 2 SGA: small for gestational age; CI: confidence interval; IgE: immunoglobulin E; Der p 1: Dermatophagoides pteronyssinus. *B and 95% CIs were estimated with potential confounders including maternal age, primiparity, marital state, past history of hypertension, type I or II diabetes, abnormal pregnancy, body mass index (BMI) at beginning of pregnancy, maternal weight gain during pregnancy, smoking and alcohol during pregnancy, maternal education level, annual family income and place of recruitment in multivariate analysis. ‡Number of mothers without missing value

95% CI: 0.96-1.62). AD was associated with an increased odds of SGA in both the univariate and multivariable analyses (OR 1.11, 95% CI: 1.01-1.23; aOR 1.11, 95% CI: 1.00-1.24, respectively). There was also a significant linear relationship between AD and SD scores for weight ($B = -0.02$, 95% CI: -0.04 to -0.00).

In this study, no association was found between maternal asthma and SGA (aOR 1.06, 95% CI: 0.94 to 1.21), but the SD score for height was inversely associated with asthma ($B = -0.02$, 95% CI: -0.04 to -0.00). Additionally, in the subgroup analysis of asthmatic mothers, multivariable logistic regression analysis showed that those with nonatopic asthma were more likely to have an SGA infant (aOR 1.59, 95% CI: 1.11 to 2.29) than those with atopic asthma (Figure S1). On the other hand, in the analysis of nonasthmatic mothers, no significant difference in the odds of SGA was found between nonatopic mothers and atopic mothers (aOR 0.95, 95% CI: 0.86 to 1.06). In the additional analysis of the interaction terms for asthma and primiparity, history of abnormal pregnancy and maternal weight gain, no significant results were found for SGA (data not shown).

To the best of our knowledge, this report is the first report to evaluate the associations of having an SGA infant with allergic features in Japanese pregnant women based on data from a nationwide birth cohort study. This study revealed that mothers with a higher total IgE level or a history of AD had increased odds of delivering an SGA and/or low-birthweight infant. We also confirmed that nonatopic asthma was associated with greater odds of SGA than atopic asthma. The mechanisms responsible for SGA delivery in mothers with allergic features were unclear in our study. The association of SGA with maternal total IgE production found in this study may indicate that the whole maternal atopic condition

can affect the growth of the foetus in some way. With regard to atopic dermatitis, a retrospective cohort study with pregnant women exposed to topical corticosteroids reported a significantly increased odds of low birthweight when the amount of potent or very potent topical corticosteroids used exceeded 300 g during the entire pregnancy.⁸ Topical corticosteroids are thought to influence birthweight or to function as a marker of eczema severity. With regard to asthma, past studies demonstrated that chronic maternal hypoxia could retard the growth of the foetus.^{4,9} Generally, nonatopic asthma tends to be more severe and may be less responsive to standard therapy than atopic asthma.¹⁰ These facts, together with our results, indicate that the severity of maternal allergic diseases might play a more important role in SGA than maternal sensitization to IgE. These findings were consistent with this conclusion because the subgroup analysis of "nonasthmatic" mothers in our study compared to "nonatopic" mothers and "atopic" mothers did not show any significant differences in the odds of SGA delivery (Figure S1).

Some limitations should be taken into account when interpreting our results. Information about the severity of the allergic diseases and the treatments used was not collected, and it was unclear whether the diseases were in an active or remission state during pregnancy. If we were able to focus on only active diseases during pregnancy, we may have been able to show a greater impact of allergic diseases on SGA delivery. Further studies accounting for the effect, if any, of corticosteroid use and disease activity and severity during pregnancy are necessary to clarify these issues.

In summary, this study suggested that maternal AD, nonatopic asthma and high total IgE production increase the odds of SGA

birth. The severity of maternal allergic disease might play a more important role in SGA than maternal sensitization itself. Our results highlighted the comorbidity of maternal allergic disorders and SGA offspring and suggested that whether or not IUGR occurs, and greater attention needs to be paid to this association when following pregnant women with AD and asthma in a clinical setting.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interests.

ORCID

K. Yamamoto-Hanada  <http://orcid.org/0000-0003-1288-9620>
 K. Ishitsuka  <http://orcid.org/0000-0002-2944-7012>
 M. Konishi  <http://orcid.org/0000-0002-1255-3644>
 L. Yang  <http://orcid.org/0000-0002-3936-6371>
 H. Saito  <http://orcid.org/0000-0002-6630-8337>
 Y. Ohya  <http://orcid.org/0000-0002-1560-3942>

M. Saito¹

K. Yamamoto-Hanada¹ 

K. Pak²

T. Ayabe¹

H. Mezawa¹

K. Ishitsuka¹ 

M. Konishi¹ 

L. Yang¹ 

K. Matsumoto¹

H. Saito¹ 

Y. Ohya¹ 

The Japan Environment and Children's Study (JECS) Group

¹Medical Support Center for the Japan Environment and Children's Study, National Center for Child Health and Development, Tokyo, Japan

²Department of Clinical Medicine (Biostatistics), Kitasato University
 School of Pharmacy, Tokyo, Japan
 Email: yamamoto-k@ncchd.go.jp

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Cannabis allergy: A diagnostic challenge

To the editor,

In the absence of a validated confirmatory test to document cannabis allergy, physicians use skin prick-prick testing with cannabis buds or leaves to confirm their clinical suspicion of a cannabis allergy.¹⁻⁴

Obviously, this approach is difficult to standardize as results are dependent on the source material. Our earlier study⁵ revealed that a basophil activation test (BAT) with an nsLTP rich cannabis extract could reliably diagnose cannabis allergy but leaves room for improvement. Here, we take advantage of the newly expressed Can s 3 protein⁶ to develop 3 flow cytometric diagnostics for cannabis allergy; a BAT with rCan s 3, a BAT with a crude CS extract, and a bead assay (CBA) quantifying sIgE to rCan s 3.

Twelve patients reporting immediate respiratory and cutaneous symptoms (as detailed in Table S2) on exposure to cannabis were

Abbreviations: BAT, basophil activation test; CA, cannabis allergic participants; CBA, cytometric bead array; CI, confidence interval; CS, *Cannabis sativa*; CTA, cannabis tolerant but atopic participants with pollen and LTP sensitizations; HC, healthy controls; NPV, negative predictive value; nsLTP, nonspecific lipid transfer protein; PPV, positive predictive value; rCan s 3, recombinant Can s 3 protein from *Cannabis sativa*; sIgE, specific immunoglobulin E.

Appendix

Members of the Japan Environment and Children's Study (JECS) as of 2017 (principal investigator, Toshihiro Kawamoto): Reiko Kishi (Hokkaido Regional Center for JECS, Hokkaido University, Sapporo, Japan), Nobuo Yaegashi (Miyagi Regional Center for JECS, Tohoku University, Sendai, Japan), Koichi Hashimoto (Fukushima Regional Center for JECS, Fukushima Medical University, Fukushima, Japan), Chisato Mori (Chiba Regional Center for JECS, Chiba University, Chiba, Japan), Shuichi Ito (Kanagawa Regional Center for JECS, Yokohama City University, Yokohama, Japan), Zentaro Yamagata (Koshin Regional Center for JECS, University of Yamanashi, Chuo, Japan), Hidekuni Inadera (Toyama Regional Center for JECS, University of Toyama, Toyama, Japan), Michihiro Kamijima (Aichi Regional Center for JECS, Nagoya City University, Nagoya, Japan), Takeo Nakayama (Kyoto Regional Center for JECS, Kyoto University, Kyoto, Japan), Hiroyasu Iso (Osaka Regional Center for JECS, Osaka University, Suita, Japan), Masayuki Shima (Hyogo Regional Center for JECS, Hyogo College of Medicine, Nishinomiya, Japan), Yasuaki Hirooka (Tottori Regional Center for JECS, Tottori University, Yonago, Japan), Narufumi Suganuma (Kochi Regional Center for JECS, Kochi University, Nankoku, Japan), Koichi Kusuhara (Fukuoka Regional Center for JECS, University of Occupational and Environmental Health,

Kitakyushu, Japan), and Takahiko Katoh (South Kyushu/Okinawa Regional Center for JECS, Kumamoto University, Kumamoto, Japan).

Table S1. Summary of participant baseline characteristics among infants and mothers in the JECS birth cohort (n=90,206)

Characteristics		
Infant Data		
Birth Weight	Mean (SD), g	3061.5 (367.8)
Birth Height	Mean (SD), cm	49.1 (1.9)
Gender	Female, n(%)	44225 (49%)
Gestational Age	Mean (SD), weeks	39 (1.1)
SGA *	Yes, n(%)	2870 (3.2%)
Maternal Data		
Maternal Age	<20, n(%)	757 (0.8%)
	≥20 & <35, n(%)	65324 (72.4%)
	≥35, n(%)	24125 (26.7%)
primiparity	Yes, n(%)	52311 (58%)
Current Marriage	Married, n(%)	85959 (95.7%)
	Missing, n(%)	388 (0.4%)
History of Abnormal Pregnancy	Yes, n(%)	5383 (6%)
Hypertention	Yes, n(%)	371 (0.4%)
Type 1 or 2 Diabetes	Yes, n(%)	170 (0.2%)
BMI at early Pregnancy	<18.5, n(%)	14409 (16%)
	≥18.5 & <25.0, n(%)	66009 (73.2%)
	≥25.0, n(%)	9352 (10.4%)
	Missing, n(%)	436 (0.5%)
Maternal Weight Gain	<7.0 kg, n(%)	14202 (15.7%)
	≥7.0 & <12.0 kg, n(%)	45211 (50.1%)
	≥12.0 kg, n(%)	29059 (32.2%)
	Missing, n(%)	1734 (1.9%)
Smoking During Pregnancy	Yes, n(%)	4200 (4.7%)
	NA, n(%)	651 (0.7%)
Alcohol During Pregnancy	Yes, n(%)	8966 (10%)
	NA, n(%)	393 (0.4%)
Education Completed	Junior high School, n(%)	4203 (4.7%)
	High School, n(%)	65481 (72.6%)
	University, n(%)	19448 (21.6%)
	Missing, n(%)	1074 (1.2%)

Characteristics		
Annual Family Income	>6 million yen, n(%)	22298 (26.8%)
	Missing, n(%)	6858 (7.6%)
Place of Recruitment	Hokkaido, n(%)	7043 (7.8%)
	Fukushima/Miyagi, n(%)	19981 (22.2%)
	Chiba/Kanagawa, n(%)	10661 (11.8%)
	Koshin, n(%)	6456 (7.2%)
	Toyama, n(%)	4957 (5.5%)
	Aichi, n(%)	4994 (5.5%)
	Kyoto/Osaka/Hyogo, n(%)	15068 (16.7%)
	Tottori, n(%)	2747 (3%)
	Kochi, n(%)	6275 (7%)
	Fukuoka/Kumamoto/Miyazaki, n(%)	11242 (12.5%)
	Okinawa, n(%)	782 (0.9%)
IgE (Non-specific)	≥ 170 IU/ml, n(%)	18924 (23.4%)
logIgE (non-specific)	25 percentile	3
	Median	4.1
	75 percentile	5.1
	Missing, n(%)	9164 (10.2%)
IgE Sensitization to Specific Allergens	≥ 0.35 kUA/l, n(%)	59351 (74%)
	Missing, n(%)	9983 (11.1%)
IgE Der p 1	≥ 0.35 kUA/l, n(%)	37789 (47.1%)
	Missing, n(%)	9974 (11.1%)
IgE Japanese Cedar	≥ 0.35 kUA/l, n(%)	44696 (55.7%)
	Missing, n(%)	9988 (11.1%)
IgE Hen Egg	≥ 0.35 kUA/l, n(%)	831 (1%)
	Missing, n(%)	9979 (11.1%)
IgE Animal Dander	≥ 0.35 kUA/l, n(%)	16543 (20.6%)
	Missing, n(%)	9997 (11.1%)
IgE Moth	≥ 0.35 kUA/l, n(%)	22495 (28%)
	Missing, n(%)	9993 (11.1%)
Any Allergic Diseases	Yes, n(%)	46067 (51.1%)
Asthma	Yes, n(%)	9842 (10.9%)
Allergic Rhinitis	Yes, n(%)	32630 (36.2%)

Characteristics		
Atopic Dermatitis	Yes, n(%)	14290 (15.8%)
Allergic Conjunctivitis	Yes, n(%)	8992 (10%)
Food Allergy	Yes, n(%)	4361 (4.8%)
Drug Allergy	Yes, n(%)	2328 (2.6%)
Contact Dermatitis	Yes, n(%)	1750 (1.9%)

SGA : small for gestational age; BMI: Body Mass Index; NA: not assessed ; IgE:Immunoglobulin E;
Der *p* 1: Dermatophagoides pteronyssinus.

*SGA defined as a birth weight and length below the 10th centile for gestational age based on the Japanese standards.

Figure 5. Univariate and multivariable logistic regression results for non-atopic states associated with delivery of SGA in the subgroup of asthmatic and non-asthmatic mothers.

