

ENVIRONMENTAL DETERMINANTS

Association between Prenatal and Postnatal Tobacco Smoke Exposure and Allergies in Young Children

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Background. Many studies have shown a positive association between environmental tobacco smoke (ETS) exposure and allergic disorders, whereas epidemiological evidence of the effect of maternal smoking during pregnancy on allergic diseases is inconsistent. We investigated the independent and joint effects of *in utero* exposure to maternal smoking and postnatal ETS exposure at home on allergic disorders among Japanese children. **Methods.** Study subjects were 1951 children aged 3 years. Data on maternal smoking during pregnancy and postnatal exposure to ETS at home, allergic symptoms, and potential confounders were collected through the use of a questionnaire. Outcomes were defined according to the criteria of the International Study of Asthma and Allergies in Childhood (ISAAC). **Results.** The prevalence values of symptoms of wheeze, asthma, and eczema in the previous 12 months were 22.0%, 8.8%, and 17.2%, respectively. We found that postnatal ETS exposure at home in the absence of *in utero* exposure to maternal smoking was associated with a higher prevalence of wheeze (adjusted odds ratio (OR) = 1.30, 95% confidence interval (CI): 1.01–1.67). In contrast, *in utero* exposure without subsequent postnatal ETS exposure at home or exposure to postnatal ETS at home in addition to *in utero* exposure to maternal smoking was not associated with the prevalence of wheeze. No measurable associations were observed between fetal, postnatal, or joint exposure and the prevalence of asthma or eczema. **Conclusions.** Data from this study indicate that ETS at home may be associated with a higher prevalence of wheeze among young Japanese children.

Keywords asthma, cross-sectional studies, eczema, environmental tobacco smoke, wheeze

INTRODUCTION

Maternal smoking during pregnancy and postnatal exposure to environmental tobacco smoke (ETS) has adverse effects on the health of children (1, 2). Children have been identified as a group sensitive to ETS because their respiratory and immune systems are not fully developed (2, 3). The associations between ETS exposure and allergic diseases in children have been extensively investigated (4–14); in most, but not all, studies, exposure to ETS is positively associated with wheeze, asthma, or eczema (4–10). On the other hand, epidemiological evidence of the effect of maternal smoking during pregnancy on allergic diseases is inconsistent (15–26); studies have shown positive (15–24), inverse (24), or no associations (21,24–26) between such exposure and allergic disorders.

To our knowledge, two cohort studies (25, 26) and three cross-sectional studies (10–12) have investigated the association between exposure to ETS and allergic diseases in Japanese children. Only one cohort study addressed the effects of maternal smoking during pregnancy on allergic diseases and showed that maternal smoking during pregnancy was not related to the risk of wheeze, whereas postnatal maternal smoking in the same room as the infant increased the risk of wheeze (25). However, this cited cohort study was not able to examine

the independent and joint effects of *in utero* exposure to maternal smoking and postnatal ETS exposure because the sample size was not adequate ($n = 763$) (25). A clear understanding of the association between maternal smoking during pregnancy and postnatal ETS exposure and allergic disorders among Japanese children is needed. In this cross-sectional study, we examined whether maternal smoking during pregnancy, postnatal exposure to ETS, or both prenatal and postnatal ETS exposure were associated with an increased prevalence of wheeze, asthma, and eczema in young Japanese children, using mutually exclusive exposure categories.

METHODS

Subjects

Data for this study came from the Fukuoka Child Health Study, a cross-sectional study to investigate the association between various selected factors and child health problems. In Japan, when children reach 3 years of age, the municipality of the domicile performs a physical examination. Eligible subjects for this study were those children aged 3 years who received the physical examination that was offered at all seven public health centers in Fukuoka City, a metropolitan area of Kyushu Island in southern Japan, with a total population of almost 1,414,000. During the period from June 2006 to January 2007, of the 8269 eligible subjects, we provided 8064 parents or guardians of those children with a structured self-administered questionnaire, a brief self-administered diet history questionnaire, and a stamped return envelope.

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Finally, a total of 2109 parents or guardians of the children answered the questionnaires and mailed these materials to the data management center (participation rate = 25.5%). Our research technicians completed missing answers and/or illogical data by telephone interview. This study was restricted to subjects who provided complete information on the variables under study, leaving data on 1951 children available for analysis (23.6% of all eligible children). Permission to perform this study was obtained from the ethics committee of the Faculty of Medicine, Fukuoka University.

Outcome Variables

One of the questionnaires included questions regarding wheeze, asthma, and eczema in the previous 12 months based on the International Study of Asthma and Allergies in Childhood (ISAAC) phase-I questionnaire. The definition of wheeze used in this study was determined by a positive response to the question, "Has your child had wheezing or whistling in the chest in the last 12 months?" A positive response to both the aforementioned question and another question "Has your child ever had asthma?" was considered to indicate asthma. For eczema, affirmative answers to all the following three questions in the ISAAC questionnaire were required: "Has your child ever had an itchy rash which was coming and going for at least 6 months?," "Has your child had this itchy rash at any time in the last 12 months?," and "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ear, or eyes?"

Exposure Variables and Covariates

Information on maternal smoking during pregnancy and postnatal smoking habits of adult household members (parents and other members, if present) were obtained from a structured self-administered questionnaire. For household ETS exposure, pack-months of exposure (number of packs per day multiplied by months of ETS) were calculated. The questionnaire also included questions about sex, number of siblings, breastfeeding duration, paternal and maternal history of asthma, atopic eczema and allergic rhinitis, and paternal and maternal educational levels. A paternal or maternal history of asthma, atopic eczema, and allergic rhinitis was defined as positive if the respective parents had contracted any of these allergic disorders prior to the start of the survey. Data from the brief self-administered diet history questionnaire were not used in this study.

Statistical Analyses

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multiple logistic regression analysis. The following potential confounders were identified *a priori* and were included in the multivariate model: sex, number of siblings, breastfeeding duration, paternal and maternal history of asthma, atopic eczema or allergic rhinitis, and paternal and maternal educational

level. Maternal smoking during pregnancy was classified into 2 categories (no and yes); ETS at home into 2 (never and ever); pack-months of ETS at home into 3 (none, 0.1–17.9, and ≥ 18.0); number of siblings into 3 (0, 1, and ≥ 2); breastfeeding duration into 2 (< 6 and ≥ 6 months); and paternal and maternal educational level into 3 (< 13 , 13–14, and ≥ 15 years). To examine whether prevalence increased with pack-months of ETS at home, trends of association were assessed using a logistic regression model assigning consecutive integers to the levels of the independent variable. Two-sided *p*-values less than 0.05 were considered statistically significant. All statistical analyses were performed using the SAS software package version 9.1 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

The prevalence values for symptoms of wheeze, asthma, and eczema in the previous 12 months were 22.0%, 8.8%, and 17.2%, respectively. Table 1 gives the distribution of selected factors among the 1951 children. About 70% of the subjects had one or more siblings. Approximately, 80% of the subjects were breastfed for 6 months or longer. Of the 1951 subjects, 252 (12.9%) were exposed to maternal smoking *in utero* and 828 (42.4%) were ever exposed to ETS at home (Table 2). The proportion of children with wheeze, asthma, or eczema was higher in the *in utero* exposure group than in the unexposed group and was higher in those exposed to ETS at home than in the unexposed children.

No statistically significant association was found between maternal smoking during pregnancy and the prevalence of wheeze, asthma, or eczema (Table 3). Compared with never smoking in the household, ever exposure to household smoking tended to be associated with a higher prevalence of wheeze (adjusted OR = 1.25;

TABLE 1.—Distribution of selected characteristics in 1951 children, Japan.

Variable	n (%)
Male	1033 (53.0)
Siblings	
0	603 (30.9)
1	1069 (54.8)
≥ 2	279 (14.3)
Breastfeeding duration (months)	
< 6	388 (19.9)
≥ 6	1563 (80.1)
Paternal history of asthma, atopic eczema, or allergic rhinitis	860 (44.1)
Maternal history of asthma, atopic eczema, or allergic rhinitis	941 (48.2)
Paternal educational level (years)	
< 13	528 (27.1)
13–14	296 (15.2)
≥ 15	1127 (57.8)
Maternal educational level (years)	
< 13	541 (27.7)
13–14	788 (40.4)
≥ 15	622 (31.9)

TABLE 2.—Prevalence of allergic disorders according to maternal smoking during pregnancy and postnatal ETS exposure at home.

	N	Wheeze		Asthma		Eczema	
		n	%	n	%	n	%
Maternal smoking during pregnancy							
No	1699	370	21.8	143	8.4	286	16.8
Yes	252	59	23.4	29	11.5	49	19.4
ETS at home							
Never	1123	229	20.4	89	7.9	181	16.1
Ever	828	200	24.2	83	10.0	154	18.6
Pack-months of ETS at home ^a							
None	1123	229	20.4	89	7.9	181	16.1
0.1–17.9	395	104	26.3	43	10.9	73	18.5
≥18.0	433	96	22.2	40	9.2	81	18.7
Perinatal smoking exposure status							
None	1078	218	20.2	85	7.9	174	16.1
<i>In utero</i> only	45	11	24.4	4	8.9	7	15.6
ETS at home only	621	152	24.5	58	9.3	112	18.0
Both <i>in utero</i> and ETS at home	207	48	23.2	25	12.1	42	20.3

Notes: ETS, environmental tobacco smoke.

^aNumber of packs per day multiplied by months of ETS at home.

TABLE 3.—Adjusted ORs and 95% CIs for allergic disorders according to maternal smoking during pregnancy and postnatal ETS exposure at home.

	Wheeze OR (95% CI) ^a	Asthma OR (95% CI) ^a	Eczema OR (95% CI) ^a
Maternal smoking during pregnancy			
No	1.00 Reference	1.00 Reference	1.00 Reference
Yes	1.03 [0.73, 1.43]	1.25 [0.78, 1.93]	1.17 [0.81, 1.67]
ETS at home			
Never	1.00 Reference	1.00 Reference	1.00 Reference
Ever	1.25 [0.99, 1.58]	1.22 [0.87, 1.71]	1.21 [0.94, 1.56]
Pack-months of ETS at home ^b			
None	1.00 Reference	1.00 Reference	1.00 Reference
0.1–17.9	1.41 [1.07, 1.87]	1.35 [0.90, 2.01]	1.19 [0.87, 1.62]
≥18.0	1.11 [0.83, 1.47]	1.10 [0.72, 1.65]	1.23 [0.91, 1.67]
P for linear trend	0.27	0.51	0.15
Perinatal smoking exposure status			
None	1.00 Reference	1.00 Reference	1.00 Reference
<i>In utero</i> only	1.24 [0.58, 2.43]	1.08 [0.32–2.80]	0.93 [0.37, 2.01]
ETS at home only	1.30 [1.01, 1.67]	1.17 [0.81, 1.69]	1.17 [0.89, 1.54]
Both <i>in utero</i> and ETS at home	1.14 [0.77, 1.67]	1.40 [0.82, 2.32]	1.35 [0.89, 2.01]

Notes: CI, confidence interval; ETS, environmental tobacco smoke; OR, odds ratio.

^aAdjustment for sex, number of siblings, breastfeeding duration, paternal and maternal history of asthma, atopic eczema or allergic rhinitis, and paternal and maternal educational level.^bNumber of packs per day multiplied by months of ETS at home.

95% CI: 0.99–1.58; $p = 0.06$). Also, 0.1–17.9 pack-months of ETS at home were significantly related to a 1.4-fold increased prevalence of wheeze, although the association with 18.0 or more pack-months of smoking in the household was not statistically significant. There was no significant association between being ever exposed to household smoking and the prevalence of asthma or eczema.

After mutual adjustment for maternal smoking during pregnancy and ETS exposure at home together with the confounding factors under study, we found that exposure to ETS at home, but not maternal smoking during pregnancy, tended to be positively associated with the prevalence of wheeze (further adjusted OR = 1.26; 95% CI: 0.995–1.605). There were no statistically significant associations between maternal smoking during pregnancy

or ETS exposure at home and the prevalence of asthma or eczema.

To assess the joint association of maternal smoking during pregnancy and postnatal smoking in the household, children were classified into four mutually exclusive categories: no maternal smoking during pregnancy and no postnatal ETS exposure at home (none, $n = 1078$); maternal smoking during pregnancy only (*in utero* only, $n = 45$); postnatal ETS exposure at home only (ETS at home only, $n = 621$); and both maternal smoking during pregnancy and postnatal ETS exposure at home (both *in utero* and ETS at home, $n = 207$). We found that only postnatal ETS exposure at home was associated with a higher prevalence of wheeze (adjusted OR = 1.30; 95% CI: 1.01–1.67), whereas *in utero* exposure only or both *in utero* exposure and postnatal ETS exposure at

home were not associated with wheeze. Stratified analysis based on a history of parental allergy in at least one parent revealed that a positive association of postnatal ETS exposure at home only with the prevalence of wheeze was more pronounced in children with a positive parental allergic history than in those with a negative parental allergic history (p for homogeneity of OR = 0.0009). No measurable associations were observed between fetal, postnatal, or joint exposure and the prevalence of asthma or eczema.

DISCUSSION

We found that only postnatal ETS exposure at home was associated with a higher prevalence of wheeze. On the other hand, no significant association between *in utero* exposure to maternal smoking, regardless of subsequent ETS exposure status, and the prevalence of wheeze was observed. We were not able to demonstrate any association between perinatal ETS exposure and the prevalence of asthma or eczema.

Most of the studies that investigated the association between prenatal and postnatal exposure to ETS and allergic disorders were unable to separate out the independent effect of *in utero* exposure versus postnatal exposure. Because women who smoke during pregnancy are likely to continue smoking after delivery, it has been difficult to study the independent effects of *in utero* exposure to maternal smoking and postnatal ETS exposure and the evidence for an independent effect of *in utero* exposure on allergic diseases has been inconsistent (16, 18, 24). In our study, 45 (2.3%) women reported smoking during pregnancy and no subsequent postnatal household ETS exposure for the participating child. This allowed us to assess the independent association of exposures in this subgroup of children.

The results for wheeze in our study are consistent with those from a cohort study in Denmark which showed that postnatal ETS exposure only, but not prenatal smoke exposure only, was significantly associated with an increased risk of wheeze at 14–18 years of age; the adjusted OR for wheeze relative to postnatal ETS exposure only = 1.2 (95% CI: 1.0–1.4) (24). On the other hand, our findings are in contrast to a previous cross-sectional study in school-aged children in California, which showed a greater impact of prenatal smoking on wheeze than postnatal smoking exposure (16). In the cited study (16), the adjusted OR for *in utero* exposure to maternal smoking without subsequent postnatal ETS exposure on a lifetime history of wheeze was 1.8 (95% CI: 1.2–2.6). The corresponding OR was 1.3 (95% CI: 1.1–1.5) for postnatal exposure to ETS in the absence of *in utero* exposure to maternal smoking (16). In the Tucson Children's Respiratory Study, the positive association between maternal prenatal smoking and current wheeze was a time-dependent relationship and a significant positive association was observed only

below the age of 3 years (27). The effect of exposure to tobacco smoke might vary according to the age of the child at diagnosis.

In this study, the observed relationship between postnatal ETS exposure at home only and the prevalence of wheeze was more pronounced in children with a positive parental allergic history than in those with a negative parental allergic history. This is consistent with a previous cross-sectional study among Italian schoolchildren, showing that when both ETS exposure and family atopy were present, the prevalence of current wheeze was almost tripled using the absence of both factors as the reference (22). Family history of allergic diseases might increase the subjects' susceptibility to the effects of environmental factors (28). Alternatively, it is possible that parents with allergic diseases would be more aware of their children's exposure to ETS than those without allergic diseases.

The results of this study showed that there were no associations between perinatal ETS exposure and the prevalence of asthma or eczema. Parents of children with asthma might have reported less ETS exposure than actually occurred. This type of differential exposure misclassification could lead to bias toward an inverse association. Alternatively, we cannot rule out the possibility that ETS exposure might increase the risk of respiratory infections rather than atopy (29).

That our findings did not support a dose-response relationship between ETS exposure and allergic diseases might be due to the narrow variation in cumulative ETS exposure because our subjects were relatively young.

This study had methodological strengths. Study subjects were homogeneous with respect to age and geographical background. We could control for relevant confounders.

There are some limitations that influence the interpretation of our results. First, the cross-sectional design gives no information on the temporal sequence and therefore does not allow a causal interpretation of the observed associations between ETS exposure and allergic disorders.

Second, of the 8269 eligible children in Fukuoka City, only 2015 (24.4%) were included in this analysis, leading to a potential for selection bias. Subjects who are highly concerned about health were likely to have participated in our study. We were not able to assess a difference between participants and nonparticipants because information on personal characteristics of nonparticipants was not available. Our subjects were not representative of Japanese children in the general population, and the present findings may not be generalized. In fact, educational levels in this study population were higher than in the general population. According to the 2000 population census of Japan, the proportions of men aged 35–39 years in Fukuoka City with years of education of <13, 13–14, ≥ 15 , and unknown were 39.6%, 8.0%, 43.3%, and 9.1%, respectively (30). The corresponding figures among men in this study were 27.1%, 15.2%, 57.8%, and 0.0%, respectively. Among women aged 30–34 years

in Fukuoka City, the percentage of years of education of <13, 13–14, ≥ 15 , and unknown were 41.3%, 34.4%, 16.1%, and 8.3%, respectively (30). The corresponding figures among women in this study were 27.7%, 40.4%, 31.9%, and 0.0%, respectively.

Third, although internationally standardized and validated measurement methods (ISAAC) were used to assess the symptoms of allergic disorders, misclassification may have occurred because the validity of this method is uncertain in infants: two older age groups (13–14 and 6–7 years) were studied in the ISAAC phase-I study. However, previously, epidemiological studies have used the core questions in the ISAAC phase-I study to estimate the risk of allergic diseases in infants (31, 32). In this study, skin prick tests or measurements of immunoglobulin E were not done. Therefore, the atopic status of each child was not available.

Fourth, assessment of exposure in our study was based on the questionnaire and was not validated by objective measurements, such as salivary, serum, urinary, or hair cotinine levels. Information on exposures and confounders was given retrospectively. Especially, retrospective recall of tobacco smoking is likely to have produced some misclassification of exposure. However, during pregnancy most women are very conscious of the need to restrict exposure of their developing babies to harmful substances such as tobacco smoke, so most participants would probably recall exposures correctly although some might have deliberately concealed tobacco smoking during pregnancy in order to give a socially desirable response. Misclassification is likely to be nondifferential and reduce the observed association.

Fifth, although we have adjusted our analyses for numerous potential confounders, residual confounding effects could not be ruled out. It is possible that our results remain confounded by other potentially important factors, such as indoor exposures (pets, mold, and dust).

CONCLUSIONS

This is the first epidemiological study to examine the independent and joint effects of ETS at home and *in utero* exposure to maternal smoking on allergic disorders among young Japanese children. We found that postnatal ETS exposure at home only, but not *in utero* exposure only or both *in utero* exposure and postnatal ETS exposure at home, was independently associated with an increased prevalence of wheeze. Further studies, particularly prospective studies, are needed to clarify the roles of *in utero* exposure and postnatal ETS exposure on allergic disorders.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

- Hofhuis W, de Jongste JC, Merkus PJ. Adverse health effects of prenatal and postnatal tobacco smoke exposure on children. *Arch Dis Child* 2003; 88:1086–1090.
- Cheraghi M, Salvi S. Environmental tobacco smoke (ETS) and respiratory health in children. *Eur J Pediatr* 2009; 168:897–905.
- Moya J, Bearer CF, Etzel RA. Children's behavior and physiology and how it affects exposure to environmental contaminants. *Pediatrics* 2004; 113:996–1006.
- Zuraimi MS, Tham KW, Chew FT, Ooi PL, David K. Home exposures to environmental tobacco smoke and allergic symptoms among young children in Singapore. *Int Arch Allergy Immunol* 2008; 146:57–65.
- Foliaki S, Annesi-Maesano I, Tuuau-Potoi N, Waqatakiwera L, Cheng S, Douwes J, Pearce N. Risk factors for symptoms of childhood asthma, allergic rhinoconjunctivitis and eczema in the Pacific: an ISAAC Phase III study. *Int J Tuberc Lung Dis* 2008; 12:799–806.
- Dong GH, Cao Y, Ding HL, Ma YN, Jin J, Zhao YD, He QC. Effects of environmental tobacco smoke on respiratory health of boys and girls from kindergarten: results from 15 districts of northern China. *Indoor Air* 2007; 17:475–483.
- Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. *Chest* 2005; 127:502–508.
- Behrens T, Maziak W, Weiland SK, Rzehak P, Siebert E, Keil U. Symptoms of asthma and the home environment. The ISAAC I and III cross-sectional surveys in Münster, Germany. *Int Arch Allergy Immunol* 2005; 137:53–61.
- Krämer U, Lemmen CH, Behrendt H, Link E, Schäfer T, Gostomzyk J, Scherer G, Ring J. The effect of environmental tobacco smoke on eczema and allergic sensitization in children. *Br J Dermatol* 2004; 150:111–118.
- Tanaka K, Miyake Y, Arakawa M, Sasaki S, Ohya Y. Prevalence of asthma and wheeze in relation to passive smoking in Japanese children. *Ann Epidemiol* 2007; 17:1004–1010.
- Kurosaka F, Nakatani Y, Terada T, Tanaka A, Ikeuchi H, Hayakawa A, Konohana A, Oota K, Nishio H. Current cat ownership may be associated with the lower prevalence of atopic dermatitis, allergic rhinitis, and Japanese cedar pollinosis in schoolchildren in Himeji, Japan. *Pediatr Allergy Immunol* 2006; 17:22–28.
- Miyake Y, Yura A, Iki M. Cross-sectional study of allergic disorders in relation to familial factors in Japanese adolescents. *Acta Paediatr* 2004; 93:380–385.
- Lee YL, Lin YC, Hsiue TR, Hwang BF, Guo YL. Indoor and outdoor environmental exposures, parental atopy, and physician-diagnosed asthma in Taiwanese schoolchildren. *Pediatrics* 2003; 112:e389–e395.
- Demir AU, Karakaya G, Bozkurt B, Sekerel BE, Kalyoncu AF. Asthma and allergic diseases in schoolchildren: third cross-sectional survey in the same primary school in Ankara, Turkey. *Pediatr Allergy Immunol* 2004; 15:531–538.
- Jaakkola JJ, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. *Am J Public Health* 2004; 94:136–140.
- Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2001; 163:429–436.
- Li YF, Langholz B, Salam MT, Gilliland FD. Maternal and grandmaternal smoking patterns are associated with early childhood asthma. *Chest* 2005; 127:1232–1241.

18. Lannerö E, Wickman M, Pershagen G, Nordvall L. Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE). *Respir Res* 2006; 7:3.
19. Murray CS, Woodcock A, Smillie FI, Cain G, Kissen P, Custovic A, NACMAAS Study Group. Tobacco smoke exposure, wheeze, and atopy. *Pediatr Pulmonol* 2004; 37:492–498.
20. Lux AL, Henderson AJ, Pocock SJ, ALSPAC Study Team. Wheeze associated with prenatal tobacco smoke exposure: a prospective, longitudinal study. *Arch Dis Child* 2000; 83:307–312.
21. Zlotkowska R, Zejda JE. Fetal and postnatal exposure to tobacco smoke and respiratory health in children. *Eur J Epidemiol* 2005; 20:719–727.
22. Pirastu R, Bellu C, Greco P, Pelosi U, Pistelli R, Accetta G, Biggeri A. Indoor exposure to environmental tobacco smoke and dampness: respiratory symptoms in Sardinian children—DRIAS study. *Environ Res* 2009; 109:59–65.
23. Agabiti N, Mallone S, Forastiere F, Corbo GM, Ferro S, Renzoni E, Sestini P, Rusconi F, Ciccone G, Viegi G, Chellini E, Piffer S. The impact of parental smoking on asthma and wheezing. *Epidemiology* 1999; 10:692–698.
24. Magnusson LL, Olesen AB, Wennborg H, Olsen J. Wheezing, asthma, hayfever, and atopic eczema in childhood following exposure to tobacco smoke in fetal life. *Clin Exp Allergy* 2005; 35:1550–1556.
25. Tanaka K, Miyake Y, Sasaki S, Ohya Y, Hirota Y, Osaka Maternal and Child Health Study Group. Maternal smoking and environmental tobacco smoke exposure and the risk of allergic diseases in Japanese infants: the Osaka Maternal and Child Health Study. *J Asthma* 2008; 45:833–838.
26. Shima M, Nitta Y, Ando M, Adachi M. Effects of air pollution on the prevalence and incidence of asthma in children. *Arch Environ Health* 2002; 57:529–535.
27. Stein RT, Holberg CJ, Sherrill D, Wright AL, Morgan WJ, Taussig L, Martinez FD. Influence of parental smoking on respiratory symptoms during the first decade of life: the Tucson Children's Respiratory Study. *Am J Epidemiol* 1999; 149:1030–1037.
28. Jaakkola JJ, Nafstad P, Magnus P. Environmental tobacco smoke, parental atopy, and childhood asthma. *Environ Health Perspect* 2001; 109:579–582.
29. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics* 2004; 113(Suppl. 4):1007–1015.
30. Statistics Bureau, Ministry of Public Management, Home Affairs, Posts and Telecommunications, Japan. 2000 Population Census of Japan. Vol. 3-2-40: Labour Force Status of Population, Industry (Major Group) of Employed Persons, and Education. Fukuoka-ken, Tokyo: Statistics Bureau, Ministry of Public Management, Home Affairs, Posts and Telecommunications, Japan, 2002.
31. Snijders BE, Thijs C, Kummeling I, Penders J, van den Brandt PA. Breastfeeding and infant eczema in the first year of life in the KOALA birth cohort study: a risk period-specific analysis. *Pediatrics* 2007; 119:e137–e141.
32. Wijga AH, Smit HA, Kerkhof M, de Jongste JC, Gerritsen J, Neijens HJ, Boshuizen HC, Brunekreef B. Association of consumption of products containing milk fat with reduced asthma risk in pre-school children: the PIAMA birth cohort study. *Thorax* 2003; 58:567–572.