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Indoor total volatile organic compounds exposure at 6 months and atopic dermatitis prevalence at 3 years in children

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Running title: Indoor TVOC exposure and atopic dermatitis

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Indoor TVOC exposure and atopic dermatitis

Abstract

BACKGROUND

Exposure to indoor air pollutants is thought to cause allergic inflammation. Volatile organic compounds (VOCs) are one of the aggravating factors of asthma and other allergic diseases. However, the influence of VOCs on development of atopic dermatitis is ambiguous in the clinical field. We therefore

investigated the associations of indoor total volatile organic compounds (TVOCs) and development of atopic dermatitis in young Korean children.

METHODS:

From the birth cohort of a MOthers and Children's Environmental Health (MOCEH) study, 257 infants whose parents agreed with the environmental measurement, were enrolled. Total VOCs were measured in infant's bedrooms at the age of 6 month. 105 parents answered a questionnaire at 36 month. Concentrations of TVOCs were divided into 2 groups by third quartile (75th). Associations between the high VOCs exposure group and development of atopic dermatitis at the age of 36 months were estimated by multivariate logistic regression.

RESULTS:

The average concentration of TVOCs was $174.7 \pm 115.1 \mu\text{g}/\text{m}^3$. We defined the high TVOCs exposure group by those with more than 75 percentile of the distribution ($242.1 \mu\text{g}/\text{m}^3$). An increased risk of atopic dermatitis was observed in the high TVOCs exposure group, after adjustment for parents history of allergy, household income, breastfeeding longer than 6 month (OR = 3.116, 95% CI 1.041-9.323). Risk of atopic dermatitis was increased when the family bought new furniture within 1 year.

CONCLUSION:

Our results showed that exposure to high concentration of VOCs during infancy, an indoor pollutant, increased the risk of atopic dermatitis at 36 months.

Key words: atopic dermatitis, child, volatile organic compounds

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Introduction

Children are more affected by allergic disease than adults (1). Little is known about the influence of the environment on the occurrence of allergic disease from the first years of life to early childhood. The prevalence of childhood atopic dermatitis in developed countries is 10–20%, and it has been known that the prevalence of atopic diseases has increased in the last 30 years (2,3) But, a studies of Japan reported that the prevalence of atopic dermatitis was not increased (4).

In Korea, the prevalence of atopic dermatitis doctor diagnosis ever in elementary school students was increased as 16.6% (1995), 24.9% (2000), 28.9%(2006) and 35.6 % in 2010 (5)(6). Many investigators have attempted to identify the cause of of atopic dermatitis, but the reason still remains unclear. The

well known risk factors of atopic dermatitis are smoking, family history of allergy and breast feeding periods. Other factors such as keeping pet, existing fungus, exposure to indoor pollutant is still controversy and moreover there are only few studies on chemical indoor pollutant, and exposure assessment with measurements is scarce. Babies spend 80-90% of the day indoors during their first year of life hence the health impact of indoor air pollutant exposure is thought to be important (7). Though exposure to indoor air pollutants possibly contributes to the development of allergic inflammation, (8) (9) (10) up to now, few epidemiological studies determined the relationship between the potentially adverse health effects like allergic disease and indoor TVOCs (11) (12).

TVOCs seems to be associated with the atopic dermatitis in early childhood. TVOCs are produced by evaporation at room temperature from paints, wood, fabrics, cleaning agents, air fresheners, cosmetics, furnishings, and floor/wall coverings (13) (14). They are composed by several materials as toluene, benzene, and formaldehyde. Exposure to TVOCs during pregnancy increased the risk of childhood asthma and atopic disease (7) (15) (16). Chemical irritants including TVOCs also clearly affected immune function (17) (18) but their roles are relatively understudied compared with other environmental factors, such as aeroallergens. Very limited data are available concerning TVOCs effects on human skin and dermatitis, although the dermal route is important for resorption and significantly contributes to the whole body burden (19).

Research is required to determine how early contact of the infant with increased VOCs levels in the dwellings, contribute to the development of atopic dermatitis in later in childhood. We investigated

whether the indoor TVOCs chemical burden of infant with 6 month resulted in the prevalence of atopic dermatitis after 36 months of life.

Methods

1. Population and study design

A hospital and community based birth cohort named MOthers and Children's Environmental Health (MOCEH) in which a total of 1,751 pregnant women were enrolled was initiated from May 2006 to December 2012, in 3 regions (Seoul, Cheonan, and Ulsan), Republic of Korea. Environmental assessment in the baby's bedroom at 6 months was conducted for 257 infants from the MOCEH cohort study, whose parents agreed with the environmental measurement (chemical pollutants). Approval for this study was obtained from the Institutional Review Board of Ewha Mokdong hospital, Dankook University hospital and Ulsan university hospital.

Separately from the 383 mother who were conducted measurement of indoor pollutant, we conducted the measurement of indoor pollutant from 257 babies at 6 months. In those 257, the number of subjects available data of TVOCs were 192 and 87 subjects were not available because they did not answer the questionnaire at 36 months.

The characteristics studied included the baseline, gender, anthropometric parameters of the child, family history of allergic diseases (asthma, eczema, and rhinitis), previous obstetric history (parity, gravidity), socio-economic status (education and family income), children's health outcomes, medical history, environment and lifestyle characteristics and family living conditions. These data were based on parent self-administered questionnaires completed when infants were 6, 12, 24, and 36 months old. During the study, some participants withdrew and gave no answers to atopic dermatitis; therefore, at 36 months, 105 of the initially recruited 192 children's questionnaires had parental responses to atopic dermatitis of infants at 3 years of age and to questions about general information about the dwellings.

2. Measurement of TVOCs

The environmental technician visited the home and made direct measurements. They sampled air pollutants including TVOCs, by using a passive sampler (3M 3500 OVM Badge), placed in the infant's bedrooms to assess personal exposure at 6 month. Air samples collected for 24 hours were analyzed by gas chromatography/mass spectrometry (GC/MS) for TVOCs. We pick the detected VOCs from n-hexane to n-hexadecane by gas chromatography/mass spectrometry and then quantify them by converting a mass unit of toluene. The composition of TVOCs were pentane, o-xylene, m-xylene, p-xylene, toluene, MEK(methyl ethyl ketone), n-hexane. And the highest apportionment was Methyl ethyl Ketone and the next one was toluene.

3. Health outcomes

A trained staff used a questionnaire to investigate the participants' characteristics. Most questions were derived from previously validated questionnaires, Korean version of the International Study on Allergies and Asthma in Childhood (ISAAC) protocol that included a standardized questionnaire according to an enriched version of the ISAAC standardized protocol (20). We choose the definition of atopic dermatitis as the questionnaire "Was your child ever diagnosed with atopic dermatitis by a doctor?" as the health outcome of interest was the dermatitis symptoms.

4. Blood samples for atopic biomarkers

Measurement of eosinophil count and total immunoglobulin (Ig) E and interleukin (IL)-10 was performed to investigate the helper T cell 2 (Th2) immune responses. Venous blood samples were drawn from the child at age 36 months and stored at -70 °C until analysis. Blood total IgE levels were measured by commercially available paper radioimmunosorbent test kits (Pharmacia Diagnostics, Uppsala, Sweden); the limit of detection for total IgE was 0.5 pg/ml. Blood eosinophils were counted with an automatic blood cell counter (XE-2100, Sysmex, Tokyo, Japan). IL-10 was measured by a quantitative sandwich enzyme immunoassay technique (Quantikine, Human IL-10 Immunoassay, R&D System, Minneapolis, MN); the LOD for IL- 10 was 1 pg/ml.

5. Statistical analysis

Continuous value (cut off at 75th) of TVOC exposure at the third quartile (75th percentile), were categorized as 2 groups *i.e.* low and high exposure groups. The association between the prevalence of atopic dermatitis and VOC exposure level was analyzed by logistic regression analysis for estimating ORs and their 95% CIs with Hosmer-Lemshow stastic.

Allergy history of parents, location of residence (center), family income, mother's education and parity, gestational age, and birth weight were investigated by the chi square test, t-test. If the variables were non parmetric we analysed using non parametric test as Fisher's exact test and Mann-Whiteny test.

We used the widely known confounding factors such as allergy history of parent, family income and breastfed longer than 6 months. Bought a new furniture within 1 year and other environmental materials were investigated by the multivariate logistics regression analysis with the same confounding factors.

The biomarkers for allergic disease as continuous variables were transformed to log to obtain the normal distribution. The 2 groups were compared by the t-test. All statistical analyses were performed by SPSS version 18.0 (SPSS, Chicago, IL, USA).

RESULT

1. Study populations and characteristics and indoor environmental materials

The average concentration of TVOCs was $174.7 \pm 115.1 \mu\text{g}/\text{m}^3$. We determined that the high TVOCs exposure group was more than 75 percentile ($242.1 \mu\text{g}/\text{m}^3$).

Characteristics of subjects in the analysis did not differ from the total cohort those not included in the analysis (n=1494, *i.e.* infants without data for TVOC exposure and/ or atopic dermatitis occurrence) with regard to gender, siblings, parental history of allergy and location. Of the subjects who were not included, 36.0 % of children were born as a first baby in their family, and infants who had parental history of allergy were 39.4%.

Table 1 showed the comparing main characteristics of the 105 infants with all information available and the 152 infants included in the study and lost to follow up. The loss of one center(rural area, Cheonan) was significantly high (45.3%). The system and human resources of Cheonan center following up the infant and mother were weaker than other centers. The TVOCs of loss subjects were significantly low and that's because of the lower level of TVOCs in Cheonan center (Appendix 1.) The children lost follow up had less breast feeding period and were more in the case of 1st baby.

There was marginal significant smoking at home ($p=0.075$) and the number children with High TVOC were lower in the the rural area($p=0.038$) (Table 2)

Characteristics between subjects having atopic dermatitis ever *vs.* not having atopic dermatitis ever, was shown table 3.(In the case of buying new furniture with 1yr, children with atopic dermatitis ever at 36 months were significantly high ($p=0.08$) and boys were more in case of atopic dermatitis ($p=0.039$)

Adjusted odds ratio for atopic dermatitis increased to 3.489 (95 % CI, 1.300-9.365) with recently bought new furniture after controlling covariates, such as parents history of allergy, family incomes, and breastfeeding longer than 6 month.

2. Atopic dermatitis and TVOC exposure

There was a significant association between the high TVOC exposure group and atopic dermatitis at 36 months, but no significant associations at 12 and 24 months. We used the confounding factors for), allergy history of parents, household income and breastfed longer than 6 months. Adjusting for these confounding factors, the high TVOC group had about 3 times significantly higher prevalence of AD than the low TVOC group (OR 3.116, 1.041-9.323) (Table4).

3. Serum biomarkers for Th2 immune responses and allergic disease

We found no significant differences in log transformed total IgE, eosinophil counts and IL-10, between the high TVOC groups and low TVOC groups (Table 5.). Additionally, there were significant differences in biomarkers between participant patients with atopic dermatitis and without atopic dermatitis.

Discussion

We found in our cohort study, that children who were exposed to high level of TVOCs at 6 months of life had a significantly higher prevalence rate of atopic dermatitis after about 3 years, as compared with children exposed to low level of TVOCs.

An ISSAC study of elementary school students in Korea, showed that the prevalence of atopic dermatitis ever diagnosed by a doctor were 35.6 % in 2010 (6). The rate of atopic dermatitis in preschool children was 35.9% (20).The prevalence of atopic dermatitis in our study was 29.0% in the total cohort of

children; and in this TVOCs study, the prevalence rate were 30.3% with no differences in prevalence among the 3 regions.

The Korean Ministry of Environment recommended values of "Indoor air quality control in public use facilities", is 500 $\mu\text{g}/\text{m}^3$ for TVOCs. A particularly stringent recommendation of 400 $\mu\text{g}/\text{m}^3$ was applied for TVOCs in medical facilities, including maternity facilities. Currently, there is no specific standard for the permissible exposure level to TVOCs; the Environmental Protection Agency of United State suggests that Permissible Exposure Level of 750 $\mu\text{g}/\text{m}^3$, and an action level of 500 $\mu\text{g}/\text{m}^3$ from the Occupational Safety and Health Administration (OSHA). In our results, the mean TVOCs level ($348.3 \pm 87.5 \mu\text{g}/\text{m}^3$) of high TVOCs group. The TVOCs level were lower than national recommendations of indoor TVOCs exposure concentrations, however the higher quartile groups had a significantly higher risk for atopic dermatitis.

The Leipzig's Allergy Risk Study (LARS) investigated the influence of typical indoor-contaminant burdens on the development of allergy and atopic symptoms associated with excretion of certain VOCs metabolites over a 5-yr period. The authors found an association between eczema and exposure to toluene, and between eczema and increased excretion of the toluene metabolite (21). This study reached similar conclusions to our study. Cumulative prevalence rates of atopic dermatitis correlated with estimated benzene, in accordance with another study (22).

The rationale for studying irritant chemical exposure in atopic disease pathogenesis is that exposure to chemicals, and to irritant chemicals, during critical windows of maternal pregnancy/early life also contribute to the prevalence of atopic disease (23). The exposure of TVOCs in early infancy lead to increasing risk of atopic dermatitis later. We carried out the analysis atopic dermatitis at 12 and 24 months by using chi-square test and binary logistic regression test, but significant associations were not observed. We supposed the main reason is that atopic dermatitis is a chronic inflammation and it takes time from occurrence to diagnosis.

A previous population-based cohort study showed that indoor VOCs exposure induced T cell polarization toward the type 2 phenotype (10). Generally, serum eosinophils and total IgE are increased in atopic dermatitis patients (24) (25). Wieslander et al (26) reported that blood eosinophil counts were significantly higher among subjects living in newly painted dwellings. Interleukin (IL)-10 is an important immunoregulatory cytokine produced by many cell populations (27) and IL-10-producing B cells were shown to suppress allergic airway inflammation in mice through induction of pulmonary regulatory T cells (28)

Despite the expectations of increased serum biomarkers for Th2 immune responses and allergic disease in our participants, we could not find differences between the high and low TVOCs exposure groups in the serum markers for allergic inflammation, including eosinophil counts, total IgE and IL-10. Other indicator cells, cytokines, or signal pathway of Th2 inflammation in children, require investigation in a follow up study to determine the pathophysiology of pediatric atopic dermatitis.

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We found that buying new furniture within 1yr at 6 months of age had risk to the prevalence atopic dermatitis at 36 month. A study observed higher atopic dermatitis in the presence of new furniture, as previously documented by Clarisse et al. (29) who showed that newer materials had higher formaldehyde levels. More research is needed on specific relationships of indoor chemicals such as formaldehyde emitted by new furniture, and atopic dermatitis.

The strength of this study was its prospective cohort design and there is some research on the exposure to TVOCs and respiratory symptoms, but rarely with atopic dermatitis or skin inflammations. Our prospective studies in cohort populations targeted atopic dermatitis as a chronic inflammatory.

Several limitations of our study are required to be discussed. One of them was related to the power of our study, as subject numbers for sub analyses were low. It may have been insufficient to elicit some relationships or confirm some results that were close to the significant level. Higher air humidity and higher temperature also correlated with higher levels of these volatile organic chemicals (23), we however could not control for these factors in our study. The health data were self-reported which could have been a limiting factor in the present study. Nevertheless, the observed prevalence of atopic dermatitis was consistent with other literature.

In conclusion, the current study showed different environmental triggers for the occurrence of atopic dermatitis depending on levels of TVOCs. Further larger studies and experimental studies are needed to reveal the mechanisms of atopic dermatitis. No subjects in our study exceeded the permissible level of TVOCs according to the national indoor air quality guideline. Therefore, it is generally advisable to

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minimize exposure to indoor TVOCs during infancy, and exposure to TVOCs should be minimized during early childhood to prevent allergies and atopic dermatitis.

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Table 1. Comparison of 105 infants with all information available and 87 infants lost to follow-up

	Included (N=105)	infants Follow-up infants (N=87)	loss p- value
Mean concentration of TVOCs ($\mu\text{g}/\text{m}^3$)	194.17(169.9-218.4)	148.87 (124.5-173.2)	0.003*
Male : female	54:50	42:43	0.731
Allergy history of parents	41/87 (47.1%)	26/61 (42.6%)	0.588
Gestational age(wk)	38.8 $\pm$ 1.8	38.5 $\pm$ 2.1	0.334
Birth weight(g)	3.26 $\pm$ 0.5	3.16 $\pm$ 0.5	0.177
Birth order			
1 st	38/105 (36.2%)	43/76 (56.6%)	0.018*
2 nd	42/105 (40.0%)	25/76 (32.9%)	
3 rd to over	25/105 (23.8%)	8/76 (10.5%)	
Breastfed > 6 month	82/105 (78.1%)	28/57 (49.1%)	0.000*
Location			
Urban area(Seoul)	41 (39.0%)	24 (27.5%)	
Rural area (Cheonan)	23 (21.9%)	40 (45.9%)	0.002 *
Industrial area(Ulsan)	41 (39.0%)	23 (26.3%)	
Family income (1,USD, per month)			
<2000	16 (18.1%)	15 (24.6%)	0.476
20000-4000	59 (67.0%)	35 (57.4%)	
$\geq$ 4000	13 (14.7%)	11 (18.0%)	
Smoking at home	34/87 (39.1%)	31/60(51.7%)	0.176

TVOCs, total volatile organic compounds; MOCEH, mother and children environmental health
 High and low VOCs divided by upper 75 percentile value of the VOCs distribution of the study subjects
 (242.1 $\mu\text{g}/\text{m}^3$)

*p=0.05

Table 2. Characteristics of 105 infants and indoor environmental factors by level of TVOCs

	Low TVOCs (<75 th) group (N=71)	High TVOCs (≥75 th) group (N=34)	p- value
Mean concentration of TVOCs (μg/m ³)	123.5 ± 58.3	348.3 ± 87.5	
Male : female	35:36	19:15	0.528
Allergy history of parents	28 (38.9%)	13 (39.4%)	0.130
Gestational age(wk)	38.76±1.69	38.93±2.13	0.968
Birth weight(g)	3256.27±445.9	3272.73±515.7	0.623
Birth order			
1 st	29 (40.3%)	9 (27.3%)	0.381
2 nd	28 (38.9%)	14 (42.4%)	
3 rd to over	15 (20.8%)	10 (30.3%)	
Breastfed > 6 month	55 (76.4%)	27 (81.8%)	0.618
Location			
Urban area(Seoul)	23 (31.9%)	18 (54.5%)	
Rural area (Cheonan)	20 (27.8%)	3 (9.1%)	0.038*
Industrial area(Ulsan)	29 (40.3%)	12 (36.4%)	
Family income			
(1,USD, per month)			
<2000	12 (18.8%)	4 (16.7%)	0.89
20000-4000	42 (65.6%)	17 (70.8%)	
≥4000	10 (15.6%)	3 (3%)	

Mother's education

(≥High school)	71 (98.6%)	33 (100%)	1.00
Smoking at home	21 (33.3%)	13 (54.2%)	0.075
Use of humidifier (yes)	17 (26.6%)	4 (19.0%)	0.409
Use of air freshener (yes)	4 (6.2%)	4 (16.7%)	0.206
Use of mosquito repellent incense (yes)	27 (42.2%)	8 (33.3%)	0.476
Use of polish	8 (12.5%)	4 (16.7%)	0.729
Use of hair sprayer (yes)	19 (29.7%)	11 (45.8%)	0.207
Use of perfume (yes)	1 (1.6%)	1 (4.2%)	0.473
Buying new furniture within 1 yr (yes)	22 (34.9%)	8 (33.3%)	1.000
Papering walls recently (yes)	14 (21.9%)	5 (20.8%)	0.916
Moving in/out within 1yr (yes)	7 (11.1%)	1 (4.2%)	0.436

TVOCs, total volatile organic compounds; MOCEH, mother and children environmental health

High and low VOCs divided by upper 75 percentile value of the VOCs distribution of the study subjects (242.1 $\mu\text{g}/\text{m}^3$)

Fisher's exact test for non-parametric statistics,

*p=0.05

Table 3. Characteristics of 105 infants and indoor environmental factors by atopic dermatitis ever diagnosis

	Atopic dermatitis (+)	Atopic dermatitis (-)	P value
TVOC mean concentration ($\mu\text{g}/\text{m}^3$)	211.7 $\pm$ 125.9	189.8 $\pm$ 128.9	0.437
Male: female	24:12	30:38	0.039*
Allergy history of parents	12/36	38/68	1.000
Gestational age(wk)	39.1 $\pm$ 1.3	38.6 $\pm$ 2	0.239
Birth weight(g)	3.3 $\pm$ 0.46	3.23 $\pm$ 0.46	0.482
Breast feeding>6m	31/36	51/69	0.214
Location			
Urban area(Seoul)	16	25	0.648
Rural area (Cheoan)	8	15	
Industrial area(Ulsan)	12	29	
Family income (1,USD, per month)			
<2000	5	11	0.964
20000-4000	20	39	
$\geq$ 4000	4	9	
Smoking at home	14/29(48.3%)	20/58(34.5%)	0.249
Use of humidifier (yes)	8/29(27.6%)	13/59 (22.0%)	0.601
Use of air freshener (yes)	1/29(3.4%)	7/59 (11.9%)	0.263
Use of mosquito repellent incense (yes)	12/29(41.4%)	23/59(39.0%)	1.000
Use of insecticide (yes)	3/29 (10.3%)	9/59 (15.3%)	0.744
Use of polish (yes)	0/29 (0.0%)	1/59 (1.7%)	1.000
Use of hair sprayer (yes)	8/29 (0.0%)	22/59 (1.7%)	0.475
Use of perfume (yes)	1/29(3.4%)	1/59 (1.7%)	1.000
Buying new furniture within 1yr (yes)	16/29 (55.2%)	14/58 (24.1%)	0.008*
Papering walls recently (yes)	7/29 (24.1%)	12/59(20.3%)	0.784
Moving in/out within 1yr (yes)	1/29 (3.4%)	7/58 (12.1%)	0.260
Pet	2/29	2/59	0.596
Fungus	7/29(24.1%)	14/59(23.7%)	1.000

TVOCs, total volatile organic compounds

Fisher's exact test for non-parametric statistics

*p=0.05

Table 4. Associations between the level of total VOC exposure and atopic dermatitis

VOCs exposure		No. of Total subjects	No. of Atopic dermatitis	Unadjusted Analysis Odd Ratio (95% CI)	Adjusted Analysis Odd Ratio (95% CI) *
Low ($<75^{\text{th}}$)	TVOCs group	71	20 (27.8 %)	1.0	1.0
High ($\geq 75^{\text{th}}$)	TVOCs group	34	16 (48.5%)	2.447 (1.010-5.757)	3.116(1.041-9.323)

These odds ratios and 95% CIs adjusted for allergy history of parents, household income and breastfed longer than 6month

VOCs, volatile organic compounds

High and low VOCs divided by upper 75% of the VOCs distribution of the study subjects ($242.1 \mu\text{g}/\text{m}^3$)

Table 5. Biomarkers of allergic disease by the level of total VOC exposure

N=93	Low TVOC	High TVOC	P-value
Total IgE (pg/mL)	86.26 $\pm$ 129.65	184.17 $\pm$ 461.11	0.142
IL-10 (pg/mL)	2.17 $\pm$ 1.918	2.41 $\pm$ 2.999	0.709
Eosinophil count(/ μl)	248.84 $\pm$ 210.829	216.40 $\pm$ 97.753	0.313

* p < 0.05.

TVOCs, total volatile organic compounds; IgE, immunoglobline E; IL-10, interleukin-10

Appendix 1. The levels of TVOCs and atopic dermatitis prevalence according to the centers

	Seoul	Cheonan	Ulsan	P value
TVOCs($\mu\text{g}/\text{m}^2$)	217 $\pm$ 144.2 ^a	120.0 $\pm$ 76.7 ^a	185.8 $\pm$ 116.2	< 0.01
Atopic dermatitis	16 (39.0 %)	12 (29.3 %)	8 (34.8 %)	0.648
Using ANOVA, ^a Turkey HSD p=0.03				

Appendix 2. Multiple Logistic Regression Results for predicting atopic dermatitis at 36 month

	β Coefficient	S.E.	P-value	Exp(β)	95% CI
Log TVOCs	0.875	0.430	0.042	2.399	1.033-5.574
Allergy history of parents	0.182	0.579	0.754	1.199	0.385-3.731
Breast feeding>6m	1.113	0.766	0.147	3.043	0.678-13.668
Family income	-1.081	0.772	0.161	0.339	0.075-1.541