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Asthma and allergy in children with and without prior measles mumps, and rubella vaccination

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Abstract

Background: The aim of this study was to determine whether measles, mumps and rubella (MMR) vaccination administered in early childhood was associated with asthma and allergic diseases at ages 5, 7 and 13 years in a birth cohort as the existing literature on the association between measles vaccination and allergic disease is inconclusive.

Methods: In the Faroe Islands, 640 children were followed from birth. Follow-up examinations were performed at ages 5, 7 and 13 years. They included physical examinations and maternal questionnaires about the child's health. At age 7 total and grass-specific IgE was quantified in serum, and at age 13 the children underwent skin prick tests (SPT). At the examinations the child's vaccination card was reviewed.

Results: At age 5, 533 of 555 children had been vaccinated for MMR. After confounder adjustment we found early life MMR vaccination to be associated with a two-third reduction in the odds of asthma (OR: 0.33, 95% CI: 0.12; 0.90) and hypersensitivity/allergy (OR: 0.32, 95% CI: 0.11; 0.88) at age 5, and the substantially decreased odds of asthma were replicated at age 13 (OR: 0.22, 95% CI: 0.08; 0.56). At age 7 serum total IgE was reduced by 62.8% (CI 95%: −84.3%; −11.9%) in the vaccinated children. MMR vaccination was not significantly associated with allergic rhinoconjuctivitis symptoms, eczema, or SPT reactions at age 13.

Conclusions: MMR vaccination early in life may have a protective effect against allergy at least up to age 7 and against asthma through age 13 years.

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Keywords

Allergy; Asthma; Children; Measles-Mumps-Rubella Vaccination

Introduction

Since the finding of an association between history of measles infection and a reduced risk of skin test-positivity to house dust mite among adolescents and young adults in Guinea-Bissau (1), debate has emerged whether introduction of measles vaccinations and the subsequent reduction of measles infections has played a role in the rise in asthma and allergic diseases in the developed world. Both positive (2–4) and negative (5, 6) associations have been found between measles infection and asthma and/or allergic diseases. The existing literature on the association between measles vaccination and allergic disease is likewise inconclusive. Some studies have found measles vaccination to be associated with reduced risk of asthma and/or allergic diseases (5, 7), whereas other studies found either a positive or no association (3, 4, 8–10).

Therefore, the aim of this study was to further explore this potential association by utilizing data from a prospective cohort of Faroese children that contained information of children's measles, mumps and rubella (MMR) vaccination history as well as information on asthma and allergic diseases at ages 5, 7 and 13 years.

Methods

In the Faroe Islands, a birth cohort was formed from consecutive spontaneous births during years 1997–2000. Informed consent was obtained from 640 mothers of singleton children. A cord blood sample was obtained and total IgE concentrations were quantified by ImmuniCAP (Phadia, Uppsala, Sweden). Total IgA concentrations were quantified by an in-house ELISA using a rabbit anti-IgA capture antibody and a peroxidase-conjugated rabbit anti-IgA detection antibody followed by detection using *o*-phenylenediamine substrate (all reagents from DakoCytomation, Glostrup, Denmark). Samples with IgA concentrations higher than 50 μg/ml were likely contaminated with maternal blood (11) and IgE measurements from these samples were therefore not used. Obstetric variables, including duration of gestation, birth weight, and parity were obtained as well as information about maternal smoking during pregnancy (12).

Follow-up examinations were performed at ages 5, 7 and 13 years along with a physical examination and a maternal questionnaire followed by an interview on the child's current and past medical history. In addition to the main outcomes of interest in this study, the interview at age 5 covered questions on number of siblings, duration of breastfeeding, parental smoking in the home, use of day care and childhood infections. At age 13 it covered questions on genetic disposition to asthma and allergic disease.

Vaccines

The Faroe Islands follow the Danish vaccination schedule, in which MMR vaccination at the time of this study was administered at age 15 months and 12 years. At the 5-year

examination, the child's vaccination card was inspected and all vaccination dates were registered. At age 13, the questionnaire on the child's medical history included a question on whether the child had received the MMR vaccination scheduled at 12 years of age.

Asthma and allergic diseases

At age 5, parents were asked whether the child had been diagnosed with or was suspected to suffer from asthma, or if the child had been diagnosed with hypersensitivity or allergy. At ages 5, 7 and 13 years, a single pediatrician (US) determined presence of current wheezing by auscultation. If the pediatrician had noted that the child had a cold, we assumed that the wheeze was not an asthma symptom. The same pediatrician also examined all children at ages 5, 7 and 13 for dermatitis/eczema, and at age 13 the findings from this examination were graded according to a score for atopic dermatitis (SCORAD) (13). Since clinical examinations provide only a cross-sectional evaluation, asthma or eczema could be missed due to their variable clinical presentation or reduced severity from successful treatment. Therefore, a diagnosis of asthma or eczema could not be made on basis of auscultation or clinical examinations alone. At age 7 a blood sample was drawn and total IgE and grass-specific IgE were quantified (12). Grass IgE concentrations exceeding 0.35 kUA/L were considered to indicate sensitization. At age 13 parents were asked whether the child had ever suffered from asthma. In accordance with the International Study of Asthma and Allergies in Childhood (ISAAC), they were asked to indicate whether the child had (1) suffered from wheezing in the past 12 months; (2) suffered from sneezing, running or blocked-up nose except for when the child had a cold or were sick in the past 12 months and if so whether it had been accompained by itching running/tearing eyes (current rhinoconjunctivitis symptoms), and (3) whether the child had ever suffered from an itching rash that comes and goes for at least 6 months (eczema ever) (14, 15).

At age 13 the children also participated in a structured interview using the ISAAC video (16). The video contained five scenes of young people with breathing problems. The children were asked to indicate if they had ever experienced breathing problems as shown in the video and, if so, if it had been experienced in the last year (17). In accordance with previous studies we reported answers to the first video sequence (wheeze at rest in the past 12 months) (14). Finally, at age 13 the children underwent a skin prick test (SPT) with extracts (Soluprick, ALK, Hørsholm, Denmark) of five common allergens (birch/grass pollen, dog/cat dander, and house dust mite (*D. pteronyssinus*)). Any SPT with a wheel size larger than or equal to three millimeters was considered positive.

Statistical methods

Children who attended the 5-year examination but were missing information about all childhood vaccinations were excluded from the study if the subject record stated that the parents did not bring the vaccination card at the 5-year examination. If the children had no childhood vaccinations registered and no notes were made in the record, children were kept in the analyses and were assumed to not have received any vaccines. Children who had had measles, or for whom no information was provided about this disease, were excluded from the analyses. Because measles infection may have an effect on asthma and allergic diseases that is similar to that of the vaccination, excluding these children avoids any association

being obscured by previously-infected children being in either the vaccinated or the unvaccinated groups. Those that did and did not participate in the follow-up examinations were compared with respect to all information obtained and used in this study.

Chi square or Wilcoxon rank-sum tests were performed to determine the marginal association between MMR vaccination and asthma and allergic disease measures at ages 5, 7 and 13 years.

Variables known to be associated with development of asthma, and/or allergic diseases (sex (18, 19), maternal smoking during pregnancy (18), premature birth (18), birth weight (20), cord blood IgE (21), breastfeeding (22), number of siblings (19), parental smoking in the home (18, 19), day care attendance (19), and genetic disposition (18, 19)) were evaluated for their association with MMR vaccination. In addition, associations between MMR vaccination before age 5 and both age at the examination and MMR vaccination at age 12 were also evaluated. Associations were tested using Chi square or Wilcoxon rank-sum tests.

Logistic regression models were performed to determine the association between early childhood MMR vaccination and asthma and allergic disease. To avoid weak models due to a low number of cases, we did not use asthma and allergic disease measures with prevalence below 10%. Linear regression models were performed to determine association between early childhood MMR vaccination and total serum IgE at age 7. To obtain variance homogeneity and normally distributed residuals, serum IgE concentration was log-transformed and estimates of association were subsequently converted to express the percent change in IgE. Variables found to be significantly associated with MMR vaccination ($p<0.05$) were included in all regression models. Models including all potential confounders were also performed. At age 13 years, analyses were also performed in which models included “Asthma” or “Hypersensitivity/allergy” as indicated in the questionnaire at age 5. Finally, sensitivity analyses were performed by excluding children lacking information about all childhood vaccinations at age 5, since we could not rule out the possibility that missing information was due to not having seen the vaccination card rather than vaccines not being given. Data was analysed in Stata (version 13).

Ethics

The Faroese cohort study was performed in accordance with the Helsinki Declaration and approved by the ethical review committee serving the Faroe Islands and the institutional review board at the Unites States institution.

Results

At age 5, a total of 580 children (90.6 %) attended the examination. Among these, five were lacking information about all childhood vaccinations and the subject record indicated that they had not brought their vaccination card to the examination. They were therefore excluded from the analyses. Seven children had had measles and 13 children were missing information about whether they had had the disease. These 20 children were also excluded, thus leaving 555 children (86.7 % of the original cohort) eligible for analyses at age 5 years. The 85 children from the original cohort who did not participate or were excluded contained

a greater proportion of boys and of first-born children, although the sex difference between those who did and did not participate was not significant. Among the 555 children eligible for analyses at age 5, 519 (93.5%) also attended the age-7 examination, and 489 (88.1%) also attended the age-13 examination. Children who did not attend the age-7 examination had lower umbilical cord IgE and were breastfed for a shorter period of time. No significant differences were seen between those who did and did not attend the age-13 examination.

At 5 years of age, 533 (96.0 %) of the 555 children had received their first MMR vaccine. Distribution of asthma, wheezing and allergic diseases in relation to MMR vaccination is shown in Table 1. MMR vaccination before age 5 was significantly associated with reduced risk of asthma and hypersensitivity/allergy at age 5, reduced risk of high grass specific IgE at age 7, and reduced risk of having had asthma at age 13. Insignificant tendencies were seen towards reduced risk of wheezing at age 5, reduced total IgE at age 7, and reduced risk of allergic diseases at age 13 among children vaccinated with MMR before age 5. MMR vaccination at age 12 was associated with neither asthma, wheezing nor allergic diseases at age 13. Receiving first MMR vaccination before age 5 was significantly associated with reduced birth weight, receiving second MMR vaccination at age 12, and not having a family history of chronic bronchitis or asthma (Table 2).

After adjusting for birth weight and family history of chronic bronchitis/asthma, MMR vaccination before age 5 was associated with an approximately two-thirds reduction in the odds of having asthma and hypersensitivity/allergy at age 5 (Table 3). At age 7, MMR-vaccinated children had 62.8% lower total serum IgE than non-MMR-vaccinated children (Table 4) and at age 13, odds of asthma were reduced by approximately four-fifths among children that had been MMR-vaccinated before age 5. MMR vaccination was not significantly associated with allergic rhinoconjuctivitis symptoms, eczema, or SPT reactions at age 13, but the odds of these allergic diseases tended to be lower among MMR vaccinated children (Table 3). Adjusting for all potential confounders, performing sensitivity analyses, and at age 13 adjusting for asthma/allergy at age 5 weakened the results but did not substantially change them.

Discussion

Despite the low number of unvaccinated children, the present study found that MMR vaccination in early childhood was significantly associated with reduced IgE levels at age 7, reduced odds of asthma at age 5 and 13 and of hypersensitivity/allergy at age 5 when assessed by questionnaire, though not with allergic diseases at age 13. This finding is in accordance with previous studies finding inverse relationships between measles/mumps vaccination and asthma and allergic diseases at age 5 (7), asthma at age 13–15 (5) but not allergy at age 13–15 (5), although other studies found no such associations (3, 4, 8–10).

The strength of the present study is its prospective design with detailed information about health outcomes and potential confounders being collected at several time points. In addition, selection bias is unlikely due to the high participation rate in this study.

A number of limitations, however, should be considered. Very few children in this study did not receive MMR vaccination (n=22), which reduces the power to detect associations between MMR vaccinations and the asthma and allergic disease outcomes. Consequently we were unable to perform adjusted analyses using outcome measures with low prevalence. Among the low-prevalence outcomes, except for wheezing at the clinical examinations at ages 5 and 13, the unadjusted analyses showed the same tendencies as when using asthma and allergic disease measures with higher prevalence. However, only the inverse association between MMR vaccination and positive grass IgE was significant. To identify children with asthma in the adjusted analyses, we relied solely on the parent's answer to the question whether or not the child had asthma. This question has previously been shown to have a high Youden's index (23) in relation to bronchial hyperreactivity (24) and clinical asthma (25), and we therefore believe that it is a valid measure, despite the fact that we did not find the same results using wheezing as an outcome measure in the unadjusted analyses.

Family history for asthma and allergy or early signs of these diseases in the form of airway infections or eczema could conceivably result in parents being more reluctant to have their children vaccinated. However, taking family history into account did not remove the associations between MMR vaccination and asthma and allergic diseases. Furthermore, the association between MMR vaccination and asthma at age 13 was still significant after adjusting for asthma at age 5, thus suggesting that MMR vaccination given before age 5 was associated with reduced odds of asthma developed later on. It therefore seems that children who received MMR vaccination early in life had lower risks of allergy at age 5, atopy at age 7 and asthma at both age 5 and age 13.

A Th2-biased immune response facilitating the production of IgE and eosinophil modulation contributes to the susceptibility and development of asthma and allergy (26). Viral infections promote a Th1-biased immune response (27) and live viral vaccines, such as those for measles, mumps, and rubella, may promote a similar response. This is supported by the observation of high concentrations of the Th1 signature cytokine IFN-γ and low concentrations of the Th2-signature cytokine IL-4 in children following measles vaccination (28, 29). Additionally, natural measles infection may protect against asthma and allergic diseases (5, 6). Therefore, differences in the prevalence of allergy and asthma between vaccinated and unvaccinated children in the present study may be due to the vaccine's elicitation of a Th1-biased response that was sufficiently similar to that of natural infection that it also provided protection from allergy and asthma.

Conclusion

Our findings support the notion that MMR vaccination may provide beneficial effects in preventing childhood allergy and asthma. Larger prospective studies are needed to further understand the nature and magnitude of such potential effects.

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Table 1:

Distribution of asthma, wheezing, allergic disease and serum IgE concentrations by Measles, Mumps and Rubella (MMR) vaccination

		Received MMR vaccine before age 5 years			Received MMR vaccine at age 12 years		
Variable	**Overall**	**No**	**Yes**	**p** *	**No**	**Yes**	**p** *
Age 5 years							
Asthma (questionnaire), % (n/N)	14.3 (78/546)	36.4 (8/22)	13.4 (70/524)	0.003			
Current wheezing without a cold (physical exam), % (n/N)	5.5 (30/549)	14.3 (3/21)	5.1 (27/528)	0.07			
Hypersensitivity/allergy (questionnaire), % (n/N)	13.6 (74/544)	42.9 (9/21)	12.4 (65/523)	<0.001			
Eczema (physical exam), % (n/N)	8.8 (48/547)	9.5 (2/21)	8.7 (46/526)	0.90			
Age 7 years							
Current wheezing without a cold (physical exam), % (n/N)	7.7 (40/518)	5.6 (1/18)	7.8 (39/500)	0.73			
Eczema (physical exam), % (n/N)	9.5 (49/518)	11.1 (2/18)	9.4 (47/500)	0.81			
Serum total IgE (kUA/L), median (N)	21.9 (425)	30.5 (15)	21.75 (410)	0.10			
Positive serum grass IgE (> 0.35 kUA/L), % (n/N)	8.9 (38/425)	26.7 (4/15)	8.3 (34/410)	0.01			
Age 13 years							
Asthma ever (questionnaire), % (n/N)	17.0 (83/489)	47.4 (9/19)	15.7 (74/470)	<0.001	12.7 (9/71)	17.7 (74/418)	0.30
Wheezing in the past 12 months (questionnaire), % (n/N)	6.8 (33/489)	10.5 (2/19)	6.6 (31/470)	0.50	8.5 (6/71)	6.5 (27/418)	0.54
Wheezing at rest in the past 12 months (ISAAC video questionnaire), % (n/N)	3.5 (17/489)	5.3 (1/19)	3.4 (16/470)	0.67	2.8 (2/71)	3.6 (15/418)	0.74
Current wheezing without a cold (physical exam), % (n/N)	2.0 (10/489)	0.0 (0/19)	2.1 (10/470)	0.52	4.2 (3/71)	1.7 (7/418)	0.16
Allergic rhinoconjunctivitis symptoms in the past 12 months (questionnaire), % (n/N)	12.1 (59/489)	21.1 (4/19)	11.7 (55/470)	0.22	14.1 (10/71)	11.7 (49/418)	0.57
Eczema ever (questionnaire), % (n/N)	20.9 (102/489)	31.6 (6/19)	20.4 (96/470)	0.24	19.7 (14/71)	21.1 (88/418)	0.80
Reaction to any allergen in skin prick test, % (n/N)	38.7 (189/489)	52.6 (10/19)	38.1 (179/470)	0.20	36.6 (26/71)	39.0 (163/418)	0.70
Eczema (physical exam), % (n/N)	7.8 (38/488)	11.1 (2/18)	7.7 (36/470)	0.59	5.7 (4/70)	7.8 (34/418)	0.48

* Binary outcomes were tested using chi square and continuous outcomes (total IgE at age 7) were tested using Wilcoxon rank sum test

Table 2:

Cohort characteristics by MMR vaccination at age 5

Variables		Overall	Received MMR vaccine before age 5: No	Received MMR vaccine before age 5: Yes	p *
Sex, girls, % (n/N)		47.0 (261/555)	31.8 (7/22)	47.7 (254/533)	0.15
Age at 5-year examination, median (N)		4.95 (555)	4.93 (22)	4.95 (533)	0.51
Age at 7-year examination, median (N)		7.53 (518)	7.51 (18)	7.53 (500)	0.45
Age at 13-year examination, median (N)		13.22 (489)	13.28 (19)	13.22 (470)	0.73
Premature birth (duration of gestation <37 weeks), % (n/N)		2.0 (11/555)	0.0 (0/22)	2.1 (11/533)	0.50
Maternal smoking during pregnancy, % (n/N)		164/555 (29.5)	8/22 (36.4)	156/533 (29.3)	0.48
Birth weight (g), median (N)		3750 (555)	4025 (22)	3700 (533)	0.01
IgE concentration in cord blood (kUA/L)[1], median (N)		0.07 (494)	0.11 (20)	0.07 (474)	0.12
Total months of breastfeeding, median (N)		9 (552)	7.75 (22)	9 (530)	0.32
Number of older siblings (at age 5)	0, % (n/N)	24.3 (135/555)	9.1 (2/22)	25.0 (133/533)	0.39
	1, % (n/N)	34.1 (189/555)	40.9 (9/22)	33.8 (180/533)	
	2, % (n/N)	28.1 (156/555)	31.8 (7/22)	28.0 (149/533)	
	>=3, % (n/N)	13.5 (75/555)	(18.2 (4/22)	13.3 (71/533)	
Number of younger siblings (at age 5)	0, % (n/N)	61.4 (340/554)	72.7 (16/22)	60.9 (324/532)	0.40
	1, % (n/N)	33.9 (188/554)	27.3 (6/22)	34.2 (182/532)	
	2, % (n/N)	4.7 (26/554)	0.0 (0/22)	4.9 (26/532)	
Parental smoking in the home at age 5 years, % (n/N)		26.5 (146/552)	36.4 (8/22)	26.0 (138/530)	0.28
Use of day care at age 5 years, % (n/N)		92.4 (507/549)	90.5 (19/21)	92.4 (488/528)	0.74
Received MMR vaccine at around age 12 years, % (n/N)		85.5 (418/489)	68.4 (13/19)	86.2 (405/470)	0.03
Family history of chronic bronchitis or asthma	No, % (n/N)	56.9 (278/489)	26.3 (5/19)	58.1 (273/470)	0.01
	From one parent, % (n/N)	33.3 (163/489)	63.2 (12/19)	32.1 (151/470)	
	From both parents, % (n/N)	4.7 (23/489)	0.0 (0/19)	4.9 (23/470)	
	Do not know, % (n/N)	5.1 (25/489)	10.5 (2/19)	4.9 (23/470)	
Family history of eczema in children, allergic eczema and hay fever	No, % (n/N)	38.0 (186/489)	42.1 (8/19)	37.9 (178/470)	0.85
	From one parent, % (n/N)	44.2 (216/489)	47.4 (9/19)	44.0 (207/470)	
	From both parents, % (n/N)	11.2 (55/489)	5.3 (1/19)	11.5 (54/470)	
	Do not know, % (n/N)	6.5 (32/489)	5.3 (1/19)	6.6 (31/470)	
Family history of allergy	No, % (n/N)	48.0 (234/488)	36.8 (7/19)	48.4 (227/469)	0.68
	From one parent, % (n/N)	32.8 (160/488)	42.1 (8/19)	32.4 (152/469)	
	From both parents, % (n/N)	7.8 (38/488)	5.3 (1/19)	7.9 (37/469)	
	Do not know, % (n/N)	11.5 (56/488)	15.8 (3/19)	11.3 (53/469)	

*Categorical variables were tested using chi square and continuous variables were tested using Wilcoxon rank sum test

[1]3 children with IgA > 50 μg/ml were excluded

Table 3:

OR for asthma and allergic diseases at ages 5 and 13 (MMR-vaccinated/non-MMR-vaccinated)

	Adjustment for variables associated to MMR [1]			Adjustment for additional potential confounders [12]			Adjustment for asthma/allergy at age 5 [13]			Sensitivity analyses [14]		
Variable	**N**	**OR (95% CI)**	**p**	**N**	**OR (95% CI)**	**p**	**N**	**OR (95% CI)**	**p**	**N**	**OR (95% CI)**	**p**
5 years												
Asthma (questionnaire)	483	0.33 (0.12; 0.90)	0.03	425	0.32 (0.10; 1.05)	0.06				479	0.55 (0.16; 1.82)	0.33
Hypersensitivity/allergy (questionnaire)	481	0.32 (0.11; 0.88)	0.03	421	0.36 (0.11; 1.21)	0.10 *				477	0.36 (0.11; 1.19)	0.09
13 years												
Asthma ever (questionnaire)	489	0.22 (0.08; 0.56)	0.002	431	0.16 (0.05; 0.53)	0.003	483	0.24 (0.07; 0.82)	0.02	485	0.31 (0.10; 0.93)	0.04
Allergic rhinoconjunctivitis symptoms in the past 12 months (questionnaire)	489	0.64 (0.19; 2.07)	0.45	431	0.63 (0.14; 2.71)	0.53	481	0.79 (0.22; 2.76)	0.71	485	0.65 (0.17; 2.47)	0.52
Eczema ever (questionnaire)	489	0.73 (0.26; 2.10)	0.57	431	0.46 (0.14; 1.52)	0.21	481	0.65 (0.24; 1.76)	0.39	485	0.65 (0.20; 2.08)	0.47
Reaction to any allergen in skin prick test	489	0.59 (0.23; 1.53)	0.28	431	0.47 (0.16; 1.40)	0.18	485	0.73 (0.24; 2.23)	0.59	485	0.44 (0.15; 1.28)	0.13

[1] Adjusted for birth weight and family history of chronic bronchitis/asthma. The analyses at age 13 years are additionally adjusted for whether the child had received the second MMR vaccine before the 13-year examination.

[2] Additional adjustment for sex, premature birth, maternal smoking during pregnancy, log(cord blood IgE), breastfeeding, number of older siblings, number of younger siblings, parental smoking in the home, day care, family history of eczema in children/allergic eczema/hay fever, family history of allergy, and age at the examination.

[3] The asthma ever analysis is adjusted for asthma (questionnaire) at age 5, and the allergic rhinoconjunctivitis symptoms, eczema ever, and reaction to SPT analyses are adjusted for hypersensitivity/allergy (questionnaire) at age 5.

[4] Excluding children without any vaccine information.

* The hypersensitivity/allergy analysis could not be adjusted for premature birth as none of the prematurely born children had allergy at age 5.

Table 4:

Change in serum total IgE concentrations at age 7 with MMR vaccination

	Adjustment for variables associated to MMR [1]			Adjustment for additional potential confounders [12]			Sensitivity analyses [13]		
Variable	**N**	**% change (95% CI)**	**p**	**N**	**% change (95% CI)**	**p**	**N**	**% change (95% CI)**	**p**
Age 7 years									
Serum total IgE	396	−62.8 (−84.3; −11.9)	0.03	352	−49.5 (−79.5; 24.6)	0.14	393	−56.7 (−83.2; 11.5)	0.08

[1] Adjusted for birth weight and family history of chronic bronchitis/asthma.

[2] Additional adjustment for sex, premature birth, maternal smoking during pregnancy, log(cord blood IgE), breastfeeding, number of older siblings, number of younger siblings, parental smoking in the home, day care, family history of eczema in children, allergic eczema, and hay fever, family history of allergy, and age at the examination.

[3] Excluding children without any vaccine information.