

Mode of delivery and development of atopic disease during the first 2 years of life

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It has been hypothesized that cesarean delivery might have an impact on the development of atopic diseases because of its gut flora modulating properties. In the present study, we analysed the association between cesarean delivery and atopic diseases using data of 2500 infants enrolled in the LISA-Study, a German prospective multicenter birth cohort study. Data on symptoms and physician-diagnosed atopic diseases were gathered by questionnaires shortly after birth and at infant's age 6, 12, 18, and 24 months. In addition, sensitization to common food and inhalant allergens was assessed by measuring specific immunoglobulin E (IgE) using the CAP-RAST FEIA method at the age of 2 yr. Confounder-adjusted odds ratios (aOR) with 95% confidence intervals (CI) were calculated by multiple logistic regression. We found a positive association between cesarean delivery and occurrence of at least one episode of wheezing [aOR 1.31 (95% CI 1.02–1.68)] and of recurrent wheezing [1.41 (1.02–1.96)] during the first 2 yr of life. Furthermore, effect estimates for allergic sensitization defined as at least one specific IgE ≥ 0.70 kU/l against any allergen [1.48 (0.98–2.24)], against food allergens [1.64 (1.03–2.63)], and against inhalant allergens [1.75 (0.98–3.12)] were increased. Symptoms of atopic dermatitis [1.21 (0.92–1.59)], physician-diagnosed atopic dermatitis [1.04 (0.79–1.39)], and symptoms of allergic rhinoconjunctivitis [1.40 (0.80–2.44)] were only marginally increased in children delivered by cesarean section. In conclusion, our results suggest that cesarean delivery may be an additional risk factor for wheezing and allergic sensitization at least to food allergens up to the age of 2 yr. This should be considered when cesarean section is done for other than medical reasons.

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Prevalence of atopy has increased during the last decades and atopic diseases have become one of the major health concerns of the industrialized nations. Hereditary and environmental factors that influence atopy development have already been identified (1, 2). Recently, it has been hypothesized that infants delivered by cesarean section may have an elevated risk for atopic diseases compared with infants born vaginally (3–5).

It is well-known that the gut bacterial flora has immunomodulatory properties (6, 7). Several studies indicated differences in the microflora related to atopy. A Finish study reported

fewer bifidobacteria and more clostridia at the age of 3 wk in faecal samples of infants that developed allergic sensitization in the first year of life compared with infants that did not (8). A comparison of allergic and non-allergic 2-yr-old children in Sweden and Estonia showed differences in the indigenous intestinal flora, with fewer lactobacilli, bifidobacteria and bacteroides and more aerobic microorganisms in allergic infants (9). Moreover, a clinical trial demonstrated the potency of probiotics in primary prevention of atopic dermatitis in infants at high risk (10) and it has been shown that colonization with bifidobacteria was delayed in infants delivered by cesarean section (11).

*The LISA Study Group is given in appendix.

Considerations whether cesarean delivery increases the risk for atopy development might gain even more in significance as elective cesarean section at women's own request and without medical indication is at issue not only in scientific articles.

As several preceding studies on this topic had conflicting results (3, 4, 12), the aim of this study was to investigate the association between cesarean section and cumulative incidence of atopic symptoms, wheezing, physician-diagnosed atopic disease and allergic sensitization in the first 2 yr of life using data from a large prospective birth cohort study in Germany.

Subjects and methods

Subjects

We analysed data from the LISA-Study on 'Influences of life-style factors on the immune system and the development of allergies in childhood'. In this prospective cohort study, 3097 healthy full-term neonates were enrolled between November 1997 and January 1999 in the four German cities Munich, Leipzig, Wesel, and Bad Honnef. Exclusion criteria have been described in detail elsewhere (13).

The aim of the LISA-Study was to investigate immunoglobulin E (IgE)-dependent allergic symptoms or diseases in the first 2 yr of life and to determine parameters of maturation and activation of the immune system. Data were collected by parental-completed questionnaires and diaries at regular time intervals during the follow-up of 2 yr. The study protocol was approved by the local ethic committees.

For this analysis, we used information from the structured interviews shortly after birth, and at infant's age 6, 12, 18, and 24 months, respectively.

Information on the mode of delivery was obtained from the 'Mutterpass', a preventive medical check up documentation for pregnant women in Germany, and was dichotomized according to whether a cesarean section had been carried out or not.

The level of maternal education was defined by a combination of the highest school degree and professional training.

Definition of atopic diseases

Atopic disease was assumed when the parents reported physician's diagnosis or typical symptoms in the past 6 months in the questionnaires at infant's age 6, 12, 18, and 24 months.

Symptomatic atopic dermatitis was defined as itching eczema that was not restricted to the scalp and the skin underneath the diaper, and that was either recurrent or persisted more than 14 days or was reported in two successive questionnaires, both times with a duration of more than 7 days.

Symptomatic allergic rhinoconjunctivitis was defined as runny nose, sneezing attacks or conjunctivitis on both sides without infection of the upper airways.

As wheezing may indicate different phenotypes of airway obstruction (14), we used three definitions for categorization: first, ever wheezing defined as wheezing respiratory sounds that persisted more than 3 days. Second, recurrent wheezing defined as more than three episodes with a duration of 3 days each and separated by at least 7 days. Third, ever wheezing for more than 3 days without respiratory infections.

Cumulative incidences of symptomatic atopic dermatitis, all three categories of wheezing, and physician-diagnosed atopic dermatitis were calculated for the first 2 yr of life. Cumulative incidences of symptomatic allergic rhinoconjunctivitis, physician-diagnosed allergic rhinoconjunctivitis and physician-diagnosed asthma were solely calculated for the second year of life.

Determination of total and specific IgE

Cord blood IgE and specific IgE at the age of 2 yr were determined with the CAP-RAST FEIA (Pharmacia Diagnostics, Freiburg, Germany) according to the manufacturer's instructions. The limit of detection for total IgE was 0.35 kU/l. Specific sensitization to common food allergens (egg, cow's milk, wheat, peanut, soybean, cod fish) and to inhalant allergens (house dust mites, cockroach, cat, mixed grasses, birch pollen, mixed moulds) was defined as a specific IgE value of at least 0.35 kU/l (CAP class ≥ 1). Furthermore, specific sensitization with a specific IgE level of at least 0.70 kU/l (CAP class ≥ 2) was analysed.

Statistical methods

Differences in prevalences and cumulative incidences were tested by chi-square test. *p*-Values < 0.05 were considered statistically significant.

Crude associations between mode of delivery and confounding factors or health outcomes were described using odds ratios (ORs) with 95% confidence intervals (CI). Multiple logistic regression analyses were performed to calculate ORs adjusted for potential confounding factors (aOR).

Variable and model selection was performed by backward elimination using the log-likelihood ratio test. The log-likelihood ratio test or deviance test is a method for testing the fit of a simpler model against a more complex model (15). The starting model was a complex model which included forced-in variables and further potential confounding variables. Gender, study area, and parental history of atopy were defined as forced-in variables besides the variable on mode of delivery as exposure variable. Maternal smoking in the second and third trimester of pregnancy, birth weight, the level of maternal education, presence of older siblings and exclusive breast-feeding for at least 4 months were defined as potential confounders to be selected or removed in the procedure of variable selection. The statistical software package SAS for

Windows (Version 8.01, SAS Institute, Cary, NC, USA) was used for all calculations.

Results

For 3018 of 3097 infants enrolled in the LISA Study, information about the mode of delivery was available. In case of twins, only the first born was considered for this analysis, therefore 24 infants were excluded. Finally, we restricted our analysis to 2500 infants for whom data of all questionnaires during the follow-up of 2 yr were available.

Table 1 shows the basic characteristics and potential confounding factors of the study population according to the mode of delivery.

Comparing the two groups of infants, there were no significant differences in gender, parental

Table 1. Basic characteristics and potential confounding factors of the study population (N = 2500) according to mode of delivery

Variable	Cesarean section (n = 435)			Vaginal delivery (n = 2065)			p-value*
	N	n	%	N	n	%	
Study area	435			2065			0.03
Munich		239	54.9		1043	50.5	
Leipzig		113	26.0		607	29.4	
Wesel		51	11.7		194	9.4	
Bad Honnef		32	7.4		221	10.7	
Gender	435			2065			0.12
Male		240	55.2		1055	51.1	
Female		195	44.8		1010	48.9	
Parental history of atopy	435			2059			0.07
None		192	44.1		979	47.6	
One parent atopic		169	38.9		814	39.5	
Both parents atopic		74	17.0		266	12.9	
Maternal history of asthma	430	25	5.8	2044	139	6.8	0.45
Cord blood IgE ≥ 0.35 kU/l	209	68	32.5	1411	460	32.6	0.99
Level of maternal education	431			2033			0.28
Very high		163	37.8		732	36.0	
High		111	25.8		520	25.6	
Intermediate		112	26.0		609	30.0	
Low		45	10.4		172	8.5	
Maternal age at delivery ≥ 30 yr	434	302	69.6	2064	1383	67.0	0.30
Maternal smoking during pregnancy	418	42	10.1	1964	144	7.3	0.06
Presence of older siblings	434	164	37.8	2065	992	48.0	<0.0001
Gestational age (week of delivery)	423			2034			0.58
38–41		385	91.0		1868	91.8	
≥ 42		38	9.0		166	8.2	
Birth weight (g)	435			2065			<0.0001
2500–2999		79	18.2		252	12.2	
3000–3499		172	39.5		826	40.0	
3500–3999		114	26.2		741	35.9	
≥ 4000		70	16.1		246	11.9	
Period of exclusive breast-feeding							
At least 1 month	433	308	71.1	2059	1703	82.7	<0.0001
At least 4 months	432	222	51.4	2055	1233	60.0	0.001
At least 6 months	430	146	34.0	2031	843	41.5	0.004
Physician-diagnosed diarrhea							
before age of 6 months	434	29	6.7	2055	195	9.5	0.06
Physician-diagnosed upper airway infection							
before age of 1 yr	428	326	76.2	2047	1549	75.7	0.83

*Chi-square test.

history of atopy, maternal history of asthma, level of maternal education, maternal age at delivery, elevated cord blood IgE levels, occurrence of physician-diagnosed diarrhea before the age of 6 months and occurrence of physician-diagnosed upper airway infections before the age of 1 yr.

The proportion of infants that had older siblings and that were exclusively breast-fed for a period of at least 1, 4, or 6 months was significantly higher in the group of the vaginally delivered infants. Differences according to the study area and birth weight were also significant.

Incidence rates and effect estimates of the associations between cesarean delivery and atopic symptoms, wheezing, physician-diagnosed atopic disorders and allergic sensitization during the first 2 yr of life are shown in Tables 2 and 3.

For almost all outcome variables of symptoms or diagnoses the cumulative incidence was higher in infants delivered by cesarean section (Table 2). In multivariate analyses, these differences were statistically significant for occurrence of at least one episode of wheezing and recurrent wheezing (Table 3).

Allergic sensitization was also more frequent in the group of infants delivered by cesarean section (Table 2). The adjusted ORs increased when specific IgE levels of 0.7 kU/l (at least CAP class 2) were used as cut-point and gained statistical significance for sensitization to food allergens (Table 3).

Discussion

Up to now research concerning the association between mode of delivery and development of atopic disease has produced conflicting results.

Kero et al. (3) analysed data from Finish health registers and found the cumulative incidence of asthma at the age of 7 years to be significantly higher in children born by cesarean section than in those vaginally delivered. In a second study on a birth cohort of 219 children they found a trend toward more positive skin prick reactions at that age. Data of a Finish prospective birth cohort that involved 1953 adults analysed by Xu et al. (4) revealed a strong effect of cesarean section on physician-diagnosed asthma in adulthood, but showed no effects for atopy, allergic rhinoconjunctivitis and atopic

Table 2. Cumulative incidence of allergic sensitization and diseases at the age of 2 yr according to mode of delivery

Variable	Cesarean section (n = 435)			Vaginal delivery (n = 2065)			p-value*
	N	n	%	N	n	%	
Atopic symptoms and wheezing							
Atopic dermatitis	401	95	23.7	1940	386	19.9	0.09
Allergic rhinoconjunctivitis†	433	17	3.9	2051	62	3.0	0.33
At least one episode of wheezing	414	118	28.5	2002	477	23.8	0.04
Recurrent wheezing	397	60	15.1	1935	221	11.5	0.04
Wheezing without respiratory infection	385	12	3.1	1899	67	3.5	0.69
Physician-diagnosed atopic diseases							
Atopic dermatitis	426	78	18.3	2012	348	17.3	0.62
Allergic rhinoconjunctivitis†	423	7	1.7	1999	18	0.9	0.16
Asthma†	425	1	0.2	1018	10	0.5	0.47
Allergic sensitization against							
At least one allergen	345			1677			
CAP class ≥1		50	14.5		197	11.8	0.16
CAP class ≥2		33	9.6		114	6.8	0.07
At least one food allergen	348			1681			
CAP class ≥1		39	11.2		153	9.1	0.22
CAP class ≥2		26	7.5		79	4.7	0.03
At least one inhalant allergen	345			1676			
CAP class ≥1		23	6.7		69	4.1	0.04
CAP class ≥2		17	4.9		51	3.0	0.08
Recurrent wheezing							
And allergic sensitization‡	315	4	1.3	1570	33	2.1	0.33

*Chi-square test.

†In the second year of life.

‡CAP class ≥1 against at least one allergen of any kind.

CAP class ≥1: specific IgE ≥0.35 kU/l.

CAP class ≥2: specific IgE ≥0.70 kU/l.

Table 3. Associations between health outcomes at the age of 2 yr and delivery by cesarean section

Variable	Crude association		Multiple logistic regression	
	OR	95% CI	aOR	95% CI
Atopic symptoms and wheezing				
Atopic dermatitis	1.25	0.97–1.61	1.21†	0.92–1.59
Allergic rhinoconjunctivitis*	1.31	0.76–2.27	1.40‡	0.80–2.44
At least one episode of wheezing	1.27	1.01–1.62	1.31§	1.02–1.68
Recurrent wheezing	1.38	1.01–1.88	1.41¶	1.02–1.96
Wheezing without respiratory infection	0.88	0.47–1.64	0.92	0.49–1.74
Physician-diagnosed atopic dermatitis	1.07	0.82–1.41	1.04**	0.79–1.39
Allergic sensitization against				
At least one allergen				
CAP class ≥1	1.27	0.91–1.78	1.27**	0.89–1.80
CAP class ≥2	1.45	0.97–2.18	1.48††	0.98–2.24
At least one food allergen				
CAP class ≥1	1.26	0.87–1.83	1.25§	0.85–1.84
CAP class ≥2	1.64	1.03–2.59	1.64¶	1.03–2.63
At least one inhalant allergen				
CAP class ≥1	1.66	1.02–2.71	1.73‡‡	1.04–2.89
CAP class ≥2	1.65	0.94–2.90	1.75§§	0.98–3.12

OR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

*In the second year of life.

After backward elimination in multiple logistic regression modelling, OR were adjusted for gender, study area, parental history of atopy, maternal smoking in second and third trimester of pregnancy and additionally for:

†Level of maternal education, birth weight.

‡Exclusive breast-feeding for a period of at least 4 months.

§Level of maternal education, presence of older siblings, exclusive breast-feeding for a period of at least 4 months.

¶Level of maternal education, presence of older siblings.

**Level of maternal education, exclusive breast-feeding for a period of at least 4 months, birth weight.

††Level of maternal education.

‡‡Exclusive breast-feeding for a period of at least 4 months, birth weight.

§§Birth weight.

CAP class ≥1: specific IgE ≥0.35 kU/l.

CAP class ≥2: specific IgE ≥0.70 kU/l.

dermatitis. Nafstad et al. (5) demonstrated that uterus-related complications in pregnancy increased the risk of having asthma and allergic rhinitis at the age of 4 yr.

In contrast, by analysing data derived from an English birth cohort of 24,690 children, McKeever et al. (12) found no convincing evidence that babies born by cesarean section had an increased risk of developing allergic disease.

There are methodological issues that may have contributed to these differences: in the study of Xu et al. (4), only 5% of the adults of the cohort were delivered by cesarean section and almost all of these sections resulted from emergency situations. Because infants that were premature or had a low birth weight or other problems were not excluded in this study and these problems may themselves increase the risk of developing asthma, asthma could be overestimated in the

cesarean group. The other studies investigated children, resulting in a much shorter follow-up period.

Data of our birth cohort of 2500 healthy full-term infants showed a slightly elevated risk for some manifestations of atopy in children born by cesarean section up to the age of 2 yr. We differentiated in our analysis between symptoms and physician's diagnosis of atopic disease.

Atopic dermatitis is the most common manifestation of atopy in early childhood whereas allergic rhinoconjunctivitis and asthma are rare in the first 2 yr of life (16, 17).

In our study, symptoms of atopic dermatitis were reported in about every fifth case and were, as well as physician-diagnosed disease, slightly but not significantly more frequent in the group of infants delivered by cesarean section.

Because of the low cumulative incidence of physician-diagnosed allergic rhinoconjunctivitis in our cohort, we calculated OR only for incidence of reported symptoms. These risk estimates were slightly, but not statistically significant elevated. Physician-diagnosed asthma was extremely rare up to the age of 2 yr in our cohort. Therefore, we did not perform multivariate analysis.

Wheezing, however, may be positively associated with the later development of asthma, especially if it is recurrent, occurs without respiratory infection, or is combined with other predictors or risk factors (18, 19). Our results reveal a positive association between cesarean delivery and occurrence of at least one episode of wheezing and recurrent wheezing. At least a subgroup of these children might be considered at risk to develop asthma (14).

In contrast, we found a very low cumulative incidence and no positive association between cesarean delivery and wheezing without respiratory infection. This may be because of the fact that the children were only 2 yr old and at this age the most common cause of airway obstruction is viral infection (14). The proportion of atopic wheezers defined as infants with recurrent wheezing and specific sensitization to at least one allergen (CAP class ≥1) was too low to allow for further analyses.

Although atopic symptoms and allergic sensitization are not always congruent, there is evidence that sensitization in early childhood may be a predictor for the development of later atopy (20). Our data indicate that cesarean delivery may increase the risk of allergic sensitization. Effect estimates for sensitization to any allergen, to at least one food allergen, and to at least one inhalant allergen at the level of CAP class ≥2 were increased, reaching statistical significance in

case of sensitization to at least one food allergen (total N = 105, cesarean section N = 26). As has been shown by others (21), infancy sensitization to food allergens in most cases starts earlier than sensitization to inhalant allergens. The number of infants in our cohort sensitized to at least one inhalant allergen at the level of CAP class ≥ 2 (total N = 68, cesarean section N = 17) might have been too low at the age of 2 yr to also yield a statistically significant association. The effect estimate for sensitization to at least one inhalant allergen using the cut-point CAP class ≥ 2 was in the same magnitude compared with the OR for the cut-point CAP class ≥ 1 [aOR 1.75 (95% CI 0.98–3.12), total N = 68, and 1.73 (1.04–2.89), total N = 92, respectively].

Noticeable is the fact that in our cohort physician-diagnosed diarrhea during the first 6 months of life was more frequent in the group of infants that was delivered vaginally. Since in this group the infants had more often older siblings, we assume that this reported diarrhea was rather caused by viral infections than an effect of gut colonization.

We consider selection bias because of loss to follow-up unlikely, as the rate of cesarean section does not differ between the whole study population and the population used for analysis. After excluding second twins, the rate of cesarean section was 17.9% (535/2994) in the group of those infants for whom information about the mode of delivery was available. In the study population comprising infants with a complete follow-up until age 2 yr and blood samples at the age 2 yr it was 17.4% (435/2500) and 17.2% (349/2031), respectively.

Although the follow-up period was relatively short in our cohort and stool samples were not available, we consider our results valid. The cohort and the number of infants delivered by cesarean section are representative and reporting bias seems unlikely. In addition, parents completed questionnaires every 6 months, therefore recall bias, especially concerning possible confounders, would not be a major issue.

In conclusion, we found that cesarean delivery may be an additional risk factor for wheezing and allergic sensitization at least to food allergens up to the age of 2 yr. This should be considered when cesarean section is done for other than medical reasons.

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Appendix

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