



Original Contribution

Delivery by Cesarean Section and Early Childhood Respiratory Symptoms and Disorders

The Norwegian Mother and Child Cohort Study

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Studies have indicated that children delivered by cesarean section are at an increased risk of developing wheezing and asthma. This could be the result of an altered immune system development due to delayed gut colonization or of increased neonatal respiratory morbidity. The authors examined the associations between delivery by cesarean section and the development of wheezing, asthma, and recurrent lower respiratory tract infections in children up to 36 months of age among 37,171 children in the Norwegian Mother and Child Cohort Study. Generalized linear models were used in the multivariable analysis. Children delivered by cesarean section had an increased likelihood of current asthma at 36 months of age (relative risk = 1.17, 95% confidence interval: 1.03, 1.32), and the association was stronger among children of nonatopic mothers (relative risk = 1.33, 95% confidence interval: 1.12, 1.58). No increased risk of wheezing or recurrent lower respiratory tract infections was seen among children delivered by cesarean section. Findings were similar among children delivered by acute and elective cesarean section. In conclusion, children delivered by cesarean section may have an increased risk of current asthma at 36 months, but residual confounding cannot be excluded. In future prospective studies, investigators should reexamine this association in different age groups.

asthma; cesarean section; respiratory sounds; respiratory tract infections

Abbreviations: BMI, body mass index; CI, confidence interval; LRTI, lower respiratory tract infection; MBRN, Medical Birth Registry of Norway; MoBa, Norwegian Mother and Child; RR, relative risk.

The prevalences of wheezing and asthma are high, with asthma affecting approximately 300 million people worldwide (1). Prenatal and early life exposures might increase the likelihood of a person's developing respiratory disorders. Two hypotheses exist for why children delivered by cesarean section may have an increased susceptibility to wheezing and asthma. One potential explanation is the altered gut colonization seen among these children, which might result in an altered development of their immune system (2–4). Another potential explanation is the increased neonatal respiratory morbidity among children delivered by cesarean section, which is associated with increased risk of developing wheezing and asthma (5, 6). Rising cesarean section rates in Western countries make such a potential relation

an important public health concern, and a steady increase in the number of cesarean sections over the last decades has also been seen in Norway (7).

Previous studies in which delivery by cesarean section and development of wheezing or asthma were examined have varied in sample size, age group, follow-up time, case definition, and control of confounding factors. A subgroup of previous studies included registry-based or larger cohort studies (8–14). Two meta-analyses of several of these studies found 18% and 20% increases in the likelihood of asthma among persons delivered by cesarean section (15, 16). One registry-based study examined the association between delivery by cesarean section and asthma in the Norwegian population (14), but investigators were unable to adjust for

maternal smoking during pregnancy and prepregnancy body mass index (BMI), measured as weight in kilograms divided by height in meters squared. In a Finnish registry-based study, investigators found that the association between delivery via cesarean section and asthma was restricted to children diagnosed at 36 months of age or younger (13), making it interesting to reexamine the association in this young age group. Multivariable adjustments in previous studies resulted in small changes of the identified associations, highlighting the difficulty in identifying influencing factors.

It is challenging to disentangle whether the previously identified increased development of respiratory symptoms and disorders among children delivered by cesarean section is the result of delivery by cesarean section or if it is due to factors that influence the likelihood of a cesarean delivery and/or respiratory disorders. Potential influencing factors include prepregnancy, pregnancy, perinatal, and early childhood factors, such as maternal chronic or atopic conditions, smoking during pregnancy, prepregnancy BMI, and pregnancy complications, as well as gestational age and birth weight, which have been linked to wheezing and asthma development (17–22). Recurrent lower respiratory tract infections (LRTIs) in early childhood have been associated with both persistent wheezing and asthma exacerbations (23, 24). An increase in recurrent LRTIs among children delivered by cesarean section could be evidence that delivery by cesarean section is a risk factor for asthma. No previous study has examined the association between cesarean section delivery and recurrent LRTIs. The aim of the present study was to examine the associations between delivery by cesarean section and the development of wheezing, asthma, and recurrent LRTIs in children up to 36 months of age.

MATERIALS AND METHODS

Study population

The Norwegian Mother and Child (MoBa) Cohort Study is a pregnancy cohort study administered by the Norwegian Institute of Public Health. Details of the study have been described previously (25, 26). Briefly, pregnant women were recruited between 1999 and 2008, at approximately 18 weeks of gestation, from 39 out of the 50 maternity units in the country that recorded more than 100 births annually. A total of 38.5% of all invited pregnant women agreed to participate in the study. Questionnaires were filled out by the participating mothers at the time of recruitment, in the 22nd gestational week, in the 30th gestational week, and when the child was 6, 18, and 36 months of age (27). Data from version V of MoBa were used, in which a total of 108,904 children were included. All children from multiple births were excluded from the present study ($n = 3,805$). Among the 84,932 participants who so far have received the 36-months questionnaire, the response rate has been 59.1%. The sample for the current study included the 37,171 children for whom information was available from the questionnaires administered at the 18th and 30th gestational weeks and when the child was 6, 18, and 36 months of age. This study population included 3,232 groups of

siblings. Data from the MoBa study were linked to the Medical Birth Registry of Norway (MBRN). The study was approved by the Norwegian Data Inspectorate and the Regional Ethics Committee for Medical Research.

Outcomes

The outcomes examined were wheezing, asthma, and recurrent LRTIs. The presence of wheezing symptoms was ascertained when the child was 18 months of age and was defined as maternal report of the child's experiencing at least 1 episode with wheezing, whistling, or chest congestion between 6 and 18 months age. No information on wheezing symptoms was gathered when the child was 6 or 36 months of age. Asthma was classified at 36 months on the basis of maternal report of the child's currently having asthma. LRTIs were classified on the basis of maternal report of infections with respiratory syncytial virus, pneumonia, or bronchitis before the child was 18 months of age or a child's experiencing infections with pneumonia or bronchitis between 18 and 36 months of age. Recurrent LRTIs were defined as 3 or more episodes of LRTIs before 36 months of age on the basis of previous epidemiologic evidence linking 3 or more LRTIs with asthma exacerbations (28).

Exposure

Information on mode of delivery was gathered from the MBRN. The exposure of interest was delivery by cesarean section as opposed to all vaginal deliveries. Cesarean section was further classified into acute, elective, or unspecified cesarean section. No distinction was made regarding whether the vaginal delivery was induced or spontaneous or whether it was instrumental (requiring the use of forceps or vacuum extraction) or noninstrumental.

Covariates

Factors that could plausibly influence the associations examined were identified on the basis of literature and preanalytical assumptions. Data on maternal prepregnancy factors gathered from MoBa questionnaires included BMI (categorized according to World Health Organization guidelines (<18.5 , 18.5 – 24.9 , 25 – 29.9 , or ≥ 30) (29)), completed years of education (≤ 12 , 13 – 15 , or ≥ 16 years), and atopic status (asthma, hay fever, atopic dermatitis, animal hair allergies, and/or other allergies). Data on maternal chronic conditions (cardiovascular heart disease, hypertension, chronic renal disease, and/or diabetes) were gathered from the MBRN. Pregnancy-related data gathered from MoBa questionnaires included information on maternal smoking during pregnancy and preference for delivery by cesarean section. Preference for cesarean section included the mother's agreeing to a question asked during pregnancy stating that, if she could choose, she would deliver by a cesarean section. Pregnancy-related data on pregnancy complications gathered from MBRN included pre-eclampsia/eclampsia, pregnancy-induced hypertension, and HELLP syndrome (hemolytic anemia, elevated liver enzymes, and low platelet count), in addition to duration of membrane rupture (<12 hours, 12 – 24 hours, and >24 hours).

Information gathered at the time of delivery included maternal age (<25, 25–34, or >34 years), previous delivery by cesarean section, marital status (married or cohabitating vs. other), parity (primiparous vs. multiparous), infant's gender, birth weight in grams (<2,500, 2,500–2,999, 3,000–3,499, 3,500–4,000, or >4,000), and gestational age in weeks (<37, 37–39, 40–41, or >41), all gathered from the MBRN. Information on whether the child was still breastfed at 6 months of age and day care attendance before 18 months was gathered through the use of MoBa questionnaires.

Analysis

Differences in demographic and perinatal factors by mode of delivery were examined through the use of chi-squared tests. Generalized linear models with the log-link function were used to report relative risks and 95% confidence intervals. Separate models were fitted for wheezing, asthma, and recurrent LRTIs. Multivariable models were adjusted for all covariates identified. We controlled for categorical variables with more than 2 categories by using dummy variables. The aim of the analysis was to attempt to isolate the direct association between delivery by cesarean section and respiratory disorders, and we therefore controlled for intermediate factors, such as breastfeeding and day care attendance. Robust variance estimations with cluster adjustments were used to account for siblings. The first step in the analysis controlled for all covariates through regular adjustment. In the second step, we controlled for the 2 intermediate factors through inverse probability weighting, based on the product of the probabilities of the intermediate factors in the exposure groups, as evidence has indicated that regular adjustment of intermediate factors might introduce confounding (30). The primary analysis was a complete-case analysis. In the multivariable analysis, 90.7% of observations were available in the analysis of wheezing, 91.2% for the analysis of asthma, and 88.6% for the analysis of recurrent LRTIs. A sensitivity analysis was therefore conducted by using a multiple imputation model. A total of 10 imputed data sets were generated through multivariate normal regression, a Markov chain Monte Carlo method using data augmentation, which is appropriate for imputation of continuous and dichotomous variables (31). The imputation model included all of the covariates identified, the exposure, the 3 outcomes, and the cluster variable. Effect modification by gestational age, maternal atopic status, and child's gender was explored, as previous studies have indicated differences in the associations examined by these factors. Wald tests were used to examine the statistical significance of several coefficients in the multivariable models at the same time and to examine the differences between groups. All *P* values presented are 2 sided, with a 5% significance level. Data analysis was conducted by using STATA, version 11 (StataCorp LP, College Station, Texas).

RESULTS

The children in the study population were born between 2001 and 2007. The proportion of children delivered by cesarean section was 13.5%, of which 57.1% were delivered

via acute cesarean section, 35.1% were delivered via elective cesarean section, and 7.8% were delivered via unspecified cesarean section. Children delivered by cesarean section were more likely than children delivered vaginally to have mothers who were older, single, and primiparous; had a preference for delivery by cesarean section; were classified as overweight or obese before pregnancy; had a lower educational level, chronic or atopic disorders, pregnancy complications, and longer duration of membrane rupture; and had delivered previously by cesarean section (Table 1). Furthermore, children delivered by cesarean section were more likely to be male, to have been exposed to smoking during pregnancy, and to have a lower birth weight and shorter gestational age, whereas they were less likely to still be breastfed at 6 months of age (Table 1). The cumulative incidence of wheezing between 6 and 18 months of age was 40.4%, the prevalence of current asthma at 36 months of age was 6.3%, and cumulative incidence of recurrent LRTIs by 36 months of age was 4.6%. We found no differences by birth year in the proportion of cesarean sections or the burden of wheezing, asthma, or LRTIs. Among children with current asthma at 36 months of age, 79.9% had experienced wheezing between 6 and 18 months of age and 22.1% had experienced recurrent LRTIs.

Children delivered via cesarean section had a higher incidence of wheezing, asthma, and recurrent LRTIs than did children delivered vaginally (wheezing: 42.7% vs. 40.0%; asthma: 8.0% vs. 6.0%; and recurrent LRTIs: 5.7% vs. 4.5%). A positive association between delivery by cesarean section and current asthma at 36 months of age remained after multivariable adjustment, with a relative risk of 1.17 (95% confidence interval (CI): 1.03, 1.32), whereas no association was seen between delivery by cesarean section and development of wheezing or recurrent LRTIs (Table 2). The findings were similar among those delivered by elective and acute cesarean section, as indicated by results from Wald tests (Table 2). Maternal parity, gestational age, and maternal prepregnancy BMI were the factors that exerted the strongest influence on the associations. The associations were attenuated if the mother was multiparous or had a normal prepregnancy BMI or if the child had a higher gestational age. These findings did not change when we used inverse probability weighting to control for breastfeeding and day care attendance (Table 2). When comparing the associations from the complete-case analysis with the associations identified through multiple imputation, we found that the results were similar (Table 2). The largest difference in these 2 analytical approaches was seen for the association between delivery via elective cesarean section and asthma, with a relative risk of 1.22 (95% CI: 1.01, 1.48) in the complete-case analysis and a relative risk of 1.16 (95% CI: 0.97, 1.40) after incorporating multiple imputation.

Maternal atopic status was a potential effect modifier of the association between cesarean section delivery and asthma ($P = 0.05$), with a stronger association in children of non-atopic mothers (relative risk (RR) = 1.33, 95% CI: 1.12, 1.58) than in children of atopic mothers (RR = 1.03, 95% CI: 0.87, 1.23) (Table 3). In addition, a tendency for stronger associations between delivery by cesarean section and asthma with recurrent LRTIs was seen among children of lower

Table 1. Distribution of Demographic and Perinatal Factors by Mode of Delivery Among Children Participating in the Norwegian Maternal and Child Cohort Study, 2001–2007^a

Variable	Total (n = 37,171), %	Cesarean Delivery (n = 5,020), %	Vaginal Delivery (n = 32,151), %
Maternal age at delivery, years			
<25	9.2	7.8	9.4
25–34	73.6	69.3	74.3
>34	17.2	22.9	16.3
Maternal marital status			
Married/cohabitating	97.3	96.7	97.4
Other	2.7	3.3	2.6
Maternal parity			
Primiparous	47.0	54.0	45.9
Multiparous	53.0	46.0	54.1
Gender of child			
Male	51.2	53.3	50.9
Female	48.8	46.7	49.1
Maternal educational level, years			
≤12	33.1	37.8	32.4
13–15	44.7	41.3	45.2
≥16	22.2	20.9	22.4
Maternal prepregnancy body mass index ^b			
<18.5	2.9	2.1	3.0
18.5–24.9	66.0	55.8	67.6
25–29.9	22.0	26.4	21.3
≥30	9.1	15.7	8.1
Maternal smoking during pregnancy			
Yes	7.8	9.1	7.6
No	92.2	90.9	92.4
Maternal indication of personal preference for cesarean section			
Yes	4.4	16.6	2.6
No	95.6	83.4	97.4
Maternal previous delivery by cesarean section			
Yes	7.3	24.6	4.5
No	92.7	75.4	95.5
Maternal chronic conditions before pregnancy ^c			
Yes	2.1	3.7	1.8
No	97.9	96.3	98.2

Table continues

gestational age, but it was not statistically significant (Appendix Table 1). Furthermore, stronger associations between delivery by cesarean section and development of asthma and recurrent LRTIs were found among girls, but these gender differences were also not statistically significant (Appendix Table 2).

Examining differences between the chosen study population and the other MoBa children who had reached 36 months of age at the time of the current study and were born before the end of 2007 but for whom we did not have information

from all the questionnaires used in the present study, we found that the study population contained fewer children with mothers in the youngest age group, fewer children of single mothers, fewer children of mothers who smoked during pregnancy, more children of first-time mothers, and more children of mothers with some university-level education. Compared with other MoBa children, those in the study population also had lower birth weights and shorter gestational ages and were more likely to have been delivered by cesarean section.

Table 1. Continued

Variable	Total (n = 37,171), %	Cesarean Delivery (n = 5,020), %	Vaginal Delivery (n = 32,151), %
Pregnancy complications ^d			
Yes	6.9	17.2	5.3
No	93.1	82.8	94.7
Duration of membrane rupture			
<12 hours before delivery	86.7	86.9	86.7
12–24 hours before delivery	6.9	6.1	7.0
>24 hours before delivery	6.4	7.0	6.3
Birth weight, g			
<2,500	2.5	8.6	1.6
2,500–2,999	8.3	10.1	8.0
3,000–3,499	28.8	24.5	29.5
3,500–4,000	37.5	32.3	38.3
>4,000	22.8	24.5	22.6
Gestational age, weeks			
<37	4.6	11.9	3.4
37–39	38.3	48.3	36.7
40–41	48.8	29.6	51.9
>41	8.3	10.2	8.0
Child still breastfed at 6 months of age			
Yes	73.9	67.9	74.9
No	26.1	32.1	25.1
Child in day care before 18 months of age			
Yes	48.9	47.8	49.1
No	51.1	52.2	50.9
Mother atopic ^e			
Yes	34.2	36.5	33.8
No	65.8	63.5	66.2

^a All *P* values from chi-squared tests were <0.05 except for day care attendance before 18 months of age. Fewer than 5% of observations for each factor examined were missing.

^b Weight (kg)/height (m)².

^c Maternal chronic conditions before pregnancy included diabetes mellitus, congestive heart failure, chronic hypertension, and/or kidney disease.

^d Pregnancy complications were defined as pregnancy-induced hypertension, gestational diabetes, preeclampsia/eclampsia, HELLP syndrome (hemolytic anemia, elevated liver enzymes, and low platelet count), abruptio placenta, or placenta previa.

^e Atopy was defined as parental self-report of asthma, hay fever, atopic dermatitis, animal hair allergies, or other allergies.

DISCUSSION

Children delivered by cesarean section had increased risk of current asthma at 36 months of age. This increase in asthma among children delivered by cesarean section was higher among children of nonatopic mothers than among children of atopic mothers. In contrast, no increased risk of wheezing or recurrent LRTIs was identified. The findings were similar among children delivered by acute and elective cesarean section and were seemingly not due to an indirect association with breastfeeding or day care attendance. The increase in the rate of asthma among children delivered by cesarean section was similar to that identified in 2 previous meta-analyses

(15, 16). To our knowledge, the present study is the largest pregnancy cohort study in which the association between delivery by cesarean section and development of wheezing and asthma was examined while controlling for a wide range of influencing factors, as well as the first in which the association between delivery by cesarean section and recurrent LRTIs was examined.

Five large studies have previously identified increased wheezing or asthma in people delivered by cesarean section (8, 9, 11, 13, 14), whereas 2 studies found no such increase (10, 12). Among studies that distinguished between age of disease classification (12, 13, 32–34), several have indicated stronger associations among children who had asthma at a

Table 2. Associations Between Mode of Delivery and Development of Wheezing, Asthma, and Lower Respiratory Tract Infections in a Subgroup of Children Participating in the Norwegian Mother and Child Cohort Study Who Were Born Between 2001 and 2007 ($n = 37,171$)^a

Exposure Categories	No. of Cases	Total No.	%	Crude		Adjusted ^b		Adjusted Inverse Probability Weighting ^c		Adjusted Multiple Imputation ^{b,d}		
				RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Wheezing at 18 months of age												
Vaginal delivery	12,668	31,628	40.1	1		1		1		1		
Overall cesarean section	2,106	4,929	42.7	1.07	1.03, 1.10	1.03	0.99, 1.07	1.03	0.99, 1.08	1.03	0.99, 1.07	
Acute cesarean section	1,207	2,819	42.8	1.07	1.02, 1.12	1.04	0.99, 1.09	1.04	0.99, 1.09	1.03	0.98, 1.08	
Elective cesarean section	731	1,726	42.4	1.06	1.00, 1.12	1.00	0.94, 1.07	1.00	0.94, 1.07	1.01	0.95, 1.08	
Current asthma at 36 months of age												
Vaginal delivery	1,918	31,804	6.0	1		1		1		1		
Overall cesarean section	398	4,951	8.0	1.33	1.20, 1.48	1.17	1.03, 1.32	1.16	1.03, 1.31	1.15	1.02, 1.29	
Acute cesarean section	234	2,825	8.3	1.37	1.20, 1.56	1.19	1.03, 1.38	1.19	1.03, 1.38	1.20	1.05, 1.38	
Elective cesarean section	146	1,739	8.4	1.39	1.18, 1.63	1.22	1.01, 1.48	1.21	1.00, 1.47	1.16	0.97, 1.40	
Recurrent LRTIs before 36 months of age												
Vaginal delivery	1,374	30,829	4.5	1		1		1		1		
Overall cesarean section	274	4,807	5.7	1.28	1.13, 1.45	1.07	0.92, 1.25	1.07	0.92, 1.25	1.08	0.93, 1.24	
Acute cesarean section	143	2,736	5.2	1.17	0.99, 1.39	1.01	0.83, 1.22	1.01	0.83, 1.22	1.03	0.86, 1.23	
Elective cesarean section	111	1,687	6.6	1.48	1.22, 1.80	1.19	0.95, 1.48	1.18	0.95, 1.47	1.15	0.93, 1.41	

Abbreviations: CI, confidence interval; LRTI, lower respiratory tract infection; RR, relative risk.

^a A Wald test was used to test differences in the associations by acute and elective cesarean section. The *P* values were 0.402, 0.809, and 0.213 in the models of wheezing, asthma, and recurrent LRTIs, respectively.

^b Model was adjusted for maternal age at delivery, maternal marital status, maternal parity, child's gender, maternal educational level, maternal prepregnancy body mass index, maternal smoking during pregnancy, maternal indication of personal preference for cesarean section, maternal previous delivery by cesarean section, maternal chronic conditions before pregnancy, pregnancy complications, duration of membrane rupture, birth weight, gestational age, child's still being breastfed at 6 months of age, child's being in day care at 18 months of age, and maternal atopy.

^c This model was adjusted for all of the covariates presented above but controlled for breastfeeding at 6 months of age and day care attendance before 18 months of age through inverse probability weighting.

^d Multiple imputation was completed by using multivariate normal regression through data augmentation, a Markov chain Monte Carlo method appropriate for imputation of dichotomous variables. A total of 10 imputations were generated.

younger age, and one study found the association exclusive to asthma before 36 months of age (13). In contrast, one meta-analysis found a weaker association between delivery by cesarean section and asthma in studies in which subjects younger than 10 years of age were included (15), whereas another meta-analysis found reduced heterogeneity between studies when only pooling results from studies in which the subjects were younger than 18 years of age (16). Some studies found an increase in asthma in children delivered by cesarean section only among girls (35, 36). Two studies identified a stronger association between cesarean section and asthma among children of atopic mothers (12, 33), whereas one found a stronger association among children of nonatopic mothers (37), similar to that identified in the present study. Furthermore, previous studies have indicated that the increase in asthma among those delivered by cesarean section is higher among children of younger gestational age (14, 38), but differences by gestational age were not statistically significant in the present study. Finally, some studies found stronger associations among children delivered by acute cesarean section as opposed to elective cesarean

section (14, 39), whereas others found no such difference (9, 10, 13).

The hygiene hypothesis suggests that increased disease development among children delivered by cesarean section could be the result of delayed gut colonization due to lack of contact with maternal vaginal fecal flora, resulting in an altered immune system development (2, 4, 40). Children delivered by elective cesarean section are hypothesized to have less exposure to maternal vaginal fecal flora compared with those delivered by acute cesarean section (14). Considering this hypothesis, the association between cesarean section and the development of respiratory symptoms and disorders would be expected to be stronger among those delivered by elective cesarean section, a theory not supported by the findings of previous studies or the current study. Only about 37% of children who have problems with wheezing early in life have persistent wheezing symptoms at 10 years of age (41), whereas atopic manifestation usually occurs at school age (42). Differences in the association between cesarean section delivery and asthma between age groups might therefore reflect the different asthma phenotypes (42).

Table 3. Associations Between Mode of Delivery and Development of Wheezing, Asthma, and Lower Respiratory Tract Infections Stratified by Maternal Atopic Disease in a Subgroup of Children Participating in the Norwegian Mother and Child Cohort Study Who Were Born Between 2001 and 2007 ($n = 37,171$)^a

Exposure Categories	Atopic Mother ($n = 12,699$)						Nonatopic Mother ($n = 24,472$)						P for Interaction Term ^c		
	No. of Cases	Total No.	%	Crude		Adjusted ^b		No. of Cases	Total No.	%	Crude			Adjusted ^b	
				RR	95% CI	RR	95% CI				RR	95% CI		RR	95% CI
Wheezing at 18 months of age															
Vaginal delivery	4,739	10,715	44.2	1		1		7,929	20,913	37.9	1		1		0.317
Cesarean section	826	1,808	45.7	1.03	0.98, 1.09	1.00	0.94, 1.06	1,280	3,121	41.0	1.08	1.03, 1.13	1.05	1.00, 1.11	
Current asthma at 36 months of age															
Vaginal delivery	938	10,747	8.7	1		1		980	21,057	4.6	1		1		0.052
Cesarean section	180	1,811	9.9	1.14	0.98, 1.32	1.03	0.87, 1.23	218	3,140	6.9	1.49	1.29, 1.72	1.33	1.12, 1.58	
Recurrent LRTIs before 36 months of age															
Vaginal delivery	563	10,458	5.4	1		1		811	20,371	4.0	1		1		0.721
Cesarean section	122	1,771	6.9	1.28	1.06, 1.54	1.09	0.87, 1.37	152	3,036	5.0	1.26	1.06, 1.49	1.06	0.86, 1.29	

Abbreviations: CI, confidence interval; LRTI, lower respiratory tract infection; RR, relative risk.

^a The unspecified cesarean sections were excluded in the stratified analysis of acute and elective cesarean sections ($n = 391$).

^b Adjusted for maternal parity, age, premature rupture of membranes, previous delivery by cesarean section, educational level, prepregnancy body mass index, child's gender, smoking during pregnancy, gestational age, birth weight, breastfeeding, early day care attendance, pregnancy complications, maternal chronic conditions before pregnancy, and preference for delivery by cesarean section.

^c Interaction on the multiplicative scale was tested by adding a product term between delivery by cesarean section and maternal atopy in the multivariable model.

Children delivered by cesarean section have increased neonatal respiratory morbidity (43, 44), which is also linked to the development of wheezing and asthma (5, 6, 45). The shorter gestational age and increased neonatal respiratory morbidity among children delivered by cesarean section reflect the importance of a suboptimal intrauterine environment that is influenced by maternal age, smoking, chronic conditions, pregnancy complications, and prepregnancy BMI (46), factors known to also increase the likelihood of wheezing and asthma (18, 19, 47). Pregnant women who indicate that they prefer to give birth by cesarean section might be mothers with increased health awareness. For example, women with poorly controlled asthma or higher socioeconomic status could be more likely to want to deliver by cesarean section (48, 49). The stronger association between cesarean delivery and asthma among children of nonatopic mothers might indicate that delivery by cesarean section is not an important risk factor in children with a hereditary predisposition. The tendency for a stronger association between delivery by cesarean section and development of asthma among children of lower gestational age could reflect an underdevelopment of the lungs, decreased respiratory health, and an increased susceptibility to infections among children of lower gestational age (50).

Strengths of the current study include the large sample size, prospective data collection, and wide range of factors for which we controlled. Only a few previous studies have been able to distinguish between acute and elective cesarean section, and no previous study has examined the association between cesarean section delivery and recurrent LRTIs. The present study controlled for several factors that previous studies had not been able to examine, including identification of the importance of maternal prepregnancy BMI, and we were

also able to distinguish that the positive association between cesarean section delivery and asthma was not due to an indirect association with breastfeeding or day care attendance. The prospective data collection reduced the risk of recall bias and decreased the likelihood that mothers would differentially report information on potential confounders based on their child's disease status.

Several limitations also need to be addressed. Relying on maternal report of respiratory symptoms and disorders might have resulted in misclassification. The prevalence of maternal reports of a child's having asthma at 7 years of age in MoBa had a strong agreement with registered use of antiasthmatic medications in the Norwegian Prescription Database (51). However, classification of asthma at 36 months of age might not be a good indication of asthma at school age. The frequency of wheezing episodes was not registered, making it difficult to address the severity of wheezing symptoms. Because women were recruited in the middle of pregnancy, it is unlikely that a selection bias based on cesarean section delivery and/or child respiratory disorders occurred at this point, as both events occurred after this time. However, the children with the necessary follow-up information for the present study included a lower proportion of deliveries by cesarean section. As mothers of children with respiratory symptoms and disorders might be less likely to have continued participation because of the burden of having a child with a chronic illness, a selection bias cannot be excluded. However, because of the substantial development of asthma medication and management over the last decades, most children experiencing asthma today have fewer and less severe asthma attacks.

In conclusion, children delivered by cesarean section might have an increased risk of current asthma at 36 months of age,

especially children of nonatopic mothers. The findings were influenced by confounding factors, which increased the possibility of residual confounding. Factors that might have contributed to residual confounding include an underlying child pathology, epigenetic mechanisms, and maternal psychosocial factors. Further prospective studies should attempt to reexamine these relations in different age groups.

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(Appendix follows)

Appendix Table 1. Association Between Mode of Delivery and Development of Wheezing, Asthma, and Lower Respiratory Tract Infections Stratified by Gestational Age in a Subgroup of Children Participating in the Norwegian Mother and Child Cohort Study Who Were Born Between 2001 and 2007 (*n* = 37,171)

Exposure Categories	Gestational Age, weeks																<i>P</i> for Interaction Term ^a
	<37 (<i>n</i> = 1,698)				37–39 (<i>n</i> = 14,170)				40–41 (<i>n</i> = 18,084)				>41 (<i>n</i> = 3,068)				
	No. of Cases	Total No.	%	Adjusted ^b RR 95% CI	No. of Cases	Total No.	%	Adjusted ^b RR 95% CI	No. of Cases	Total No.	%	Adjusted ^b RR 95% CI	No. of Cases	Total No.	%	Adjusted ^b RR 95% CI	
Wheezing at 18 months of age																	
Vaginal delivery	500	1,084	46.1	1	4,705	11,565	40.7	1	6,445	16,334	39.5	1	969	2,522	38.4	1	0.474
Cesarean section	276	588	46.9	1.04 0.91, 1.17	992	2,363	42.0	1.01 0.95, 1.07	614	1,452	42.3	1.05 0.98, 1.13	214	501	42.7	1.10 0.97, 1.24	
Current asthma at 36 months of age																	
Vaginal delivery	94	1,084	8.7	1	742	11,635	6.4	1	943	16,429	5.7	1	132	2,534	5.2	1	0.533
Cesarean section	74	585	12.7	1.23 0.84, 1.81	196	2,385	8.2	1.24 1.03, 1.49	94	1,449	6.5	1.13 0.91, 1.40	33	506	6.5	1.15 0.76, 1.76	
Recurrent LRTIs before 36 months of age																	
Vaginal delivery	65	1,048	6.2	1	517	11,276	4.6	1	664	15,927	4.2	1	122	2,460	5.0	1	0.191
Cesarean section	55	561	9.8	1.43 0.90, 2.27	139	2,316	6.0	1.16 0.93, 1.46	64	1,415	4.5	1.02 0.78, 1.35	15	491	3.0	0.70 0.40, 1.22	

Abbreviations: CI, confidence interval; LRTI, lower respiratory tract infection; RR, relative risk.

^a Interaction by gestational age was tested in a model with first-, second-, and third-degree variables of gestational age and corresponding multiplicative interaction terms. The *P* values are from Wald tests of the significance of the 3 interaction terms.

^b Adjusted for maternal parity, age, premature rupture of membranes, previous delivery by cesarean section, educational level, prepregnancy body mass index, child's gender, smoking during pregnancy, breastfeeding, early day care attendance, pregnancy complications, maternal chronic conditions before pregnancy, preference for delivery by cesarean section, and maternal atopy.

Appendix Table 2. Association Between Mode of Delivery and Development of Wheezing, Asthma, and Lower Respiratory Tract Infections Stratified by Gender in a Subgroup of Children Participating in the Norwegian Mother and Child Cohort Study Who Were Born Between 2001 and 2007 (*n* = 37,171)

Exposure Categories	Girls (<i>n</i> = 18,136)								Boys (<i>n</i> = 19,035)								<i>P</i> for Interaction Term ^a
	No. of Cases	Total No.	%	Crude		Adjusted ^b		No. of Cases	Total No.	%	Crude		Adjusted ^b				
				RR	95% CI	RR	95% CI				RR	95% CI	RR	95% CI			
Wheezing at 18 months of age																	
Vaginal delivery	5,624	15,526	36.2	1		1		7,044	16,102	43.7	1		1		0.221		
Cesarean section	908	2,302	39.4	1.09	1.03, 1.15	1.05	0.99, 1.12	1,198	2,627	45.6	1.04	1.00, 1.09	1.01	0.96, 1.07			
Current asthma at 36 months of age																	
Vaginal delivery	740	15,629	4.7	1		1		1,178	16,175	7.3	1		1		0.129		
Cesarean section	157	2,306	6.8	1.44	1.22, 1.70	1.32	1.09, 1.60	241	2,645	9.1	1.25	1.09, 1.43	1.09	0.93, 1.27			
Recurrent LRTIs before 36 months of age																	
Vaginal delivery	548	15,129	3.6	1		1		826	15,700	5.3	1		1		0.233		
Cesarean section	116	2,235	5.2	1.43	1.18, 1.74	1.22	0.96, 1.54	158	2,572	6.1	1.17	0.99, 1.38	0.99	0.82, 1.20			

Abbreviations: CI, confidence interval; LRTI, lower respiratory tract infection; RR, relative risk.

^a Interaction on the multiplicative scale was tested by adding a product term between child's gender and cesarean section in the multivariable model.

^b Adjusted for maternal parity, age, premature rupture of membranes, previous delivery by cesarean section, educational level, prepregnancy body mass index, smoking during pregnancy, gestational age, birth weight, breastfeeding, early day care attendance, pregnancy complications, maternal chronic conditions before pregnancy, preference for delivery by cesarean section, and maternal atopy.