

Effects of Breastfeeding on Respiratory Symptoms in Infancy

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Objective To assess the impact of potential risk factors on the development of respiratory symptoms and their specific modification by breastfeeding in infants in the first year of life.

Study design We prospectively studied 436 healthy term infants from the Bern-Basel Infant Lung Development cohort. The breastfeeding status, and incidence and severity of respiratory symptoms (score) were assessed weekly by telephone interview during the first year of life. Risk factors (eg, pre- and postnatal smoking exposure, mode of delivery, gestational age, maternal atopy, and number of older siblings) were obtained using standardized questionnaires. Weekly measurements of particulate matter <10 μg were provided by local monitoring stations. The associations were investigated using generalized additive mixed model with quasi Poisson distribution.

Results Breastfeeding reduced the incidence and severity of the respiratory symptom score mainly in the first 27 weeks of life (risk ratio 0.70; 95% CI 0.55-0.88). We found a protective effect of breastfeeding in girls but not in boys. During the first 27 weeks of life, breastfeeding attenuated the effects of maternal smoking during pregnancy, gestational age, and cesarean delivery on respiratory symptoms. There was no evidence for an interaction between breastfeeding and maternal atopy, number of older siblings, child care attendance, or particulate matter <10 μg .

Conclusions This study shows the risk-specific effect of breastfeeding on respiratory symptoms in early life using the comprehensive time-series approach.

Acute respiratory infection is a major cause of morbidity and hospitalization among young children worldwide. Several hereditary risk factors,^{1,2} perinatal factors,³⁻⁵ factors associated with immune development (maternal atopy, asthma),^{6,7} as well as environmental factors are known to increase the risk of lower respiratory tract disease in infants. Pre- and postnatal maternal smoking, and environmental exposure to particulate matter <10 μg (PM₁₀) and nitrogen dioxide, are correlated with more respiratory symptoms in the first year of life.^{1,8,9}

Breastfeeding is generally accepted to be protective against respiratory symptoms in early life.^{2,10-14} Furthermore, growing knowledge indicates that breastfeeding may differentially affect susceptible subgroups. A number of studies found evidence of a protective effect of breastfeeding against respiratory infection, particularly in the first 4-6 months of life.^{2,10,12-15} Other studies have reported a protective effect of breastfeeding only in girls¹⁶⁻¹⁸ and in the first born child.¹⁹ Some studies have suggested that breastfeeding reduced the adverse effects of smoking²⁰⁻²² and air pollution²⁰ exposure on respiratory morbidity. However, most studies are cross-sectional^{16,17,20,22,23} and, therefore, prone to bias, due to the close concordance of lifestyle factors and socioeconomic status, which relate to smoking rates, inhabiting polluted areas, and breastfeeding. In developed countries, breastfeeding mothers tend to have a higher education status and smoke less.^{24,25} Moreover, it is unknown whether breastfeeding may favorably influence the association of respiratory symptoms with the mode of delivery and gestational age.

We hypothesize that the protective effect of breastfeeding might be specifically modified dependent on the nature of the exposure to hereditary, perinatal, or environmental risk factors. In order to test our hypothesis, we aim to investigate whether breastfeeding can modify the relationship of respiratory symptoms with age, hereditary risk factors (sex, maternal atopy, and maternal asthma), perinatal factors (gestational age and cesarean delivery), and environmental factors (PM₁₀, prenatal and postnatal tobacco exposure, number of older siblings, and child care attendance) within the prospective Bern-Basel Infant Lung Development (BILD) birth cohort study from Switzerland. We look at these effects in healthy term infants, using a statistical time series approach that accounts for breastfeeding status and environmental air pollutant exposure on a week-by-week basis. The novelty of our approach is that we made comparisons within the same child on a weekly basis, so the effect of common confounders was minimized.

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BILD	Bern-Basel Infant Lung Development
GAMM	Generalized additive mixed model
PM ₁₀	Particulate matter <10 μg
RR	Risk ratio

Methods

Data was taken from the ongoing prospective BILD birth cohort study²⁶ and included 436 unselected healthy newborns born in Bern, Switzerland between April 1999 and November 2013, with complete information about breastfeeding status. Recruitment, and inclusion and exclusion criteria are described elsewhere.^{1,26} Written consent was obtained from all parents, and the Ethics Committees of the Regions of Basel and Bern approved the study.

Outcome

As previously described,^{1,8,26,27} respiratory symptoms (cough, wheezing, and difficulty breathing) were collected in weekly telephone interviews conducted by study nurses using a standardized symptom score (**Table I**; available at www.jpeds.com) with high sensitivity for lower respiratory tract infection and particularly reflects the burden of disease and health care utilization. Day and night time respiratory symptom scores range from 0-4, with scores ≥ 3 indicating severe symptoms (eg, repeated sleep disturbances, admission to hospital, or general practitioner called). The outcome was the overall symptom score calculated as the sum of day and night-time symptom scores (total possible range 0-8).

Breastfeeding

Mothers were asked weekly about their breastfeeding status until they completely stopped breastfeeding. Any breastfeeding was defined as exclusive breastfeeding, or receiving breast milk and other solids or liquids, and was treated as a binary time-dependent variable (yes or no for each week under observation). Because supplementation with formula and the introduction of solids were not regularly assessed in a standardized manner, these factors were not considered for further analysis.

Risk Factors

Detailed information on risk factors was obtained either at enrollment or during the weekly telephone interviews using a standardized questionnaire described elsewhere.²⁶ Risk factors included maternal history of atopy (defined as either atopic asthma, atopic rhinitis, or atopic dermatitis), mode of delivery (vaginal or cesarean delivery), parental educational level (low = less than 4 years of apprenticeship; middle = at least 4 years of apprenticeship, and high = tertiary education) as a marker of socioeconomic status, number of older siblings (0, 1, and ≥ 2), child care attendance, maternal smoking during pregnancy, postnatal parental smoking, and housing conditions. Cotinine levels were tested in the first urine to validate maternal smoking status. Average weekly air pollution levels in the week preceding the interview were quantitatively measured and modeled, as previously described.⁸

Statistical Analyses

Time-series data for each child consisted of weekly measures of respiratory symptom score, breastfeeding status, and time-dependent variables (eg, week of age, PM₁₀ exposure, tem-

perature, and week of study [includes seasonal variation]) (**Figure 1**; available at www.jpeds.com). The smooth (nonlinear) function of week of study also allowed us to control for unmeasured time-varying confounders such as flu epidemics. Respiratory symptom scores with a large number of zeroes (ie, weeks without respiratory symptoms) had an overdispersed Poisson distribution with a mean greater than a variance. Thus, we analyzed data using the generalized additive mixed model (GAMM) with quasi-Poisson distribution allowing for overdispersion. To account for possible temporal correlation among respiratory symptoms within each child we included an autoregressive structure with lag 1.

We first investigated the relationship between the respiratory symptom score and each exposure of interest adjusting only for week of study (includes seasonal variation), and week of age (simple model). We then adjusted (adjusted model) for exposures of interest and known confounders: sex, birth weight, gestational age, mode of delivery, maternal atopy, number of older siblings, child care attendance, maternal smoking during pregnancy, maternal education, distance to major roads, weekly average of temperature, week of study, week of age, and weekly average of PM₁₀. In order to assess the potential effect of modification by breastfeeding on the association between age, perinatal, environmental, hereditary risk factors, and respiratory symptoms, we fitted separate regression models by breastfeeding status. We included in the adjusted models the multiplicative interaction term between breastfeeding and exposure of interest to calculate *P* value for interaction.

We then repeated the analysis focusing on the first 27 weeks of life. We chose this as the cut-off because it is the median in age distribution in our study sample, and because the protective effect of breastfeeding is stronger in younger infants. **Figure 2** (available at www.jpeds.com) summarizes the statistical strategy.

In the sensitivity analysis, we selected infants without maternal smoking exposure during pregnancy (*N* = 402) in order to examine the effect of parental postnatal smoking exposure on respiratory morbidity and its modification by breastfeeding.

Estimates were expressed as a risk ratio (RR) with 95% CI. We calculated *P* trend values by applying post hoc ANOVA test. All analyses were performed with R (v 3.0.1) using mgcv package.^{28,29} A *P* value below .05 was considered to be significant.

Results

We studied 436 unselected healthy infants with complete information about their breastfeeding status from the BILD birth cohort study. Population statistics are described in **Table II**. Results from both the simple and adjusted models for the overall respiratory symptom score during first 27 weeks, and first year, of life are summarized in **Tables III** and **IV** (**Table IV**; available at www.jpeds.com),

respectively. The stratified analysis by breastfeeding and sex with *P* value for interaction are displayed in **Tables V-VIII** (**Tables VI-VIII**; available at www.jpeds.com). Additional results are available in the **Appendix** (available at www.jpeds.com).

Over the first 12 months, breastfeeding was not significantly associated with the respiratory symptom score, in either the simple or adjusted models (**Table IV**). However, a significant correlation between respiratory symptoms and breastfeeding was found in the first 6 months of life (**Table III**).

GAMM analysis showed a significant nonlinear association between week of age and respiratory symptoms in the first year of life (*P* value of <.001). The overall symptom score increased, mainly during the first 27 weeks. After that point, the symptom score did not change considerably (**Figure 3**; available at www.jpeds.com).

Table II. Characteristics of the study population (N = 436)

	Summary statistics
Anthropometrics	
Boys, n (%)	235 (53.9%)
Birth weight, mean (SD), kg	3.4 (0.4)
Length, mean (SD), cm	49 (2.0)
Gestational age, mean (SD), wk	39.8 (1.1)
Respiratory symptoms, mean (SD)	
1 y of life	
Wk with overall symptoms	5.07 (4.8)
Overall respiratory symptom score	0.25 (0.9)
27 wk of life	
Wk with overall symptoms	1.5 (2.2)
Overall respiratory symptom score	0.13 (0.6)
Duration of breastfeeding (wk)	
Breastfeeding, mean (SD)	34.7 (15.2)
Boys, mean (SD)	33.9 (15.2)
Girls, mean (SD)	35.7 (15.2)
No maternal smoking in pregnancy, mean (SD)	25.8 (16.4)
Maternal smoking in pregnancy, mean (SD)	35.7 (14.8)
Vaginal delivery, mean (SD)	34.5 (15.4)
Cesarean, mean (SD)	36.1 (14)
Risk factors	
Number of older siblings, n (%)	
1	165 (37.8%)
≥2	72 (16.5%)
Child care, n (%)	98 (22.5%)
Maternal asthma, n (%)	49 (11.2%)
Maternal atopy*, n (%)	143 (32.8%)
Maternal smoking during pregnancy, n (%)	42 (9.6%)
Parental smoking in first y of life, n (%)	89 (20.4%)
Cesarean, n (%)	69 (15.8%)
Environmental exposure	
Outdoor exposure	
Distance to major roads, mean (SD)	366.1 (508.3)
Weekly mean PM ₁₀ , mean (SD), μg/m ³	19.1 (9.9)
Weekly mean NO ₂ , mean (SD), μg/m ³	15.1 (7.3)
Weekly mean temperature, mean (SD), °C	9.7 (7.3)
Indoor exposure	
Gas stove in the home (n = 414), n (%)	32 (7.7%)
Open fireplace in the home (n = 414), n (%)	110 (26.6%)
Educational status, n (%)	
Low	118 (27%)
Middle	148 (33.9%)
High	170 (39.1%)

N, number of children; NO₂, nitrogen dioxide.

*Defined as atopic asthma, atopic rhinitis, or atopic dermatitis.

After restricting our sample size to those infants 27 weeks and younger, overall respiratory symptoms were significantly lower in breastfed infants compared with nonbreastfed ones (adjusted RR 0.70; 95% CI 0.55-0.88; **Table III**). As a consequence, our later analysis focused on respiratory symptoms during the first 27 weeks of life as a primary outcome because of the strong age-dependent association between breastfeeding and respiratory symptoms.

Male sex was a significant risk factor (adjusted RR 1.26; 95% CI, 1.03-1.54; **Table III**) for overall respiratory symptoms during the first 27 weeks of life. By stratifying according to breastfeeding status, the effect of male sex was observed in breastfed infants (RR 1.52; 95% CI 1.21-1.92; **Table V**), but not in nonbreastfed ones with evidence for interaction (*P* value for interaction = .030). In the sensitivity analysis, we performed the stratification by sex, and observed the protective effect of breastfeeding only in girls (RR 0.50; 95% CI 0.35-0.73) and not in boys (RR 0.93; 95% CI 0.68-1.27) (**Table VII**).

No significant association was found (**Table III**) between mode of delivery and respiratory morbidity. When we stratified by breastfeeding status, we observed a nonsignificant reduction of overall respiratory symptoms score in breastfed children born by cesarean (RR 0.74; 95% CI 0.53-1.04; **Table V**). In contrast, in nonbreastfed infants, the risk of having an overall respiratory symptom score 2.86 times higher was observed in the cesarean vs vaginal delivery group (95% CI 1.53-5.34; **Table V**). Further, there was significant interaction between breastfeeding and mode of delivery on respiratory symptoms (*P* value for interaction <.001).

Gestational age was not significantly associated with respiratory symptoms (**Table III**). However, in nonbreastfed children, significant decrease in respiratory morbidity occurs with an increasing gestational age (RR 0.77; 95% CI 0.61-0.97). On the other hand, there was no significant relationship between gestational age and respiratory symptoms in breastfed children in the first 27 weeks of age (**Table V**). There was significant interaction between gestational age and breastfeeding (*P* value for interaction <.001).

Smoking during the pregnancy was significantly related to respiratory symptoms in the first 27 weeks of life (adjusted RR 1.68; 95% CI 1.28-2.21; **Table III**). A stratified analysis by breastfeeding revealed the highest risk group was those infants who were not breastfed and whose mothers smoked during pregnancy (RR 3.51; 95% CI 1.66-7.40). The association between maternal smoking during pregnancy and respiratory morbidity in breastfed infants was not significant (**Table V**). In the adjusted model, the maternal smoking × breastfeeding interaction was significant (*P* value for interaction = .040; **Table V**) indicating a protective effect of breastfeeding against the harmful effects of smoking on respiratory morbidity in offspring.

The adjusted GAMM demonstrated nonsignificant positive associations of PM₁₀ with respiratory symptoms during

Table III. Analysis of factors associated with the overall respiratory symptom score during the first 27 weeks (n = 11 365)

Variables	Mean of symptom score*	Simple [†] model			Adjusted [‡] model		
		RR	95% CI	P value	RR	95% CI	P value
Breastfeeding							
No	0.27	1.0	Reference	<.001	1.0	Reference	.002
Yes	0.12	0.63	0.50-0.80		0.70	0.55-0.88	
Sex							
Girls	0.11	1.0	Reference	.009	1.0	Reference	.024
Boys	0.16	1.32	1.07-1.64		1.26	1.03-1.54	
Mode of delivery							
Vaginal	0.14	1.0	Reference	.828	1.0	Reference	.680
Cesarean	0.13	0.97	0.72-1.30		1.06	0.81-1.39	
Maternal atopy							
No	0.14	1.0	Reference	.330	1.0	Reference	.405
Yes	0.13	0.89	0.71-1.12		0.91	0.74-1.13	
Number of older siblings							
0	0.08	1.0	Reference	<.001	1.0	Reference	<.001
1	0.17	1.97	1.55-2.50		1.91	1.35-2.16	
≥2	0.21	2.38	1.81-3.12		2.83	2.11-3.81	
Child care							
No	0.14	1.0	Reference	.523	1.0	Reference	.045
Yes	0.15	1.08	0.85-1.38		1.27	1.01-1.61	
Maternal smoking in pregnancy							
No	0.12	1.0	Reference	<.001	1.0	Reference	<.001
Yes	0.28	2.19	1.67-2.87		1.68	1.28-2.21	
Gestational age, wk	0.13	0.98	0.89-1.07	.620	0.97	0.88-1.07	.564
PM ₁₀ [§]	0.13	1.13	1.05-1.22	.002	1.05	0.97-1.14	.209

n, number of wk under observation.

*Unadjusted mean of the overall symptom score.

Estimates derived from GAMM with quasi-Poisson distribution:

†Adjusted for wk of study (seasonal variation) and wk of age; and

‡Adjusted for all variables in the Table and for birth weight, maternal atopy, maternal education, older siblings, child care, weekly average of temperature, wk of study (seasonal variation), wk of age, and distance to major roads.

§RR for 10 $\mu\text{g}/\text{m}^3$ increase in the level of PM₁₀.**Table V.** Association of the overall respiratory symptom score with risk factors stratified by breastfeeding status: First 27 weeks

Exposure	Breastfeeding						P value for interaction
	Yes (n = 10 260)			No (n = 1510)			
	Mean of symptom score*	RR [†]	95% CI [†]	Mean of symptom score*	RR [†]	95% CI [†]	
Sex							.029
Girls	0.08	1.0	Reference	0.31	1.0	Reference	<.001
Boys	0.15	1.52	1.21-1.92	0.23	0.73	0.43-1.24	
Mode of delivery							
Vaginal	0.13	1.0	Reference	0.22	1.0	Reference	.329
Cesarean	0.08	0.74	0.53-1.04	0.57	2.86	1.53-5.34	
Maternal atopy							
No	0.13	1.0	Reference	0.28	1.0	Reference	.342
Yes	0.11	0.83	0.66-1.06	0.25	1.18	0.70-1.96	
Number of older sibling							
0	0.07	1.0	Reference	0.19	1.0	Reference	.945
1	0.14	2.03	1.56-2.64	0.29	0.96	0.54-1.71	
≥2	0.19	2.44	1.80-3.32	0.43	1.55	0.74-3.23	
Child care							
No	0.12	1.0	Reference	0.26	1.0	Reference	.040
Yes	0.13	1.17	0.90-1.52	0.29	1.58	0.84-2.96	
Maternal smoking in pregnancy							
No	0.11	1.0	Reference	0.20	1.0	Reference	<.001
Yes	0.19	1.32	0.93-1.86	0.53	3.51	1.66-7.40	
Gestational age, wk	0.12	1.09	0.97-1.21	0.27	0.77	0.61-0.97	.101
PM ₁₀ [§]	0.12	1.08	0.99-1.17	0.27	0.93	0.76-1.14	

*Unadjusted mean of the overall symptom score.

†RR and 95% CI derived from GAMM with quasi-Poisson distribution adjusted for all variables in the Table and for birth weight, maternal atopy, maternal education, older siblings, child care, weekly average of temperature, wk of study (seasonal variation), wk of age, and distance to major roads.

‡P value for interaction. Interaction was tested by adding the product between the breastfeeding and corresponding exposure in the adjusted model.

§RR for 10 $\mu\text{g}/\text{m}^3$ increase in the level of PM₁₀.

first 27 weeks of life, with 1.04 (95% CI 0.97-1.17) per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} , respectively (Table III). The effect of PM_{10} was stronger in breastfed infants than in nonbreastfed ones (Table V), although the interaction between breastfeeding and PM_{10} was not significant.

Discussion

In this prospective study of healthy infants from a white Central European middle-class population, we investigated the effects of individual risk factors such as age, sex, hereditary risk factors, perinatal, and environmental factors on respiratory symptoms in the first year of life, and the effect modification by any breastfeeding on each of these risk factors separately. We were able to confirm findings from other studies that the known risk factors (male sex, older siblings, and child care) were associated with more respiratory symptoms.^{1,2,14}

Maternal smoking during pregnancy and passive parental postnatal tobacco exposure are risk factors for respiratory symptoms in the first year of life.^{1,2,9,22} PM_{10} exposure in the week preceding the interview tended to be associated with an increase in overall respiratory symptoms during the first year of life, although not significant.⁸

The protective effect of breastfeeding was predominantly seen in the first 6 months of life. This finding is consistent with evidence from several studies in the literature,^{2,10,12-15} and several hypotheses related to the mechanism have been proposed. Most studies have associated the protective effect of breastfeeding with lower susceptibility to viral infections. In a few previous prospective studies, it was shown that breastfeeding reduced the occurrence of acute respiratory illness until up to 4 months of life.^{10,12,13,15} This may be partially explained by the higher concentration of the immune-modulating and antiinflammatory components in early lactation,^{12,30} as well as changes in the microbiota of breast milk.³¹

We found a stronger protective effect of breastfeeding in girls than in boys. There are several studies demonstrating that sex has an influence on the occurrence of respiratory symptoms in breastfed children in the first year of life,¹⁶⁻¹⁸ but 2 of those studies are retrospective¹⁸ and/or cross-sectional.¹⁶ Several studies explained these phenomena by sex differences in early immunity (eg, by differential responses to vaccines).^{17,18} Others hypothesized that human breast milk differently activated the immune system in boys and girls.¹⁶

The immune system is also involved in the maternal history of asthma and atopy, which are known risk factors for subsequent wheeze in offspring.³² However, both infants of atopic mothers and those showing signs of atopic dermatitis (7.3%) did not show an association with respiratory symptoms in the first year of life; and no evidence of interaction between breastfeeding and maternal atopy or atopic dermatitis of child was observed (P value $>.05$).

A protective effect of breastfeeding has been reported in a first-born infant, but not in those with older siblings,^{19,33}

with the possible mechanism that increased exposure to microorganisms in infants with older siblings overwhelms the protective effect of the breastfeeding. However, in our study we found no evidence for interaction between breastfeeding and number of older siblings.

We did not identify a relationship between gestational age and respiratory symptoms during the first year of life. Previous studies reported increased risk for neonatal morbidity⁴ and hospitalization⁵ in infants delivered in the early term period (37-38 weeks) vs the late term period (≥ 39 weeks). However, these studies used different definitions of outcomes and gestational age, and studied different age periods. In our study, respiratory symptoms increase with a decrease in gestational age in nonbreastfed infants, but not in breastfed ones. Thus, an interaction of gestational age and breastfeeding can be postulated. The underlying mechanism of the reduction of respiratory symptoms by breastfeeding may be associated with immune and nonimmune factors in the breast milk influencing the neonatal development of the lungs.³⁴

A novel and striking finding relates to cesarean delivery, which is a known and poorly understood risk factor for subsequent respiratory symptoms and asthma. Several hypotheses have been raised as to why cesarean birth may be related to later respiratory symptoms. It has been postulated that during vaginal delivery the immune system is specifically stimulated.³⁵ Others have hypothesized that bacterial colonization of the airways is modified by the birth mode.³⁶ Recent literature strongly focuses on the importance of the bacterial microbiome on the development of respiratory symptoms and asthma in young children,³⁷ and breastfeeding is known to modify the airway microbiome in offspring.³⁸ We hypothesize that such mechanisms may play a role in our finding in nonbreastfed children that the risk of respiratory symptoms is higher after cesarean vs vaginal delivery.

In our study, outdoor air pollution was estimated by accurately measured and modeled PM_{10} exposure, adjusted by season and temperature. The stratified analysis showed a stronger, but nonsignificant effect of PM_{10} air pollution in breastfed infants. This is in contrast to the findings of Dong et al.²⁰ Their retrospective study reported that breastfeeding reduced the effect of PM_{10} on respiratory symptoms in children 2-5 years of age. Because our findings are observational, we cannot make mechanistic inferences; however, chemical contamination of breast milk of mothers exposed to air pollution has been described.³⁹⁻⁴¹

Few studies describe the interaction between breastfeeding and maternal smoking on respiratory symptoms.²⁰⁻²³ In the present study, we found a modifying effect of breastfeeding on respiratory symptoms induced by prenatal smoking, but not postnatal passive smoking. Furthermore, the greater adverse effect of smoking exposure in nonbreastfed infants was observed during the prenatal, rather than the postnatal, period. A possible explanation linking the different effects of smoking exposure and PM_{10} by breastfeeding may include the difference in

tobacco and particulate matter compounds, and the time of exposure. Future research needs to obtain information as to when the mother was exposed to smoke while breastfeeding, and investigate the chemical contamination of the breast milk.

In order to study dynamic interactions between contributing factors, large datasets are needed. A prospective study design of 436 children, each with 50-54 observations, leads to 22 820 observed weeks. One strength of our study was that we sought to avoid detection bias by prospectively asking mothers weekly whether or not they are breastfeeding. This allowed us to clearly define the outcomes of breastfeeding and assess breastfeeding as a time-varying variable. One difficulty was quantifying the addition of formula supplementation (partial breastfeeding). The method of formula feeding and introduction of solids in our healthy group was heterogeneous and, therefore, statistical power did not allow us to perform a subgroup analysis. Thus, we used only the exact time point when mothers completely weaned their children. Comparing exclusive and nonexclusive breastfeeding could reinforce our findings, given that we observed a greater benefit of breastfeeding in exclusively breastfed infants.^{12,15,17,23} Despite the long study period, no systematic changes in the assessment of the exposures and outcomes were observed. A further limitation may be the low to medium levels of air pollution in Switzerland, which made it difficult to compare findings with more polluted areas of the world. Whereas risk factors were chosen a priori based on evidence from previous studies, we did not apply a Bonferroni correction for the number of interaction tests. Even after the Bonferroni correction (0.05/8 interaction tests = 0.00625) the interactions between breastfeeding and gestational age, and mode of delivery remained significant.

Our study suggests that breastfeeding attenuates the effects of risk factors such as sex, age, gestational age, cesarean delivery, and prenatal maternal tobacco smoking in healthy term infants. In contrast, there is no evidence suggesting that breastfeeding modifies the association of respiratory symptoms with maternal atopy, child care attendance, older siblings, postnatal passive smoking, or PM₁₀.

The common mechanism of the protective effects of breastfeeding needs to be elucidated in future studies. Possible hypotheses may relate to immune development and susceptibility to viral infections. We found that breastfeeding had its strongest protective effect in the first 6 months of life, in girls, and in infants exposed to maternal tobacco smoking. The most striking effect, however, was that infants born by cesarean delivery may profit the most from breastfeeding. We hypothesize that altered immune development or development of the airway microbiota after cesarean birth may be mechanisms of interest. Confirmation of these findings in future studies could have an important impact on health policy. ■

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Appendix

Of the 436 participants, 9 observations were excluded from the sample: 7 infants and 3 twin siblings did not complete the 12 months of follow-up; we did not have information about the mode of delivery, older siblings, or childcare, for 3 of the infants; and we did not have home address information for another 3 infants. Population statistics are described in detail in [Table II](#). The mean duration of breastfeeding was 34.7 weeks; it was shorter in smoking mothers than in nonsmoking mothers ([Table II](#)). Six (1.38%) infants were not breastfed at all.

Protective Effects of Breastfeeding against the Harmful Impact of Tobacco Exposure on Respiratory Symptoms

A sensitivity analysis with the additional adjustment for parental postnatal smoking exposure indicated that the effect of maternal smoking during pregnancy on overall respiratory symptoms was slightly attenuated in breastfed (risk ratio [RR] 1.24; 95% CI 0.85-1.80) and nonbreastfed infants (RR 2.72; 95% CI 1.18-6.30). The interaction between breastfeeding and maternal smoking in pregnancy remained significant (P value for interaction = .044) (data not shown).

In the subgroup of the infants without maternal smoking exposure during pregnancy ($n = 402$), postnatal parental smoking was associated with a 1.35 increased risk of overall respiratory symptom score in the first 27 weeks of life (95% CI 1.06-1.71; [Table VIII](#)). Here, we found no evidence for interaction between postnatal parental smoking exposure and breastfeeding in relation to respiratory symptoms (P value for interaction = .210; [Table VIII](#)). However, the breastfed infants tended to have fewer respiratory symptoms (RR 1.25; 95% CI 0.94-1.65) than nonbreastfed ones (RR 1.76; 95% CI 0.88-3.47) ([Table VIII](#)).

Breastfeeding and Other Factors

Being in childcare and having older siblings are important risk factors for developing respiratory symptoms in infancy ([Table III](#)). In the interaction models, we did not find evidence for interaction between either number of older

siblings and breastfeeding, or attending childcare and breastfeeding, on respiratory symptoms ([Table V](#)).

We additionally performed the analysis including week of childcare as a time-dependent variable over the entire first year of life, we found that in the first 3 months there was a lack of exposure (almost none of the infants were in child care); at the end of the first year, very few infants were still breastfed. Thus, in order to have enough statistical power with this type of analysis, we focussed on the time period between 12 and 36 weeks of age. In performing the analysis with this timeframe, we produced similar results to our first analysis, where we treated (child care) as a time independent categorical variable (data not shown).

Maternal history of atopy ([Table III](#)) and maternal asthma (data not shown) did not have an impact on respiratory morbidity in the first year of life. There was no interaction between breastfeeding and maternal atopy ([Table V](#)) or maternal asthma (data not shown).

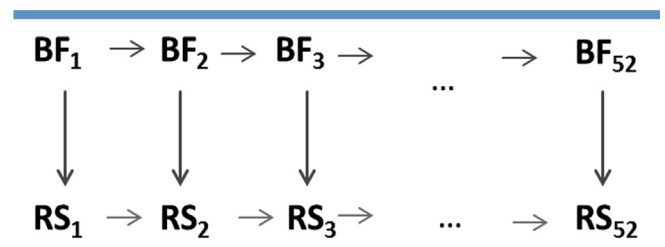


Figure 1. Schematic representation of relationship between breastfeeding and respiratory symptoms in the first year of life. BF represents the breastfeeding status and RS represents the overall respiratory symptoms score for each week under observation (the possible range from 1-50/54).

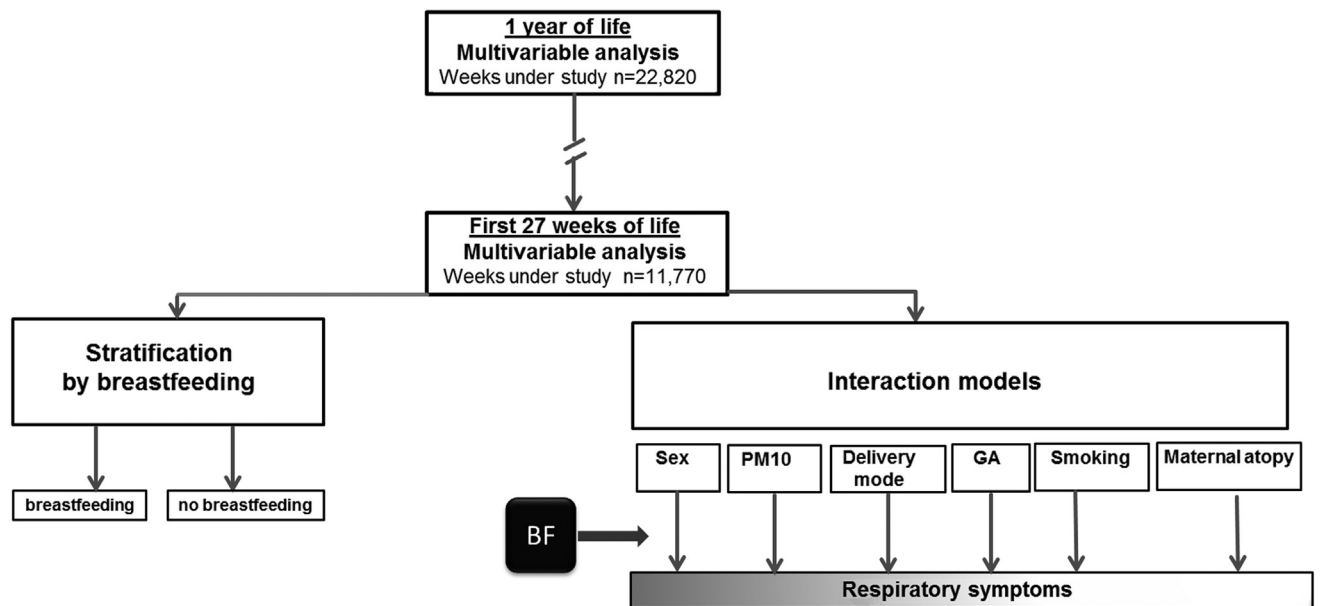


Figure 2. Flowchart of statistical analysis (first 27 weeks). Results are presented in a 2-way but congruent manner. *Right side*, the results of the GAMM with quasi-Poisson distribution describing the effect of the risk factors on symptoms and their interactions with BF ([Table III](#)). *Left side*, the association of the overall RS score with risk factors stratified by BF status ([Table III](#)).

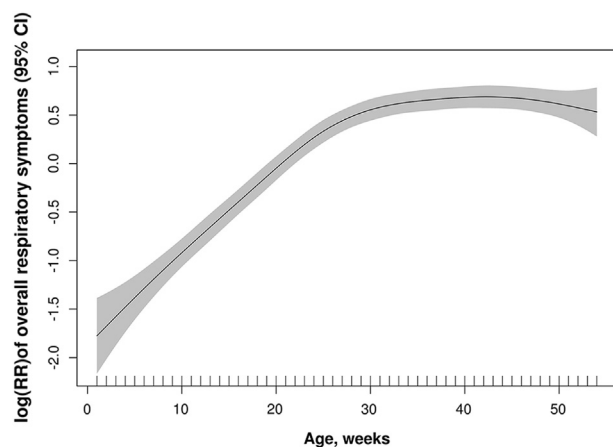


Figure 3. Change in the risk of developing overall respiratory symptoms during the first year of life ($df = 4.24$; P value $< .0001$). The *shaded regions* denote the 95% CI. Results were obtained from the GAMM adjusted for sex, gestational age, mode of delivery, breastfeeding, birth weight, maternal atopy, older siblings, child care, maternal smoking during the pregnancy, temperature, week of study, distance to major roads, maternal education, and PM_{10} .

Table I. Symptom score used in weekly phone calls*

Symptom score	Daytime symptoms (cough, wheeze, or breathing difficulties)	Night-time symptoms (cough, wheeze, or breathing difficulties)
0	None	None
1	Slight; no treatment given	Slight; sleep not disturbed
2	Required treatment but no outside help	Sleep disturbed once; no help required
3	Severe; required help from GP	Sleep disturbed more than once or child needed help
4	Very severe; admitted to hospital	Sleep very disturbed or GP called

GP, general practitioner.

*Reprinted from Silverman et al²⁷ with permission from BMJ Publishing Group Ltd.**Table IV.** Analysis of factors associated with the overall respiratory symptom score during 1 year of life (n = 22 820)

Variables	Mean of symptom score*	Simple [†] model			Adjusted [‡] model		
		RR	95% CI	P value	RR	95% CI	P value
Breastfeeding				.403			.605
No	0.35	1.0	Reference		1.0	Reference	
Yes	0.21	0.95	0.83-1.08		0.97	0.85-1.10	
Sex				<.001			.001
Girls	0.22	1.0	Reference		1.0	Reference	
Boys	0.29	1.32	1.18-1.49		1.22	1.09-1.38	
Mode of delivery				.107			.106
Vaginal	0.26	1.0	Reference		1.0	Reference	
Cesarean	0.23	0.87	0.74-1.03		0.88	0.74-1.03	
Maternal atopy				.503			.599
No	0.26	1.0	Reference		1.0	Reference	
Yes	0.24	0.96	0.84-1.09		0.97	0.86-1.09	
Number of older siblings				<.001			<.001
0	0.20	1.0	Reference		1.0	Reference	
1	0.30	1.50	1.32-1.70		1.42	1.25-1.62	
≥2	0.31	1.54	1.31-1.80		1.57	1.33-1.85	
Child care				<.001			<.001
No	0.23	1.0	Reference		1.0	Reference	
Yes	0.32	1.45	1.28-1.64		1.53	1.35-1.74	
Maternal smoking in pregnancy				.078			.052
No	0.25	1.0	Reference		1.0	Reference	
Yes	0.30	1.18	0.98-1.43		1.21	0.99-1.47	
Gestational age, wk	0.26	0.95	0.90-1.00	.051	0.95	0.90-1.002	.060
PM ₁₀ [§]	0.26	1.10	1.06-1.15	<.001	1.04	0.99-1.08	.087

*Unadjusted mean of the overall symptom score.

Estimates derived from GAMM with quasi-Poisson distribution:

†Adjusted for wk of study (seasonal variation) and wk of age; and

‡Adjusted for all variables in the Table and for birth weight, maternal atopy, maternal education, older siblings, child care, weekly average of temperature, wk of study (seasonal variation), wk of age, and distance to major roads.

§RR for 10 $\mu\text{g}/\text{m}^3$ increase in the level of PM₁₀.

Table VI. Association of the overall respiratory symptom score with risk factors stratified by breastfeeding status: 1 year of life

Exposure	Breastfed						P value for interaction [†]
	Yes (n = 15 152)			No (n = 7668)			
	Mean of symptom score [*]	RR [†]	95% CI [†]	Mean of symptom score [*]	RR [†]	95% CI [†]	
Sex							.014
Girls	0.16	1.0	Reference	0.32	1.0	Reference	
Boys	0.24	1.40	1.21-1.63	0.37	1.03	0.86-1.24	
Mode of delivery							.012
Vaginal	0.22	1.0	Reference	0.35	1.0	Reference	
Cesarean	0.15	0.72	0.58-0.90	0.40	1.02	0.80-1.30	
Maternal atopy							.372
No	0.22	1.0	Reference	0.36	1.0	Reference	
Yes	0.18	0.91	0.78-1.07	0.35	1.04	0.86-1.26	
Number of older siblings							.754
0	0.16	1.0	Reference	0.28	1.0	Reference	
1	0.24	1.51	1.27-1.79	0.40	1.34	1.10-1.64	
≥2	0.26	1.64	1.33-2.01	0.43	1.51	1.16-1.98	
Child care							.959
No	0.19	1.0	Reference	0.32	1.0	Reference	
Yes	0.27	1.48	1.26-1.75	0.46	1.53	1.25-1.87	
Maternal smoking in pregnancy							.872
Yes	0.20	1.0	Reference	0.35	1.0	Reference	
No	0.21	1.17	0.88-1.55	0.39	1.31	0.99-1.72	
Gestational age, wk	0.21	1.01	0.94-1.09	0.35	0.89	0.82-0.97	.032
PM ₁₀ [§]	0.21	1.06	1.00-1.12	0.35	1.02	0.96-1.08	.296

n, number of wk under observation.

^{*}Unadjusted mean of the overall symptom score.[†]RR and 95% CI derived from GAMM with quasi-Poisson distribution adjusted for all variables in the Table and for birth weight, maternal atopy, maternal education, older siblings, child care, weekly average of temperature, wk of study (seasonal variation), wk of age, and distance to major roads.[‡]P value for interaction. Interaction was tested by adding the product between the breastfeeding and corresponding exposure in the adjusted model.[§]RR for 10 $\mu\text{g}/\text{m}^3$ increase in the level of PM₁₀.**Table VII.** Adjusted association^{*} of the overall respiratory symptom score with the breastfeeding stratified by sex (first 27 weeks)

	Sex					
	Girls (n = 5426)			Boys (n = 6344)		
	RR	95% CI	P value	RR	95% CI	P value
Breastfeeding			.0002			.629
No	1.0	Reference		1.0	Reference	
Yes	0.50	0.35-0.73		0.93	0.68-1.27	

^{*}Estimates derived from GAMM with quasi-Poisson distribution adjusted for birth weight, gestational age, mode of delivery, maternal atopy, maternal education, maternal smoking during the pregnancy, older siblings, child care, weekly average of temperature, wk of study (seasonal variation), wk of age, distance to major roads, and PM₁₀.

Table VIII. Adjusted* association of the postnatal parental smoking with overall respiratory symptom score in infants without maternal smoking exposure during the pregnancy (N = 402) (first 27 weeks of life)

Exposure	Complete data (N = 9250)		Breastfed				P value [†]
			Yes (n = 8127)		No (n = 1123)		
	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value	
Parental smoking in the first y of life		.014		.121		.115	.206
No	Reference		Reference		Reference		
Yes	1.35 (1.106-1.71)		1.25 (0.94-1.65)		1.72 (0.88-3.37)		

N, number of individuals; n, number of observations.

*Adjusted for sex, birth weight, gestational age, maternal atopy, maternal education, older siblings, child care, breastfeeding, weekly average of temperature, wk of study (seasonal component), wk of age, distance to major roads, and PM₁₀.

†P value for interaction. Interaction was tested by adding the product between the breastfeeding and corresponding exposure in the multivariable model.