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## Long-Term Effects of Breastfeeding, Maternal Smoking During Pregnancy, and Recurrent Lower Respiratory Tract Infections on Asthma in Children

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### Abstract

The effect of breastfeeding on asthma is controversial, which may be explained by related and interacting early childhood risk factors. We assessed the joint effects of a risk-triad consisting of maternal smoking during pregnancy, breastfeeding for less than 3 months, and recurrent lower respiratory tract infections (RLRTI) on physician-diagnosed childhood asthma. The association was assessed in the Isle of Wight birth cohort study (1989–1990) using a repeated measurement approach with data collection at birth, and at ages 1, 2, 4, and 10 years. The population consists of 1,456 children recruited between January 1989 and February 1990. Prenatal smoking, breastfeeding for less than 3 months, and recurrent lower respiratory infections (RLRTI) were combined into eight risk-triads. Relative risks (RR) and 95% confidence intervals were estimated with a log-linear model. The risk-triad involving RLRTI in infancy, maternal smoking during pregnancy, and breastfeeding for less than 3 months showed a stronger association with asthma at ages 4 and 10 compared to other risk-triads (RR of 5.79 for any asthma at ages 1, 2, 4, and 10; and 3.1 for asthma at ages 4 and 10). Of the three individual risk factors, RLRTI appeared to be the major driver of the combined effects in the risk-triads. The effect of RLRTI on asthma was modified by breastfeeding. Breastfeeding for  $\geq 3$  months also attenuated the effect of prenatal smoking on asthma in children without RLRTI. A high proportion of asthma cases in childhood can be prevented by promoting breastfeeding, by preventing smoking during pregnancy, and by avoidance of recurrent lower respiratory tract infections in early childhood.

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## Keywords

asthma; cohort study; breastfeeding; smoking; child; lower respiratory tract infections

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## INTRODUCTION

The prevalence of asthma, a chronic disease of the respiratory system, has increased dramatically within the last three decades. Asthma has become a critical clinical and public health problem that is diagnosed in 7–15% of U.S. children (1–3). In order to prevent asthma, it is important to identify modifiable risk factors. This work focuses on three intertwined risk factors: smoking during pregnancy, breastfeeding for less than 3 months, and lower respiratory tract infections.

There is evidence that maternal smoking is related to diminished initiation and duration of breastfeeding (Table 1) (4–7). In addition, several studies have shown that maternal smoking during pregnancy increases the prevalence of asthma attacks in the offspring (8–17), not only in the first years but also later in childhood (18,19). Mechanistically, prenatal smoking may alter intrauterine pulmonary development and function (20) or the newborn's immune system (21).

There is also evidence that smoking during pregnancy leads to a higher risk of recurrent lower respiratory tract infection (RLRTI) in children (22,23), in particular in early childhood (12, 22,24,25). There are contradictory reports in the literature on whether the protective effect of breastfeeding against asthma persists until late childhood (the first decade of life) (4–7,26–28). Against that, breastfeeding is considered to protect against lower respiratory tract infections (29,30). In turn, RLRTI confers an increased risk of airway hyperresponsiveness, bronchial obstruction and asthma later in childhood (24,31–37). In early childhood, respiratory tract infections (viral or bacterial) resemble asthmatic manifestations (e.g., wheezy bronchitis). As the prevalence of RLRTI declines with age, this overlap diminishes and the diagnosis of asthma becomes more certain.

Previous studies that followed children at least up to age 10 have considered the individual effects of breastfeeding, smoking, and RLRTI on asthma and reported inconsistent results (Table 1) (4–7,26–28). The studies reviewed enrolled children at different ages and had varying durations of follow-up. Three of these studies found no protective effect of breastfeeding on asthma (4,6,28). Wright et al. reported a protective effect of breastfeeding conditional upon the absence of maternal asthma (5); on the other hand, Matheson et al. demonstrated an effect of breastfeeding in early childhood conditional upon the presence of maternal asthma (7). In contrast, Saarinen et al. showed that breastfeeding for more than one month was associated with a decreased prevalence of asthma at 17 years of age, independent of atopic heredity (26).

No study has yet investigated the combined effects of maternal smoking, breastfeeding for at least 3 months, and RLRTI. Since the three elements are associated (Figure 1), to some extent as intervening variables, treating them as independent risk factors (as in the reports presented here) may be inappropriate (Table 1). The purpose of this work is to characterize the joint effects of these three risk factors on childhood asthma. The three risk factors were combined into one variable, which we refer to as a risk-triad.

## METHODS

### Population and Data Collection

The Isle of Wight (IOW) Birth Cohort Study represents an unselected whole population birth cohort based on the Isle of Wight, U.K. The Isle of Wight is an island (13 × 23 miles) just off the South coast of England with a resident population of 130,000. The ethnic background of the island residents is mainly Caucasian. While the population is neither geographically nor genetically isolated, it is stable to the extent that the majority of participants in the cohort have not moved away and are thus available for follow-up. The intention was to prospectively study a whole population cohort for the development of asthma and allergic diseases and identify genetic and environmental risk factors relevant to these conditions. Enrollment took place at birth. Of the 1,536 children born on the isle between January 1, 1989 and February 28, 1990, a cohort of 1,456 consenting children was recruited after approval of the Local Research Ethics Committee. Data were collected after delivery, and at ages 1, 2, 4, and 10 years. Informed written parental consent was obtained from all participants. Details of the study population have been described elsewhere (38–40).

After delivery, maternal smoking, gender of the child, and birth weight were ascertained from birth and obstetric records and by questionnaire. At ages 1, 2, 4, and 10 years, questionnaires were used to obtain information on breastfeeding duration (we dichotomized at 3 months), RLRTI, and asthma. A study physician evaluated symptoms of asthma at ages 1, 2, 4 and 10 years. At age 10, the International Study of Asthma and Allergy in Childhood (ISAAC) written questionnaire was used to assess respiratory and allergy symptoms. At the ages of 4 ( $n = 981$ ) and 10 years ( $n = 1036$ ), skin prick tests (SPT) with a standard battery of aeroallergens were administered (41).

### Variable Definition

Any active smoking of the mother during pregnancy was coded as prenatal smoking exposure. Low birth weight was defined as less than 2,500 grams. At birth, we obtained maternal history of asthma. Recurrent lower respiratory tract infection (RLRTI) was defined as two or more episodes of parental report of chest infections, based on productive cough lasting for five or more days in the preceding 12 months. Antibiotic usage and wheezing were not prerequisites for the diagnosis of RLRTI. Information on recurrent chest infection was collected at ages 1 and 2 years. Due to the lack of consensus in the literature on the categorization of duration of breastfeeding (Table 1), we dichotomized duration into  $\geq 3$  months or  $< 3$  months. The rationale for choosing this cutoff is that breastfeeding for at least three months would potentially maximize anti-inflammatory benefits of breast milk (42), in addition to providing comparability to previous publications of this cohort (23,34,41,43–49).

The operational definition for asthma was a history of physician-diagnosed asthma and at least one episode of wheezing in the preceding 12 months. For early childhood, an alternative minimum criterion for asthma diagnosis was a history of three separate episodes of persistent wheezing ( $> 3$  days duration), because an asthma diagnosis is rarely made for infants/young children. The presence of asthma was investigator-determined using these criteria at ages 1, 2, 4 and 10 years.

Due to the associations among smoking, breastfeeding for at least 3 months, and RLRTI, and because breastfeeding  $\geq 3$  months and chest infection are also likely to represent intervening variables in the path to asthma, these three risk factors were combined into one variable with eight categories, called risk-triads.

## STATISTICAL ANALYSES

Cross-tabulation was used to assess the prevalence of asthma in the various subgroups. Because asthma was ascertained at four time periods, repeated measurements analyses were applied to obtain odds ratios and their 95% confidence intervals, controlling for confounders (gender, low birth weight [ $<2,500$  g], child's age at examination, and maternal history of asthma). The fact that the outcome variable was dichotomous and that the goal was to estimate marginal probabilities controlling for the within-child effect, provided the rationale for utilizing generalized estimated equation (GEE) analysis (50). Using GEE, we estimated the association between the different risk-triads of smoking, breastfeeding for at least 3 months, and RLRTI and the outcome, asthma. Since asthma is not a rare disease, odds ratios are likely to overestimate relative risks. To directly estimate relative risks, we applied a log-binomial model.

Because the risk-triads define mutually exclusive settings, we tested each triad separately, comparing it with the reference (non-smoking, breastfeeding for at least 3 months, and no RLRTI) and controlling for all confounders. Based on previous finding of an overlap in the diagnoses of RLRTI and asthma in early childhood, we first investigated repeated asthma occurrences from ages 1 to 10 and then compared the effect of the risk factors for asthma occurrence in later childhood (4–10 years). Data analysis was performed with the SAS system (51).

## RESULTS

Among the 1,456 children in the original cohort, 1,360 were followed to age 10, and 1,336 had information available on the three risk factors and asthma (Table 2). The proportions of smoking, breastfeeding for at least 3 months, and RLRTI were 25.3, 44.7, and 7.4%, respectively. The prevalence of asthma varied with age: 9.6% (128/1336) at age 1; 10.7% (128/1192) at age 2; 15.0% (167/1113) at age 4, and 12.8% (156/1224) at age 10.

Fourteen percent of the children whose mothers smoked during pregnancy developed RLRTI during infancy compared to 5.2% of the children without prenatal maternal smoking (data not shown). The proportion of breastfeeding  $\geq 3$  months was 26.1% in mothers who smoked and 51.1% in non-smokers. Among children breastfed  $\geq 3$  months, 5% had RLRTI in infancy whereas 9.2% of those not breastfed  $\geq 3$  months developed RLRTI.

The triad-category of no smoking, breastfeeding for at least 3 months, and no RLRTI comprised 34.4% of the study population (Table 3). Of these, 11.8% had asthma at age 10 (Figure 2). On the other hand, the category of smoking, breastfeeding  $< 3$  months, and no RLRTI made up 15.7% of the study population and 16.9% of this triad-category had asthma at age 10 (Figure 2).

Overall, triad-categories in which the children had RLRTI showed a higher prevalence of asthma at all time periods (Figure 2). Of the children who were characterized by prenatal smoking exposure, breastfeeding  $< 3$  months, and RLRTI, 53.1% had asthma at age 1 and 29% had asthma at age 10. Although exposed to prenatal smoking, children breastfed for at least 3 months who did not develop RLRTI, had the lowest prevalence of asthma overall (3.9 at age 1 and 4.5% at age 10).

When analyzing the three risk factors as independent predictors, only RLRTI showed a 4.16-fold increase in the relative risk of asthma in the first decade of life and a 2.5-fold increased risk for asthma at ages 4 and 10 (Table 3).

For the model using the risk-triads, the reference was no smoking, breastfeeding for at least 3 months, and no RLRTI (label 8, Table 3). The following contrasts are based on the principle

that variation in one factor while keeping the other two factors constant will provide information on the impact of the one factor.

When comparing children with regard to RLRTI (comparing label 1 to label 8; 2 to 5; 3 to 7; and 4 to 6; Table 3), children with RLRTI had a much higher relative risk of asthma at ages 1–10. Second, regarding breastfeeding  $\geq 3$  months and comparing label 4 and 1 (Table 3), breastfeeding for at least 3 months modified the impact of RLRTI in children not exposed to cigarette smoke (RR = 4.93 and RR = 5.51). In addition, contrasting label 2 and 3 indicates (RR = 5.79 and RR = 4.03) that breastfeeding  $\geq 3$  months also modifies the relative risk of asthma for recurrent infections if prenatal exposure to cigarette smoke is present.

Third, comparing labels 5 and 7, the presence of breastfeeding for more than three months reduces the adverse effects imposed by cigarette smoking (RR = 1.71 and RR = 0.72) also in the absence of RLRTI. Fourthly, by comparing labels 6 and 8, breastfeeding for at least 3 months is not a protective factor if none of the two other risks are present. Lastly, in children without RLRTI and breastfed for  $< 3$  months (label 5 and 6), maternal smoking during pregnancy showed an increased risk for asthma (RR = 1.71 and RR = 1.05).

Comparing the relative risks of asthma for ages 1, 2, 4 and 10 with the relative risk at age 4 and 10, provides insights into long-term effects. In addition, focusing on the relative risk at ages 4 and 10 also diminishes the problem of overlapping diagnoses of asthma and RLRTI, which may be present at ages 1 and 2. The relative risks in labels 1 to 4, indicate that RLRTI is more strongly associated with early onset asthma, but much less so with later onset. Also at ages 4 and 10, breastfeeding for at least 3 months reduces the relative risk of RLRTI (label 1 vs. 4: RR = 2.32 and 3.39) and the negative impact of prenatal smoking in children with RLRTI (label 2 vs. 3: RR = 3.10 and RR = 0.79) and without RLRTI (label 5 vs. 7: RR = 1.41 and RR = 0.47).

## DISCUSSION

This study shows that the risk-triad of recurrent lower respiratory tract infections (RLRTI) in infancy, breastfeeding  $< 3$  months, and prenatal smoking was a strong risk factor for the occurrence of asthma in the first decade. The presence of breastfeeding  $\geq 3$  months attenuates the adverse effect of RLRTI and prenatal smoking. Our findings support the assumption that the protective effect of breastfeeding  $\geq 3$  months in children affected by RLRTI or maternal smoking depends on the balance of immune, infectious, and developmental mechanisms related to this triad of risk factors.

Epidemiologic studies have shown that breastfeeding, RLRTI, and smoking are risk factors for asthma; some may have direct effects, whereas others act as intervening variables (7,13, 23,24,52). For instance, smoking during pregnancy is associated with absence of breastfeeding for at least 3 months and also increases the risk of RLRTI (Figure 1). Hence, epidemiologically, it is not appropriate to treat these variables as single independent predictors. This analytical challenge may account for the conflicting findings regarding smoking, breastfeeding, and RLRTI reported in previous studies (4–6,26). However, there are only a few studies that consider the combined effects of these risk factors. Recently, Guedes et al. reported that maternal smoking reduces the protective effect of breastfeeding (53). We believe that the risk-triad approach in this study provides an appropriate way to take the interrelatedness of these factors into account.

Our findings are not likely a result of a selection bias. The proportion of participation was 80.2% ( $n = 1167$ ), 80.6% ( $n = 1,174$ ), 83.7% ( $n = 1,218$ ), and 94.3% ( $n = 1,373$ ) at ages 1, 2, 4, and 10, respectively. This analysis is based on 86.4% of the original cohort.

Parental information and assessments by the study physician were collected prospectively for the preceding 12 months at ages 1, 2, 4, and 10. This approach reduces information bias. Repeated assessment of asthma in this sample is a strength since the analysis is not dependent on transitional occurrence of asthma at a specific age. We have previously shown that repeated measurement analysis of asthma (age 1, 2, 4, 10) estimates the risk for persistent asthma since it takes the frequency (persistence) of the occurrence into account (46).

Confounders controlled for include low birth weight, gender, child's age and maternal history of asthma in the repeated measurement analysis. Previous studies have found significant associations between low birth weight and asthma (54,55). Additionally, we chose to adjust for gender, knowing that boys appear to be more predisposed to asthma (56) and considering that the relationship between breastfeeding and asthma can differ by gender (52).

A potential limitation is that exposure definitions in our sample were based on parental reports (smoking during pregnancy, RLRTI, and breastfeeding for at least 3 months). Previous studies have shown that maternal reports of smoking were reliable (8,10,12). To avoid uncertainties with the time-order of smoking, breastfeeding for at least 3 months, and RLRTI, we choose to use smoking during pregnancy as exposure. Our data shows that all mothers who smoked during pregnancy continued to smoke after delivery.

Another limitation is the fact that the information collected did not differentiate the etiology of RLRTI. Lower respiratory tract infections in childhood may be of viral origin (influenza, parainfluenza, respiratory syncytial virus and rhinovirus) or bacterial (22,24,25). Studies based on laboratory analyses have shown that wheezing associated with rhinovirus infections is more likely to progress to asthma in childhood (25,57–60). Independent of pathogen specificity, RLRTI has been shown to be strongly associated with childhood wheezing and asthma (23, 61). Our findings are consistent with previous studies and sustain the idea that even though not differentiated, RLRTI represent a strong risk factor for asthma development (25,57–60). On the other hand, one can argue that RLRTI in infancy is not a risk factor, but an indicator of asthma. However, to be an indicator of asthma, we would anticipate that the majority of children with RLRTI at age 1 would develop asthma. Contrary to this expectation, our data show that only 62% of the children with RLRTI at age 1 had asthma at age 1, 51% at age 2, 42% at age 4, and only 25% at age 10 (data not shown).

Interestingly, the prenatal and early childhood risk-triads studied had long-term effects detectable even at age 10. All the component risk factors are modifiable. However, prevention efforts targeted at these factors may require more than a single risk factor approach, namely to improve living conditions and behavior of pregnant women. In addition, however, we also need to determine and reduce risk factors that increase the susceptibility to RLRTI.

In summary, our results contribute to the existing evidence supporting the role of maternal smoking and recurrent chest infections in asthma development and the mediator role of breastfeeding for at least 3 months. At the population level, the impact of the risk-triad depends on the prevalence of exposure in the study population. The population-attributable risk percent is the proportion of decrease in asthma cases that would be achieved if the effects of the respective triads were completely reversible and there was complete exposure cessation in the general population. We estimated this quantity using the Levin's formula (62). For instance, the prevalence of asthma at age 1 to 10 in the population could be reduced by 31% if, in combination with extending breastfeeding duration beyond 3 months, maternal smoking and recurrence of lower respiratory infection is prevented (label 2, 4, and 5 in Table 3). Focusing on age 4 and 10, breastfeeding promotion in combination with prevention of smoking and recurrence of respiratory infections, would reduce the prevalence of asthma by 17%. From a public health standpoint, due to the associations between prenatal smoking and RLRTI and

between breastfeeding and RLRTI, RLRTI prevention could be achieved through smoking cessation and breastfeeding promotion.

## CONCLUSION

We suggest that future etiologic studies not focus on individual early childhood risk factors, but apply combinations of known risk factors such as the risk-triad approach used in this analysis. We believe that our results provide strong evidence for asthma reduction by promoting breastfeeding, by preventing smoking during pregnancy, and thus reducing the risk of lower respiratory tract infections, an important risk factor for asthma in early and late childhood.

## Abbreviations

BF  $\geq$  3 m, breastfeeding for at least 3 months; BF < 3 m, breastfeeding for less than 3 months; RLRTI, recurrent lower respiratory tract infections.

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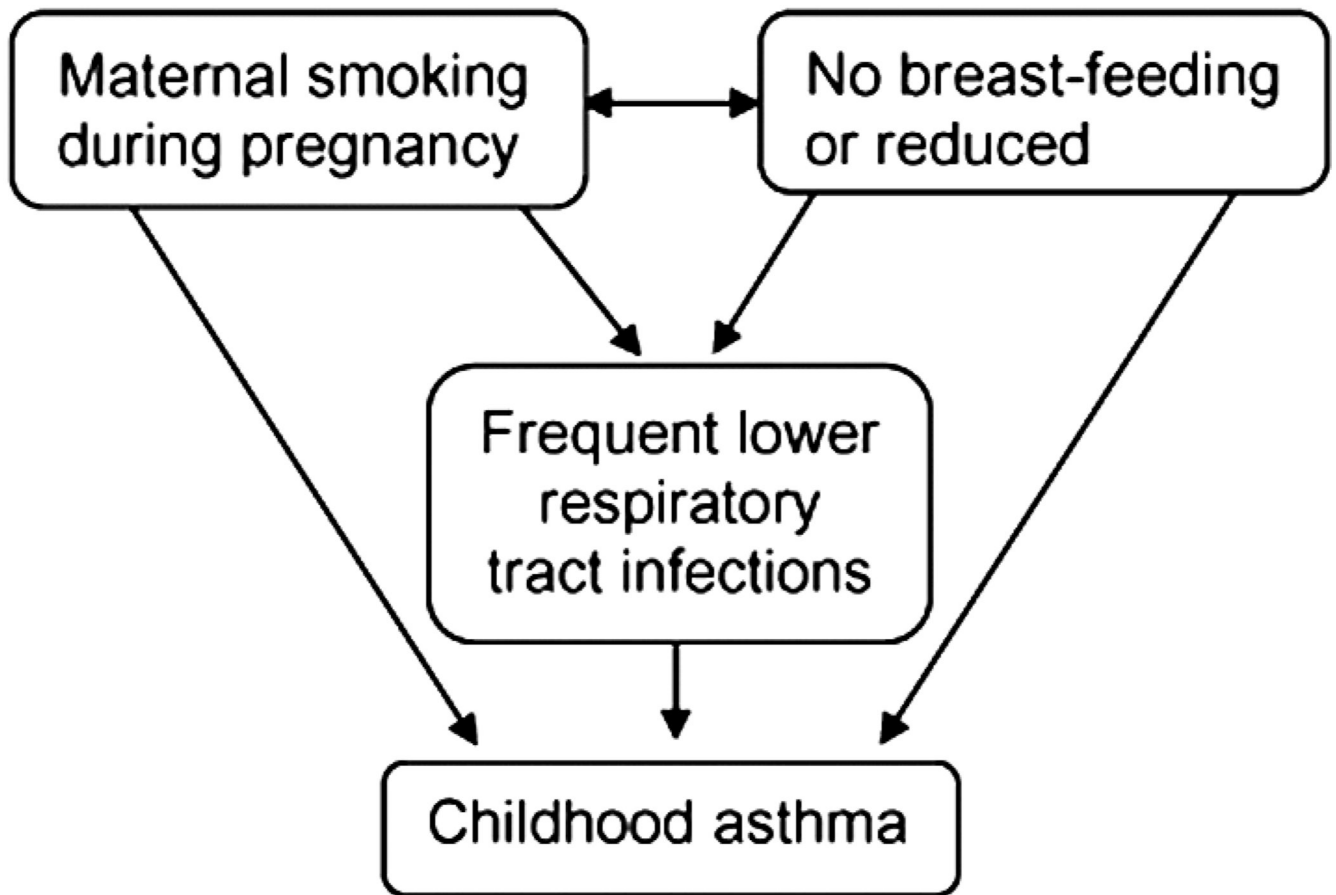
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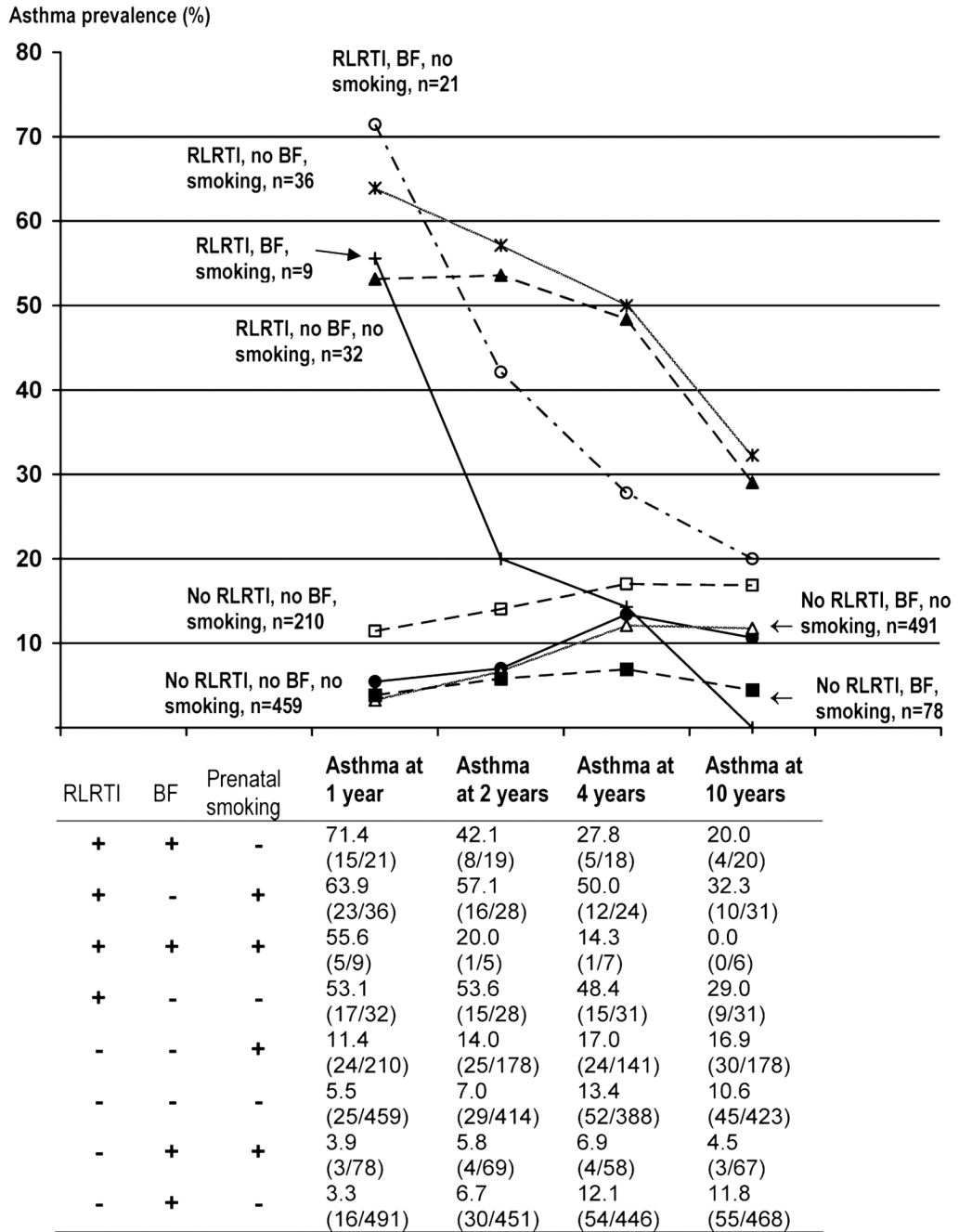


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**FIGURE 1.**  
The early childhood asthma risk-triad.



**FIGURE 2.** Prevalence of asthma at ages 1, 2, 4, 10, and the various combinations (triads) of smoking, RLRTI and breastfeeding for at least 3 months.

**TABLE 1**  
 Studies with a long-term follow-up asthma (minimum 10 years) and breastfeeding.

Author and Year	Definition of asthma	Assessed at ages	Duration of breastfeeding	Breastfeeding (BF) effects	Smoking	Respiratory tract infections (RTI)
Saarininen et al. 19954	Asthma defined as either: <ul style="list-style-type: none"> <li>• allergic asthma diagnosed</li> <li>• <math>\geq 3</math> episodes of wheezing (at 3–10 years)</li> <li>• wheezing history + <math>\geq 3</math> respirat. Infect. (at 3–5 yrs)</li> <li>• wheezing history + rhinoconjunctival symptoms</li> </ul>	3 years 5 years 10 years 17 years	$\leq 1$ months 1–6 months $\geq 6$ months	Protective against infections; Protective against respiratory allergy at 17 years (BF > 1 month)	Controlled for the effect of smoking; smoking for 5 yrs post-delivery is not associated with atopic disease in adolescence.	No association between susceptibility to RTI in infancy and atopic disease in adolescence.
Wright et al. 20017	<ul style="list-style-type: none"> <li>• Physician diagnosis of asthma + symptoms on <math>\geq 2</math> questionnaires</li> <li>• Recurrent wheeze (<math>\geq 4</math> episodes during past yr)</li> </ul>	6 years 9 years 11 years 13 years	0 < 4 months $\geq 4$ months	Children $\leq 3$ years: lower prevalence of recurrent wheeze (BF $\geq 4$ months); Children $> 3$ years: higher prevalence of recurrent wheeze if the mother had asthma.	Controlled for the effect of smoking	Predominately infectious wheeze until 6 years included. The authors acknowledge a wheeze-asthma overlap.
Takemura et al. 20019	Questionnaire: <ul style="list-style-type: none"> <li>• Ever asthma</li> <li>• Attack of wheezing</li> <li>• Physician diagnosis</li> </ul>	Age 6–13 years	0–3 months	Increased risk of asthma in children who were breastfed.	Smoking at the time of the survey, not in pre- or postnatal.	Not included
Sears et al. 20026	<ul style="list-style-type: none"> <li>• Questionnaires</li> <li>• Pulmonary function tests</li> <li>• Bronchial challenge tests</li> <li>• Allergy skin tests</li> </ul>	From age 9–26 yrs, every 2–5 yrs	0 $\geq 1$ months	Increased risk of asthma (BF $\geq 1$ month);	Controlled for the effect of smoking	Not included
Burgess et al. 20068	Questionnaire: <ul style="list-style-type: none"> <li>• Child asthma last 6 mths</li> <li>• Asthma medications</li> <li>• Days missed in school</li> <li>• Asthma-related hospital admission</li> </ul>	14 years	0 <3 weeks 3–6 weeks 7 weeks-3 months $\geq 4$ months	Increased asthma prevalence in BF children of asthmatic women; no association with asthma at 14 years	Maternal smoking was not included in the multivariate analyses; it was associated with the decision and duration of BF.	Not included
Matheson et al. 200710	Questionnaire: <ul style="list-style-type: none"> <li>• Attacks of asthma or wheezy breathing last 12 months</li> </ul>	13 years 20 years 31 years	First 3 months	BF reduced the risk for asthma in children with atopic mothers at 7 years, but increased at $> 7$ years; no	Maternal smoking was controlled for; it was related to	Controlled for pleurisy & pneumonia. Exclusive BF was protective

Author and Year	Definition of asthma	Assessed at ages	Duration of breastfeeding	Breastfeeding (BF) effects	Smoking	Respiratory tract infections (RTI)
				effect in children of non-atopic mothers.	not exclusive breastfeeding.	against pneumonia or pleurisy and bronchitis.

**TABLE 2**

Population characteristics.

Variable	Percent	n/N	Missing
Smoking during pregnancy	25.3	384/1521	15
Breastfeeding at least 3 months	44.7	600/1342	194
Chest infections in infancy	7.4	101/1374	162
Information on the three factors described above		1336	200
Boys	51.2	785/1534	2
Low birth weight ( $\leq 2500$ g)	4.1	61/1494	42
Maternal history of asthma	17.7	233/1318	218

**TABLE 3**  
Risk-ratios for the triad of smoking during pregnancy, breast feeding, and lower respiratory infections and repeated occurrence of asthma from age 1 to 10.

	Repeated measurement of asthma at ages 1, 2, 4, 10 years Number of clusters = 1491 Number of observations used = 4729		Repeated measurement of asthma at ages 4 or 10 years Number of clusters = 1426 Number of observations used = 2271	
	RR	95% CI	RR	95% CI
<b>Model with individual risk factors*</b>				
RLRTI <sup>††</sup>				
Breastfeeding ≥3 months	4.16	3.33	5.19	2.50
Prenatal smoking	0.83	0.67	1.02	0.82
	1.17	0.94	1.46	1.03
<b>Model with risk-triads*</b>				
Label	RLRTI	BF <sup>#</sup>	Prenatal smoking	n (%)
1	+	+	-	21 (1.6)
2	+	-	+	36 (2.7)
3	+	+	+	9 (0.7)
4	+	-	-	32 (2.4)
5	-	-	+	210 (15.7)
6	-	-	-	459 (34.4)
7	-	+	+	78 (5.8)
8	-	+	-	491 (36.8)
	RR	95% CI	RR	95% CI
	4.93	3.46	7.03	2.32
	5.79	4.14	8.11	3.10
	4.03	2.15	7.56	0.79
	5.51	3.88	7.82	3.39
	1.71	1.24	2.36	1.41
	1.05	0.78	1.41	0.98
	0.72	0.36	1.47	0.47
	1	Reference	1	Reference

\* Adjusted for low birth weight, maternal history of asthma, and gender.

<sup>††</sup> RLRTI, recurrent lower respiratory tract infections.

<sup>#</sup> BF, breastfeeding for at least 3 months.