


ORIGINAL ARTICLE

Epidemiology

Breastfeeding is associated with a decreased risk of childhood asthma exacerbations later in life

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Abstract

Background: Breastfeeding has been suggested to influence the risk of asthma and asthma severity in children. However, the conclusions from epidemiologic studies are inconsistent.

Methods: We used data from 960 children (aged 4-12 years) using regular asthma medication who participated in the PACMAN study. Breastfeeding exposure was based on questionnaire data and stratified into (i) ever vs never, and (ii) ≥ 6 vs < 6 months duration of breastfeeding. Asthma severity was based on the occurrence of asthma exacerbations in the preceding year and/or poorly controlled asthma symptoms during the last week of study visit. Odds ratios (ORs) were derived from univariate and multivariable logistic regression analyses.

Results: Breastfeeding was associated with a decreased risk of asthma exacerbations; adjusted (adj.) OR: 0.55 (95% confidence interval [CI]: 0.35-0.87). After stratification for duration of breastfeeding, the adj. ORs were 0.48 (95% CI: 0.27-0.84) for duration < 6 months and 0.71 (95% CI: 0.43-1.20) for duration ≥ 6 months breastfeeding. When we stratified the analysis by family history of asthma, the association between breastfeeding and asthma exacerbations was strong and statistically significant only in children with a positive family history of asthma; adj. OR: 0.34 (95% CI: 0.18-0.66). There was no association between breastfeeding and risk of poor asthma control; adj. OR: 1.04 (95% CI: 0.76-1.41).

Conclusion: In a pediatric population with asthma, children who had been breastfed had a statistically significantly lower risk of asthma exacerbations later in life compared to asthmatic children who had not been breastfed.

KEYWORDS

asthma control, asthma exacerbations, asthma severity, breastfeeding, children

1 | INTRODUCTION

Breastfeeding is associated with prevention of immune-mediated disorders such as asthma and allergic susceptibilities; implying a possible positive influence on maturation of the neonatal immune system.¹ The effect of breastfeeding on development of infants' immune system

can be explained by different mechanisms; a direct immunomodulation effect or an effect through changing the composition of the gut microbiome. Breastmilk contains high levels of factors that can help the development of a healthy immune system in the offspring such as immunoglobulins, cytokines, lactoferrin, prebiotic fibers and even unique microbes.² The composition of a healthy gut microbiome is

highly diverse, whereas reduced gut microbial diversity has been associated with a higher risk of immune-related disorders such as asthma and allergies.³⁻⁵ Breastmilk can influence the microbiome composition and activity in infants because of a presence of unique prebiotic structures and microbes present in human milk.¹

Many epidemiologic studies have studied the association between breastfeeding and the risk of asthma development and asthma severity. However, these studies have yielded conflicting results; various studies have found a beneficial effect of breastfeeding on the prevention of asthma⁶⁻¹² or reported a reduced risk of asthma severity in breastfed children,¹³ but other studies found that breastfeeding did not appear to prevent asthma, delay its onset or reduce its severity.¹⁴⁻¹⁷ These apparent inconsistent findings might be due to differences in the study designs and study population (general population vs high-risk population). The protective effect of breastfeeding on asthma development has been shown only in the cross-sectional and case-control studies, but not in the cohort studies.⁸ Breastfeeding has been associated with lower incidence rate of atopy in high-risk children.¹⁸ In addition, the definition of breastfeeding differed in previous studies; not all studies made the distinction between “exclusive breastfeeding” and “any breastfeeding.”

The age at which asthma diagnosis was assessed also varied and could influence the association. The protective effect of breastfeeding might be strongest in early childhood. Prior epidemiological studies that addressed the association between breastfeeding and risk of asthma looked at these outcomes at different ages; from 2 months to 18 years. With increasing age, the possibility of effects from other exposures influencing this association is increasing. It is also likely that the association between breastfeeding and asthma/asthma severity is influenced by some other factors, for example, duration of breastfeeding. In a recent meta-analysis, longer duration of breastfeeding (≥ 3 vs < 3 months) has been statistically significantly associated with a reduced risk of asthma in children aged 3-6 years (odds ratio [OR]: 0.84, 95% confidence interval [CI]: 0.76-0.92).¹⁰ Moreover, a very recent study reported that a shorter duration of breastfeeding (< 2 months) is associated with increased risk of current asthma at age 6 years (OR: 2.19, 95% CI: 1.29-3.71).⁷

Conclusion from previous findings is inconsistent; whether breastfeeding influences asthma severity later in life is still poorly understood and needs more studies. Therefore, in this study, we aimed to study the association between exposure to breastfeeding (ever vs never) and duration of breastfeeding on asthma severity categorized as asthma exacerbations and poor asthma control.

2 | METHODS

2.1 | Study setting and population

For this analysis, we used data from the PACMAN (pharmacogenetics of Asthma medication in Children: Medication with Anti-inflammatory effects) study which started in April 2009 by means of selecting pediatric asthma medication users from Dutch community pharmacies. Details of this study protocol have been described elsewhere.¹⁹ Children aged 4-12 years with at least 2 years of medication history available and at

least three prescriptions for any asthma drug (Anatomical Therapeutic Chemical [ATC] code R03) within the last 2 years and at least one prescription in the last 6 months were selected from pharmacies in different regions in the Netherlands. The selected children and their parents were invited to participate in the PACMAN study. The parents were asked to fill in a questionnaire to gather information about general health, allergies, asthma and respiratory symptoms, asthma control, healthcare utilization for respiratory symptoms, medication use and compliance, beliefs about medicines, environmental and sociodemographic factors. Written informed consent was obtained from all participants. The Medical Ethics Committee of the University Medical Centre Utrecht has approved the PACMAN study.

2.2 | Exposures and outcomes measurement

Exposure to breastfeeding was based on the following: (i) ever vs never breastfed—information on breastfeeding was obtained by questionnaire and dichotomized as Yes or No, and (ii) duration of breastfeeding—using questionnaire, we subdivided breastfed children by duration of breastfeeding (≥ 6 vs < 6 months).¹⁰

Two outcome parameters were used in this study to assess asthma severity: (i) asthma exacerbations defined as either prescribed courses of oral corticosteroids (OCS) and/or asthma-related visits to an emergency department (ED) in the past 12 months of study visit; and (ii) poor asthma control based on the Asthma Control Questionnaire (ACQ)-6 ≥ 0.75 in the last week of study visit).²⁰ This questionnaire assesses asthma control in the previous week by asking questions regarding nightly symptoms, limitation of normal daily activities, waking in the morning with symptoms, dyspnea, wheeze, cough, chest discomfort, sputum, colored sputum, and need to clear throat.

2.3 | Statistical analysis

Children with missing values on exposure and outcomes were excluded from data analyses. The baseline characteristics of children with and without missing data were compared. Descriptive statistics using distributions, means, and standard deviations (SDs) were used. Where possible, variables were dichotomized. Univariate and multivariable logistic regression analyses were used to estimate ORs and 95% CIs. Factors that could influence the association of breastfeeding with asthma severity including age, gender, ethnicity, mother's education, eczema, hay fever, and family history of asthma/allergy were tested as potential confounders in multivariable logistic regression analyses. Potential confounders that changed the Beta coefficient of this association by $\geq 10\%$ were included in the final models. Additionally, in a subgroup analysis we stratified this association by family history of asthma. All analyses show the ORs for ever- vs never-breastfed children (we used the never-breastfed group as the reference group). Children with missing values on breastfeeding (ever or never) were excluded from the analyses. A *P*-value of .05 was used to assess the significance of main effect associations. All statistical analyses were conducted using SPSS version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

TABLE 1 Study characteristics

	PACMAN (n = 960)
Gender (boys), n (%)	599 (62.4)
Age, mean (SD)	8.4 (2.4)
Breastfeeding, n (%)	
Ever exposed	714 (74.4)
Never exposed	246 (25.6)
Duration of breastfeeding, n (%)	
<6 mo	318 (46.5)
≥6 mo	366 (53.5)
Exacerbations, n (%)	101 (10.5)
OCS use, n (%)	60 (6.3)
ED visit, n (%)	61 (6.4)
Poor asthma control (ACQ-6 ≥ 0.75), n (%)	399 (41.6)
Allergic symptoms, n (%)	
Eczema	612 (63.7)
Hay fever	404 (42.1)
Family history of asthma ^a , n (%)	440 (45.8)
Family history of allergy ^b , n (%)	752 (78.3)

SD, standard deviation; ACQ, Asthma Control Questionnaire; OCS, oral corticosteroids; ED, emergency department visits due to asthma.

Asthma exacerbations: either OCSs use or ED visits.

Poor asthma control: based on the Asthma Control Questionnaire (ACQ-6 ≥ 0.75) in the past 1 week.

^aAt least one asthmatic parent.

^bAt least one allergic parent.

3 | RESULTS

Data were available for 960 children (mean age was 8.4 years). The majority of children in this study were boys (62%). Almost three-quarter of the population was breastfed (74%). Data on duration of breastfeeding were available for 684 children. In 366 of 684 (53.5%) children, the duration of breastfeeding was 6 months or longer. Less than half of the population reported poor asthma control (42%) during the past week, and 11% reported asthma exacerbations in the past 12 months of study visit (Table 1). There were no statistically significant differences in baseline characteristics of children with and without missing data (Table 2).

TABLE 2 Differences in baseline characteristics of children with and without missing data

	Missing data (n = 35)	No missing data (n = 960)	P-value
Gender, n (%)			
Girls	21 (52.5)	362 (37.7)	.06
Boys	19 (47.5)	598 (62.3)	
Asthma exacerbations, n (%)	1 (3.7)	101 (10.5)	.25
Poor asthma control (ACQ-6 ≥ 0.75), n (%)	10 (41.7)	399 (41.6)	.94

Asthma exacerbations: either oral corticosteroids use or emergency department visits due to asthma. Poor asthma control: based on the Asthma Control Questionnaire (ACQ-6 ≥ 0.75) in the past 1 week of study visit.

The results of univariate logistic regression analyses are presented in Table 3.

3.1 | Breastfeeding and asthma exacerbations

In multivariable logistic regression analyses, asthmatic breastfed children had a statistically significantly lower risk of asthma exacerbations; adjusted OR (adj. OR): 0.55, 95% CI: 0.35-0.87; *P*-value: .01. Age and reported eczema were confounders in this association and were included in the final model. The percentage of children with asthma exacerbations was 9% in the ever-breastfed and 15% in never-breastfed children (Pearson chi-square *P*-value = .007).

After stratification for duration of breastfeeding, the association was strong and statistically significant in breastfed children with up to 6 months duration of breastfeeding (adj. OR: 0.48, 95% CI: 0.27-0.84; *P*-value: .01) while no longer statistically significant for longer than 6 months breastfeeding; adj. OR: 0.71, 95% CI: 0.43-1.20; *P*-value: .20 (Table 4).

To evaluate the influence of family history of asthma on this association, we further stratified our analyses. Our findings showed that the association between breastfeeding and asthma exacerbations was stronger in children with a positive family history of asthma (adj. OR: 0.34, 95% CI: 0.18-0.66; *P*-value: .001), while the association was no longer statistically significant in children without a family history of asthma (adj. OR: 1.08, 95% CI: 0.55-2.14; *P*-value: .82).

3.2 | Breastfeeding and poor asthma control

No statistically significant association with poor asthma control was observed between ever-breastfed compared with never-breastfed children (adj. OR: 1.04, 95% CI: 0.76-1.41; *P*-value: .83) with no influence of different durations of breastfeeding (Table 4). For this association, family history of asthma as confounder was included in the final model.

4 | DISCUSSION

In this study, we showed that breastfeeding in asthmatic children is associated with a lower risk of asthma exacerbations, but not with a

TABLE 3 Associations between breastfeeding and asthma severity, using univariate logistic regression analyses

	Crude OR (95% CIs)	P-value
Asthma exacerbations		
Breastfeeding (ever vs never)	0.56 (0.36-0.86)	.008
Age	0.86 (0.79-0.94)	.001
Gender	1.00 (0.65-1.53)	.99
Ethnicity	0.41 (0.13-1.32)	.13
Mother's education	0.62 (0.31-1.22)	.17
Eczema	2.69 (1.60-4.52)	<.001
Hay fever	1.19 (0.78-1.80)	.43
Family history of asthma	1.08 (0.71-1.63)	.73
Family history of allergy	1.15 (0.67-1.99)	.61
Poor asthma control (ACQ-6 \geq 0.75)		
Breastfeeding (ever vs never)	1.06 (0.79-1.43)	.69
Age	0.99 (0.94-1.04)	.63
Gender	0.91 (0.70-1.19)	.51
Ethnicity	1.03 (0.62-1.71)	.92
Mother's education	0.77 (0.53-1.11)	.15
Eczema	1.21 (0.92-1.58)	.18
Hay fever	1.23 (0.94-1.60)	.13
Family history of asthma	1.55 (1.19-2.02)	.001
Family history of allergy	1.42 (1.01-2.02)	.05

Reference is never exposed group in all analyses.

Asthma exacerbations: either oral corticosteroids use or emergency department visits due to asthma.

Poor asthma control: based on the Asthma Control Questionnaire (ACQ-6 \geq 0.75) in the past 1 week of study visit.

Bold numbers: statistically significant associations.

OR, odds ratio; CI, confidence interval; ACQ, Asthma Control Questionnaire.

lower risk of poor asthma control. In a stratified analysis, asthmatic ever-breastfed children with duration up to 6 months compared to those who had not been breastfed had a statistically significantly lower risk of asthma exacerbations later in life. However, breastfeeding for longer duration (\geq 6 months) was not significantly associated with asthma exacerbations. Remarkably, stratified analyses showed that the reduced risk of breastfeeding on asthma exacerbations was even stronger in children with a family history of asthma and no longer statistically significant in a subset of children without family history of asthma.

Previous inconsistent findings regarding the effect of breastfeeding on asthma severity could be due to differences on how asthma severity is measured, for example, wheezing periods and exacerbations. Our finding concerning a decreased risk of asthma exacerbations in children exposed to breastfeeding is in line with a study from Kenya that reported a lower risk of asthma severity in children up to 10 years who had been exclusively exposed to breast milk in early life; OR: 0.4 (95% CI: 0.14-0.98).¹³ However, Rust et al showed that in children

TABLE 4 Associations between breastfeeding and asthma severity, using multivariable logistic regression analyses

	Adj. OR ^a (95% CIs)	P-value
Asthma exacerbations		
Breastfeeding (ever vs never) n = 960		
Ever exposed n = 714	0.55 (0.35-0.87)	.01
Never exposed n = 246	Reference	
Breastfeeding (duration) n = 684		
<6 mo n = 318	0.48 (0.27-0.84)	.01
\geq 6 mo n = 366	0.71 (0.43-1.20)	.20
Poor asthma control (ACQ-6 \geq 0.75)		
Breastfeeding (ever vs never) n = 939		
Ever exposed n = 695	1.04 (0.76-1.41)	.83
Never exposed n = 244	Reference	
Breastfeeding (duration) n = 669		
<6 mo n = 310	1.09 (0.77-1.56)	.63
\geq 6 mo n = 359	1.00 (0.70-1.40)	.94

Reference is never exposed group in all analyses.

Asthma exacerbations: either oral corticosteroids use or emergency department visits due to asthma.

Poor asthma control: based on the Asthma Control Questionnaire (ACQ-6 \geq 0.75) in the past 1 week of study visit.

Bold numbers: statistically significant associations.

OR, odds ratio; CI, confidence interval; ACQ, Asthma Control Questionnaire.

^aAdjusted for age, gender, ethnicity, mothers' education, eczema, hay fever, and family history of asthma/allergy.

under 6 years, breastfeeding was not associated with a decreased risk of asthma severity. In this study, the number of wheezing episodes in the prior 12 months was as an indicator of asthma severity in asthmatic children and the means of wheezing episodes were not significantly different in ever- and never-breastfed children.¹⁵

The reduced risk of breastfeeding on asthma exacerbations in our study might be explained among others by the influence of breastfeeding on the immune system.^{1,21} Breast milk contains unique microbiota that might stimulate a well-balanced composition of the infants' gut and airway microbiome.^{3,22,23} In asthmatic patients, there seems to be a microbial dysbiosis, which could make patients more prone to respiratory tract infections triggering exacerbations.³ Biesbroek et al²⁴ compared the nasopharyngeal microbial composition in the upper respiratory tract of 6-week-old exclusively breastfed and exclusively formula fed infants and showed a strong association between

breastfeeding and the nasopharyngeal microbial composition. This study showed an altered microbial pattern in breastfed children, and this pattern was associated with a reduced risk of respiratory infections.²⁴

In addition, a recent analysis of 4040 children included in the Leicester Respiratory Cohort showed that prolonged breastfeeding (>6 months) protected against bronchiolitis during the first 2 years of life, however not against other respiratory tract infections.²⁵ The role of duration of breastfeeding on the functioning of the immune system and therefore on risk of asthma and asthma severity is not clear yet. In our study, the association between breastfeeding and asthma exacerbations was only statistically significant in children who received up to 6 months of breastfeeding. In line with our findings, a recent study found a decreased risk of asthma development in children who were breastfed for up to 6 months compared to those who were not breastfed; OR: 0.7 (0.5-0.99); *P*-value: .04. This study also showed that breastfeeding for longer duration (>6 months) was not statistically significantly associated with asthma; OR: 1.5 (1.0-2.4); *P*-value: .06.⁹ However, it has been also shown that different categories in duration of breastfeeding did not change the effect estimates in this association.¹⁵ No statistically significant association between breastfeeding and a reduced risk of asthma exacerbations in children without a positive family history of asthma might be explained by differences in asthma phenotypes and underlying mechanisms. Further studies into the role of different immune reactions that might be involved in both IgE-dependent or IgE-independent asthma might elucidate potential underlying mechanisms.

The lack of a statistically significant association between breastfeeding and a lower risk of poor asthma control in this study might be due to the definition of asthma control that was used in this study. Asthma control in this study has been limited to the recall of symptoms in the past week of study visit using the ACQ questionnaire which does not necessarily translate to long-term asthma control; agreement between current and long-term asthma control has been reported to be limited.²⁶

When assessing the baseline characteristics of the children with and without missing data, the results showed no statistically significant differences in asthma severity both asthma exacerbations and poor asthma control; therefore, our study was not prone to selection bias. Some potential limitations of the present study should be acknowledged. Importantly, our study was limited by the use of questionnaire-based data that might be prone to recall bias. Previous studies have shown that mothers can remember whether they have breastfed very well, even after many years²⁷; however, this might be more difficult concerning the duration of breastfeeding. Another important limitation is the cross-sectional nature of our study. When exposure and outcome are measured at one moment (or period) in time, the risk of reverse causality would be a major problem; our data do not clearly show whether breastfeeding preceded asthma severity. The optimal design for this study is a prospective longitudinal design including pregnant women and examines the effect of breastfeeding duration on asthma severity. Also, in our study several potential confounders were not available

such as dietary habits during pregnancy and infancy, socioeconomic status, and exposure to infection/siblings. Therefore, the possibility remains that some factors which were not measured in the present study caused confounding.

In summary, although in our study breastfeeding was shown as a protective factor for asthma exacerbations, it is still unclear whether there is a causal relation between breastfeeding and asthma exacerbations during childhood. Therefore, further prospective research is warranted to confirm this association and to clarify the underlying mechanisms.

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