Accepted author's manuscript. Published in final edited form as: Pediatric Pulmonology 2020 epub. Publisher DOI: 10.1002/ppul.24733

Effect of breastfeeding duration on lung function, respiratory symptoms and allergic diseases in school-age children

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Competing interest: The authors declare no conflict of interest. **Financial Disclosure:** The authors have indicated they have no financial relationships relevant to this article to disclose.

Keywords

Breastfeeding, lung function, school-age children, allergic disease

ABSTRACT

Background

A positive effect of breastfeeding on lung function has been demonstrated in cohorts of children with asthma or risk for asthma. We assessed the impact of breastfeeding on lung function and symptoms at the age of six years in an unselected, healthy birth cohort.

Methods

We prospectively studied healthy term infants from the Bern-Basel Infant Lung Development (BILD) cohort from birth up to 6 years. Any breastfeeding was assessed by weekly phone calls during the first year of life. Risk factors (e.g. smoking exposure, parental history of allergic conditions, and education) were obtained using standardized questionnaires. The primary outcomes were lung function parameters measured at 6 years of age by spirometry (FEV_1), body plethysmography ($FRC_{pleth,}$ $TLC_{pleth,}$ R_{eff}) and FeNO. Secondary outcomes included ever wheeze (between birth and 6 years), wheeze in the past 12 months, asthma, presence of allergic conditions, atopic dermatitis, rhinitis, and positive skin prick test at the age of 6 years.

Results

In 377 children the mean breastfeeding duration was 36 weeks (SD 14.4). We found no association of breastfeeding duration with obstructive or restrictive lung function and FeNO. After adjustment for confounders we found no associations of breastfeeding duration with respiratory symptoms or presence of allergic conditions.

Conclusion

This study found no evidence of association between breastfeeding and comprehensive lung function in unselected healthy children with long-term breastfeeding. Our findings do not support the hypothesis that the duration of breastfeeding has a direct impact on lung function in a healthy population with low asthmatic risk.

Introduction

Breastfeeding has a variety of beneficial effects for children[1]. Many studies have provided clear evidence that breastfeeding reduced the risk of respiratory morbidity in early life.[2-7] The effect of breastfeeding on lung function and atopic diseases including asthma in childhood is less consistent. A meta-analysis by Dogaru *et al.* showed a protective association between breastfeeding and asthma with the strongest effect in the first two years of life,[8,9] whereas another meta-analysis reported a decreased risk of asthma in children aged 5-18 years, but in children from studies with insufficient adjustment for confounders. Furthermore the effect of breastfeeding on other allergic disease is still conflicting. [9-11]

There is some evidence that breastfeeding could improve school-aged lung function, but the positive association was seen predominantly in studies with a relatively high number of children with atopic/asthmatic mothers[12-16] or from subgroups of children of asthmatic mothers,[17] suggesting that the relationship between breastfeeding and lung function might be mediated by atopic disease. Indeed, the ALSPAC cohort of healthy unselected children, found no effect of breastfeeding on bronchial responsiveness.[18] Few studies are available linking breastfeeding with fractional exhaled nitric oxide (FeNO)[19] or more comprehensive lung function. Taken together, results seem to be heterogeneous and influenced by risk factors, categorization and duration of breastfeeding.

From a mechanistic point of view, it is unclear whether the protective effect of breastfeeding is related to inflammatory mechanisms in asthma and subsequent remodeling and impaired lung growth or whether breastfeeding directly affects lung functional development. To address the latter hypothesis, we aimed to assess the effect of breastfeeding duration on lung function at 6 years of age in a prospective unselected birth cohort study of primarily healthy children with an appropriate adjustment for confounders and comprehensive lung function outcomes such as spirometry, plethysmography and FeNO. Secondary aims were clinical markers of respiratory

and allergic diseases at the age of 6 years, such as ever wheeze, wheeze in the past 12 months, presence of allergic conditions, atopic dermatitis, rhinitis, and positive skin prick test.

Methods

Study design and subjects

Data was obtained from the ongoing prospective Basel-Bern Infant Lung Development (BILD) birth cohort, collected since 1999 in Switzerland. Pregnant women were recruited antenatally in four maternity hospitals and practices of gynecologists in the region of Bern. Unselected healthy children were followed up at 6 years after enrollment.[20] Exclusion criteria for the study were preterm delivery (<37 weeks) and significant perinatal disease, including respiratory distress and known major birth defects. Assessments were undertaken at ages 1 and 6 years. The assessment in the first year of life comprised clinical examination at the age 1 month in the study clinic, weekly phone interviews and information from perinatal records. At the age of 6 years, parents were mailed a questionnaire with questions on allergy and respiratory symptoms as well as environmental exposure, and were offered a visit to the study clinic. During the follow-up visit the history of wheeze episodes between birth and age 6, including their frequency, severity and trigger factors were recorded by trained study physicians using standardized questionnaires. Children also underwent a lung function measurement and a skin prick test. This study focuses on the follow-up assessments conducted between August 2005 and April 2018. The Ethics Committee of the Region of Bern approved the study and written consent was obtained at enrollment and again at follow-up.

Exposure: breastfeeding

During the 1st year of life mothers were asked weekly by telephone interview with a study nurse about their breastfeeding status until they completely stopped breastfeeding. *Any breastfeeding* was treated as a continuous variable in weeks.

Primary outcome: lung function at 6 years

Spirometry and body plethysmography were performed at the age of 6 years using MasterLab setup (Jaeger, Wurzburg, Germany) according to current ERS/ATS guidelines.[21] The primary spirometry outcome was FEV_1 according to ERS/ATS criteria.[22]

Body plethysmography measurements were done to assess the functional residual capacity (FRC_{pleth}), the total lung capacity (TLC_{pleth}) and the effective respiratory airway resistance (R_{eff}). FRC_{pleth} and TLC_{pleth} were assessed according to European standards[23] and R_{eff} was determined as the mean of at least five separate specific resistance loops.[24] Fractional exhaled nitric oxide (FeNO) was used as a measure of eosinophilic airway inflammation and measured online (CLD88sp FeNO analyser, ECO MEDICS, Duernten, Switzerland). Compliant to the ATS/ERS recommendations, the mean of two or three reproducible FeNO values has been reported.[25]

Secondary outcome: clinical data

Standardized questions on key clinical outcomes (e.g. wheeze, atopic dermatitis, and rhinitis) were adapted from the International Study on Asthma and Allergy in Childhood (ISAAC) questionnaire.[26]

Ever wheeze was obtained from a physician-administered questionnaire and defined as present if the question "Has your child ever had wheezing or whistling at any time in the past?" was answered positively. *Current wheeze* was defined as present if the question "Has your child had wheezing or whistling in the past 12 months?" was answered positively. According to the GINA guidelines 2018,[27] *asthma* was defined as present if there was cough/wheezing/ difficult or heavy breathing in the absence of an apparent respiratory infection in the last 12 months in combination with an asthma-medication (inhaled corticosteroids or ß-agonists) used in the last 12 months and/or a positive past history of allergic conditions (atopic dermatitis and/or rhinitis/rhinoconjunctivitis) and/or a positive family history of allergic conditions.

Rhinitis/rhinoconjunctivitis was defined as parent-reported prolonged sneezing, runny or blocked nose accompanied by ocular itching and tearing without a common cold in the last 12 months, according to international standards.[28,29]

Based on modified Hanifin and Rajka criteria,[30] *atopic dermatitis* at 6 years was defined as present if 3 of 4 major criteria were met: (1) pruritus in the last 12 months, (2) typical morphology and distribution, (3) chronic dermatitis, (4) personal or family history of atopy allergic conditions (asthma, rhinitis and/or atopic dermatitis). Infants were defined as having atopic dermatitis in the first year of life if they had at least one of the following occurrences in the first year of life: (1) pruritus or/and rashes (e.g redness, dryness and papules) with the distribution in at least 2 typical regions; (2) recurrent dermatitis/rashes within the first year of life; (3) doctor diagnosed atopic dermatitis or treatment with topical steroids. We excluded skin lesions caused by cradle cap and seborrhoeic dermatitis.

Presence of allergic conditions was defined as the presence of asthma and/or rhinitis/rhinoconjunctivitis and/or atopic dermatitis.

A skin prick (at 6 years) was defined as positive for at least one of the following measured allergens: dog dander, cat dander, dermatophagoides pteronyssinus, mixed tree pollens, mixed grass pollens, alternaria tenuis. The test was defined as positive if a weal diameter was bigger than the histamin in any of the tested allergens compared to a valid negative and a valid positive (histamine ≥ 3mm) control.[31]

Risk factors

Other risk factors included parental history of allergic conditions (defined as asthma, rhinitis or atopic dermatitis), mode of delivery (vaginal or cesarean), maternal educational level as a marker of socioeconomic status, older siblings, maternal smoking during pregnancy, and parental smoking during the first year of life.

Statistical analysis

All variables were examined in relation to their ranges, distributions, means, standard deviations, outliers and logical errors. For later analysis FeNO was log transformed. The relationship between breastfeeding and outcomes were tested for possible non-linearity. We found no evidence for the curvilinear relation of breastfeeding to lung function and clinical outcomes. In order to investigate the association of breastfeeding with pulmonary function measures, we first performed linear regression analysis with standard adjustments for age, sex, and height (baseline model). Second, we used linear regression analysis with additional adjustments for gestational length, parental history of allergic conditions, and maternal smoking during pregnancy (adjusted model). Estimates are presented as change or a percent change (for back-transformed outcomes) in the lung function parameters per week of any breastfeeding with their 95% confidence intervals (CIs). To exclude the possible effect mediation by respiratory infection in early life, we performed a sensitivity analysis with adjustment for number of weeks with respiratory symptoms accessed during the 1 year of life. We did not investigate the possible effect of modification by maternal asthma because of the low number of children with asthmatic mothers.

The association of breastfeeding with secondary outcomes was assessed using, first, univariable logistic regression, and then after adjustment for sex, maternal smoking during pregnancy, parental history of allergic conditions, and maternal education. Ever wheeze was additionally adjusted for the presence of older siblings. Results are presented as odds ratios (ORs) with 95% CIs.

All data processing and analyses were performed in STATA 15.0 (Stata Cooperation, college Station, TX) and R (Version 3.31)[32]. Significance was defined by a p-value less than 0.05 for two-sided tests.

Results

Participants

Between 1999 and 2012, 458 children were enrolled in the BILD study. Among these, 377 (82%) had a documented follow-up visit between 2005 and 2018. 8 (2%) children did not meet the inclusion criteria as described above, 73 (16%) we lost to follow-up. The characteristics of included versus non-included children are shown in the **Table S1**. There was a significant difference between included and non-included children for maternal smoking during pregnancy and parental smoking during the first year of life, and the mean duration of breastfeeding was significantly shorter in the non-included than in the included children.

32 (8%) participants did not show for the follow-up lung function test at 6 years, but sent the questionnaire back. 279 (74%) of 377 had available data on FeNO measurements. The quality control of lung function resulted in 204 children (54%) with spirometry and 263 children (70%) with body plethysmography data (**Figure S1**). **Table 1** shows the anthropometric data, potential risk factors, spirometry, FeNO and body plethysmography data for the whole study population.

Breastfeeding prevalence

Overall, 5 children (1%) were not breastfed at all, 78 (21%) were breastfed less than 6 months. The mean (SD) duration of breastfeeding for those who received breastfeeding was 36.5 (13.9) weeks. Duration of breastfeeding according to exposure characteristics at birth is shown in **Table S2**. Maternal smoking during pregnancy was only significantly associated with shorter duration of breastfeeding.

Association of breastfeeding with lung function and clinical symptoms

Duration of breastfeeding was not associated with lung function (**Table 2**). There were no substantial differences in baseline and adjusted models. Additional adjustments for maternal

education or respiratory symptoms in the first year of life did not change the effect estimates (data not shown).

In a univariable model we found significant evidence for a 2% reduction in presence of allergic conditions for each week of breastfeeding (**Table 2**). However, after control for confounders we found no evidence for association of breastfeeding with any of secondary clinical outcomes (**Table 2**).

Discussion

In this prospective cohort study of primarily healthy unselected children followed from birth until school age, we found no significant effect of breastfeeding duration on lung functional outcomes, if adjusted for known confounders. The physiological relevance of the findings was strengthened by the consistency across several functional outcomes at school age. We found no evidence of airway obstruction, altered residual or end-expiratory volume nor restricted total lung capacity. With respect to secondary outcomes, we observed that a longer duration of breastfeeding was associated with a reduced risk of atopic dermatitis in girls. For every week mothers continued breastfeeding, the risk of having atopic dermatitis was reduced by 4%. There was no significant effect of breastfeeding duration on other clinical data such as asthma, ever wheeze, current wheeze, rhinitis or positive skin prick test. Sensitivity analysis of lung function outcomes excluding children who developed asthma during preschool age showed consistent results (**Table S3**).

Primary outcomes. In contrast to asthma cohort studies,[12,13,15,17] we found no effect of breastfeeding on lung function outcomes in unselected, primarily healthy children. Similarly we could not demonstrate an effect of breastfeeding on FeNO, a marker of eosinophilic inflammation in asthma, as suggested by others[19]. Studies investigating the effect of breastfeeding on lung function are heterogeneous with regards to age (mixed preschool and school age populations), risk factors, duration and categorization of breastfeeding. Overall,

there is evidence that breastfeeding has the most consistent beneficial effect on FVC.[33] However, of the three cohort studies reporting on the effect of breastfeeding on FVC, two were based on the Isle of White cohort and one on The Tucson Children's Respiratory Study with enrolment periods from 1980 to 1984 and from 1989 to 1990, respectively.[16,34] FVC is highly cooperation-dependent in preschoolers, strict quality control criteria in our cohort did not allow us to collect a high enough sample size (**Table 1**) to confirm data from the literature. Furthermore, in comparison to our primarily healthy cohort, these cohorts (ALSPAC, the Isle of White, and Tucson Children's Respiratory Study) are characterized by lower duration of breastfeeding and higher prevalence of asthmatic/atopic mothers and maternal smoking. In addition, depending on the enrolment period, changes in environmental factors, prevalence of respiratory infection and medical care may contribute to both changes in breastfeeding duration and lung functional growth. Our findings are, however, in line with the subgroup of healthy offspring of non-asthmatic mothers, and the ALSPAC and PROBIT studies, which did not find an effect of breastfeeding on lung function.[18,35] Our findings are consistent with the hypothesis, that breastfeeding has no direct strong impact on lung functional development. Combining knowledge from other studies and our findings, we may speculate that the impact of breastfeeding on lung functional development may be a secondary effect mediated by susceptibility to early viral infections or chronic inflammatory processes at preschool age, such as described in asthma (**Figure 1**).

Secondary outcomes. In contrast to studies reporting an association between breastfeeding and allergic disease, in our unselected, primarily healthy cohort we found no effect of breastfeeding on asthma and respiratory symptoms, nor on presence of allergic conditions. This may be related to the limited sample size, which would not allow us to assess small and probably clinically less relevant effects. Another reason for contrasting results is the low prevalence of children with asthma and wheeze in our cohort compared to many other cohorts.[36,37] We have, however, found a weak protective effect on the development of atopic dermatitis. In several

studies it has been shown that breastfeeding protected children from atopic dermatitis.[38,39] Other authors could not find a protective effect at any age, from infancy through adolescence,[40,4140,41] instead, breastfeeding was associated with increased atopic dermatitis,[42-44] especially in the subgroup of children with no heredity for atopy. Consistent with that, in a systematic review and meta-analysis of 18 prospective studies, the protective effect of breastfeeding was higher in the subgroup with a positive family history of atopy.[36] Contrary to that, Kull et al. showed, based on the BAMSE birth cohort, that exclusive breastfeeding for 4 months or more reduced the risk for atopic dermatitis at 4 years by about 20%, irrespective of sensitization to common food or inhalant allergens or parental allergic diseases.[39]

Strength and limitation

Our cohort is a very homogeneous, primarily healthy, cohort. The findings remain robust even if children with asthma were removed from the analysis. However, our healthy population also sets our study apart and is one of our strengths. There are limitations in terms of the generalizability of our findings. Considering Table 1 and Table S1, the sample analyzed might not fully represent the entire population of Bern. The participants tended to come from a higher socioeconomic class and the results from the included/non-included comparison analysis with loss of less-breastfed children suggest a population bias regarding the average duration of breastfeeding. The high prevalence of breastfeeding in our study makes it impossible to provide risk estimates for breastfeeding per se (breastfed children vs non-breastfed children) and makes comparisons between studies difficult. A further difficulty was quantifying the addition of formula supplementation (partial breastfeeding). This made it difficult to assess exposure dose and might have hidden a greater benefit of exclusive breastfeeding compared to partial breastfeeding.

Furthermore, to avoid recall bias we prospectively asked mothers on a weekly basis, whether or not they were breastfeeding and identified the exact time point when mothers completely weaned their children.

Conclusion

Although we found significant breastfeeding effects on respiratory symptoms in the first 6 month of life within the same cohort,[45] this study suggests that in unselected primarily healthy children with low risk for asthma, breastfeeding duration has no relevant effect on comprehensive lung function and FeNO in healthy school-aged children.

Acknowledgments

We would like to thank our study participants and their families for their participation. We also thank also Karine Bell Hugentobler for proofreading the manuscript. Furthermore, we thank the BILD study nurses for their invaluable assistance and support.

Tables

Table 1: Characteristic of children included in the study

Table 2: Association of breastfeeding with lung function and clinical data

Figures

Figure 1: The potential causal pathway (in concordance to Waidyatillake et al[33]). We hypothesized that the effect of breastfeeding on lung function is weak and might be mediated by reducing the airway inflammation and allergic sensitisation in early childhood, and also complex interaction between breastfeeding and genetic variants on respiratory infection.[45,46] Moreover, breastfeeding may positively influence body growth that can lead to better lung function. In addition, it is possible that reported associations between breastfeeding and lung function are due to confounding factors

Supplement

Figure S1: Flow chart of the study population

Table S1: Anthropometric data of the study participants compared to non-included children

Table S2: Duration of breastfeeding stratified by exposure, N=377

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Tables

Table 1: Characteristic of children included in the study

Characteristic	Complete data	Values
Anthropometric data		
Gestational age, mean (sd), weeks	377	40 (1.17)
Gestational length, mean (sd), cm	377	55 (2.17)
Gestational weight, mean (sd), kg	377	22 (3.26)
Male sex, n (%)	377	204 (54)
Age at follow-up, mean (sd), years	345	6.03 (0.28)
Length at follow-up, mean (sd), cm	345	117.29 (5.45)
Weight at follow-up, mean (sd), kg	345	22.17 (3.26)
Risk factors		
Caesarean sectio, n (%)	377	61 (16)
Maternal smoking during pregnancy, n (%)	377	30 (8)
Parental smoking during first year of life, n (%)	377	75 (20)
Maternal history of allergic conditions[a], n (%)	377	123 (33)
Maternal asthma[b], n (%)	377	37 (10)
Paternal history of allergic conditions[a], n (%)	377	132 (35)
Paternal asthma[b], n (%)	377	67 (18)
Maternal education[c], n (%)	376	
Low		93 (25)
Middle		132 (35)
High		151 (40)
Presence of older siblings, n (%)	377	200 (47)
Exposure		
Breastfeeding		
≥1 week, n (%)	377	372 (98.7%)
No. of week with breastfeeding, mean (sd)	375	36.5 (13.9)
Primary outcomes		
Spirometry		
FEV_1, mean (sd), L	204	1.28 (0.20)
FEV1, % predicted, mean (sd)	204	100.3 (11.3)
FVC, mean (sd), L	82	1.4 (0.26)
FVC, % predicted, mean (sd)	82	100.8 (12.3)
FeNO, mean (sd) ppb	279	7.81 (6.98)
Body plethysmography		
FRC_{pleth}, mean (sd), L	260	1.07 (0.19)
TLC_{pleth}, mean (sd), L	198	2.05 (0.33)
R_{eff}, mean (sd), kPa*s/L	263	0.68 (0.20)
Secondary outcomes		
Asthma, n (%)	345	18 (5)
Ever wheezing, n (%)	345	72 (21)
Current wheezing, n (%)	345	18 (5)
Presence of allergic conditions, n (%)	346	100 (29)
Rhinoconjunctivitis, n (%)	372	71 (19)
Atopic dermatitis at 6 years, n (%)	366	38 (11)
Positive skin prick test, n (%)	302	40 (13)

[a] defined as self-reported doctor diagnosed asthma, atopic dermatitis or allergic rhinoconjunctivitis; [b] defined as self-reported doctor diagnosed asthma; [c] categorized into low (less than four years of apprenticeship), middle (four years of apprenticeship and above) and high (tertiary education).

Table 2: Association of breastfeeding with lung function and clinical data

	Baseline model[a]			**Adjusted model[b]**		
Breastfeeding (wks)	N	Coeff (95%CI)	p-value	N	Coeff (95%CI)	p-value
Spirometry						
FEV_1, ml	204	-0.46 (-1.88; 0.94)	0.513	204	-0.23(-1.65; 1.19)	0.747
Bodyplethysmography						
FRC_{pleth}, ml	260	-0.3 (-1.91; 1.31)	0.714	260	-0.14 (-1.75; 1.47)	0.866
$TLC_{pleth,}$ml	198	0.59 (-2.09; 3.27)	0.667	198	0.77 (-1.87; 3.41)	0.564
R_{eff}, ml	263	1.36 (-0.41; 3.12)	0.131	263	1.36 (-0.42; 3.15)	0.134
FeNO, ppb	276	1.00(0.99; 1.01)	0.725	276	1.00 (0.99;1.01)	0.604
	Univariable model			**Adjusted model[c]**		
Breastfeeding (wks)	N	OR (95%CI)	p-value	N	OR (95%CI)	p-value
Clinical data						
Asthma	345	0.99(0.96;1.02)	0.397	345	0.99(0.97;1.03)	0.816
Ever wheezing	345	0.99(0.97;1.01)	0.298	345	1.00(0.98;1.01)	0.634
Current wheezing	345	0.99(0.96;1.02)	0.542	345	1.00(0.97;1.03)	0.976
Presence of allergic conditions	346	0.98(0.96;1.00)	**0.018**	346	0.99(0.97;1.00)	0.068
Rhinoconjunctivitis	372	0.98(0.97;1.00)	0.071	371	0.99(0.97;1.01)	0.194
Atopic Dermatitis	366	0.98(0.96;1.00)	0.080	365	0.99(0.96;1.01)	0.187
Positive skin prick test	302	0.99(0.97;1.01)	0.379	302	0.99(0.97;1.02)	0.579

Abbreviation: N, complete data; Coeff, regression coefficient; 95% CI, 95% confidence interval; OR, odds ratio.
Effect is reported per week of breastfeeding
[a] adjusted only for anthropometric data (age, height, and sex)
[b] adjusted for sex, maternal smoking during pregnancy, and parental atopy
[c] adjusted for sex, maternal smoking during pregnancy, parental atopy, and maternal education. Ever wheezing was adjusted additionally for older siblings.

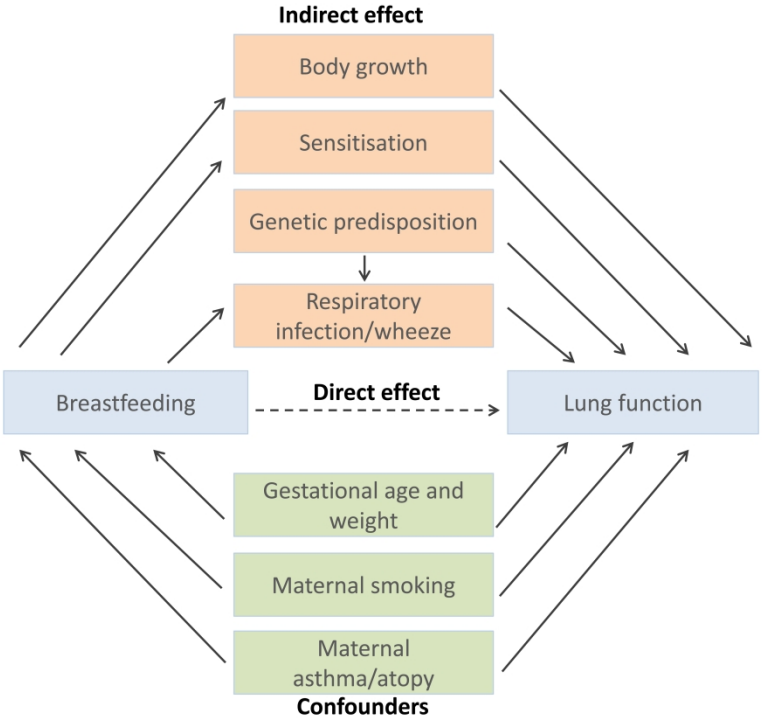

Figure 1: The potential causal pathway (in concordance to Waidyatillake et al33). We hypothesized that the effect of breastfeeding on lung function is weak and might be mediated by reducing the airway inflammation and allergic sensitisation in early childhood, and also complex interaction between breastfeeding and genetic variants on respiratory infection.45,46 Moreover, breastfeeding may positively influence body growth that can lead to better lung function. In addition, it is possible that reported associations between breastfeeding and lung function are due to confounding factors

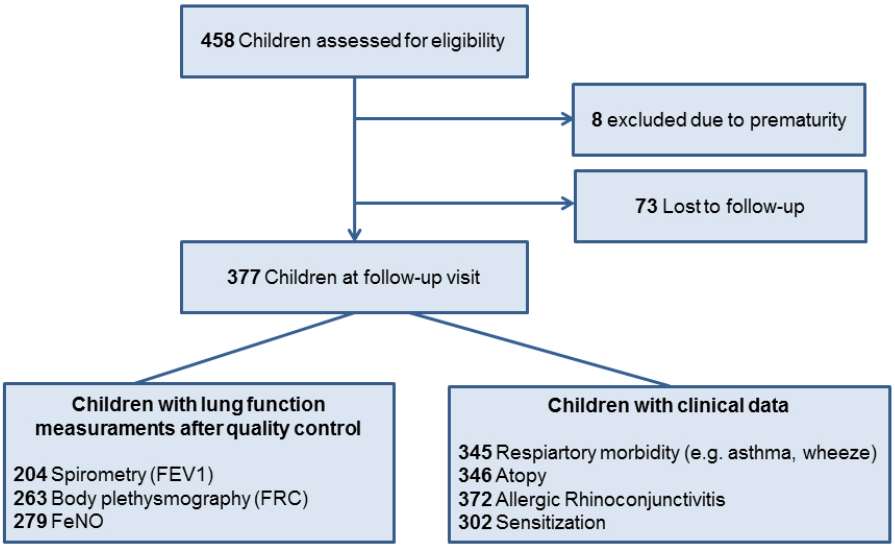

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Table S1: Anthropometric data of the study participants compared to non-included children

	Included	Non-included	p-value
Number of children	377	81	
Anthropometric data			
Male sex, n (%)	204 (54)	44 (54)	0.973
Gestational age, mean (sd), weeks	40 (1.2)	39 (1.9)	0.974
Length at birth, mean (sd), cm	49.6 (2.0)	48.9 (2.2)	0.998
Weight at birth, mean (sd), g	3392 (441)	3283 (511)	0.974
Risk factors			
Caesarean section, n (%)	61 (84)	13 (17)	0.887
Maternal smoking during pregnancy, n (%)	30 (8)	16 (20)	**0.001**
Parental smoking during first year of life, n (%)	75 (20)	26 (34)	**0.008**
Maternal history of allergic conditions[a], n (%)	123 (33)	27 (34)	0.790
Maternal asthma, n (%)	37 (10)	10 (13)	0.450
Paternal history of allergic conditions[a], n (%)	132 (35)	31 (39)	0.486
Paternal asthma, n (%)	35 (9)	12 (15)	0.120
Maternal education [b]			
low, n (%)	151 (40)	28 (40)	**0.020**
middle, n (%)	132 (35)	16 (23)	
high, n (%)	93 (25)	26 (37)	
Presence of older siblings, n (%)	200 (53)	45 (57)	0.526
Exposure			
Breastfeeding, mean (sd), weeks	36 (14)	26 (18)	**<0.001**

Values are mean (standard deviation) or number (percentage). [a] defined as self-reported, doctor-diagnosed asthma, rhinitis or atopic dermatitis; [b] categorized into low (less than four years of apprenticeship), middle (four years of apprenticeship and above) and high (tertiary education).

Table S2: Duration of breastfeeding stratified by exposure, N=377

	N (%)	Median in weeks	IQR in weeks
Study population	377		
Sex			
Male	204 (54)	39	27-47
Female	173 (46)	36	29-52
Gestational age			
≤ 40 weeks	218 (58)	36	26-47
>40 weeks	159 (42)	40	29-52
Parental history of atopy			
No	164 (44)	38.5	30-47.5
Yes	213 (56)	36	27-51
Maternal age at enrollment			
≥ *25y*	367 (97)	39	27-49
< *25y*	10 (3)	37	13-50
Maternal socioeconomic status[1]			
Low	93 (25)	36	26-48
Middle	132 (35)	35	24.5-47.5
High	151 (40)	40	30-51
Maternal smoking during pregnancy	347 (92)	**38**	28-50
No	30 (8)	**32**	30-41
yes			
Parental smoking during first year of life			
No	302 (80)	37	27-48
Yes	75 (20)	36	23-52
Older siblings			
No	177 (47)	37	27-51
yes	200 (53)	37	28-48

[1] Data were available for n=376. [2] Data were available for n=236

in bold shown the significant difference (p-value<0.05)

Table S3: Association of breastfeeding with lung function in non-asthmatic children

	Adjusted model[a]		
Breastfeeding (wks)	N	Coeff (95%CI)	p-value
Spirometry			
FEV_1, ml	195	-0.28 (-1.76; 1.20)	0.713
Bodyplethysmography			
FRC_{pleth}, ml	245	-0.04 (-1.68; 1.60)	0.958
$TLC_{pleth,}$ml	185	1.20 (-1.47; 3.88)	0.377
R_{eff}, ml	248	1.17 (-0.70; 3.04)	0.219
FeNO, ppb	266	1.00 (0.99;1.01)	0.556