Breastfeeding and lung function at school-age: does maternal asthma modify the effect?

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Claudia Kuehni, Caroline Beardsmore, Ben Spycher, Marie-Pierre Strippoli, Urs Frey and Michael Silverman designed the study, Caroline Beardsmore planned and supervised the collection of the data, Marie-Pierre Strippoli and Ben Spycher managed the data and provided consultancy on statistical analysis, Urs Frey, Michael Silverman and Caroline Beardsmore provided consultancy on lung physiology and Cristian Dogaru analyzed the data and wrote a first version of the manuscript. All authors contributed to the interpretation of the data, revised the drafts and read and approved the final manuscript.

Funding

Swiss National Science Foundation (3200B0-122341) and Asthma UK 07/048

Running head

BREASTFEEDING AND LUNG FUNCTION AT SCHOOL-AGE

Descriptor number

1.17 Epidemiology (Pediatric): Risk Factors

Word count: 3591

At a glance commentary

Scientific Knowledge on the Subject

The association between breastfeeding and lung function is a matter of debate, especially in children of asthmatic mothers.

What This Study Adds to the Field

In this cohort, breastfed children of asthmatic mothers had higher FVC, FEV_1 and FEF_{50} compared to non breastfed; our data suggest a direct effect on breastfeeding on lung growth.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

ABSTRACT

Rationale: The evidence for an effect of breastfeeding on lung function is conflicting, in particular whether the effect is modified by maternal asthma.

Objectives: To explore the association between breastfeeding and school-age lung function.

Methods: In the Leicestershire Cohort Studies we assessed duration of breastfeeding (*not breastfed, ≤3 months, 4-6 months,* and *>6 months*), other exposures and respiratory symptoms by repeated questionnaires. Post-bronchodilator FVC, FEV_1, PEF, FEF_{50} and skin prick tests were measured at age 12 years. We performed multivariable linear regression and tested potential causal pathways (N=1458).

Measurements and Main Results: In the entire sample, FEF_{50} was higher by 130 and 164 ml in children breastfed for 4-6 and >6 months respectively, compared to those not breastfed (p=0.048 and 0.041), with larger effects if the mother had asthma. FVC and FEV_1 were associated with breastfeeding only in children of asthmatic mothers (p for interaction 0.018 and 0.008): FVC was increased by 123 and 164 ml for those breastfed 4-6 or >6 months respectively (p=0.177 and 0.040) and FEV_1 was increased by 148 and 167 ml respectively (p=0.050 and 0.016). Results were unchanged after adjustment for respiratory infections in infancy and asthma and atopy in the child.

Conclusions: In this cohort, breastfeeding for over 4 months was associated with increased FEF_{50} and, in children of asthmatic mothers, with increased FEV_1 and FVC. It seems that the effect is not mediated via avoidance of early infections or atopy, but rather through a direct effect on lung growth.

Word count: 246

Key words: breastfeeding; lung function; epidemiology; maternal asthma; effect modification

INTRODUCTION

Breastfeeding has numerous advantages for infants, mothers and society, including developmental, nutritional, immunological, psychological, social, economic and environmental benefits (1). The World Health Organization and the American Association of Pediatrics therefore recommend exclusive breastfeeding for 6 months and partial breastfeeding for the first year and beyond (2). Less clear is the impact of breastfeeding on respiratory health. It is generally accepted that breastfed children have fewer respiratory infections than their non-breastfed peers, and that these are less severe (3-5).

Few studies have investigated a possible effect of breastfeeding on lung function, with heterogeneous results (Tables E1-E2 in the online data supplement) (6-11). Most found a higher forced vital capacity (FVC) or forced expiratory volume at 1 second (FEV_1) in school-age children who had been breastfed (6, 8-11). Results for other lung function measurements were more discrepant: two studies found higher peak expiratory flow rates (PEF) in breastfed children (7, 9), one study found no association with FEV_1/FVC (9) while Guilbert and co-authors reported decreased FEV_1/FVC in breastfed children, particularity in those whose mothers had asthma, suggesting a detrimental effect of breastfeeding in this subgroup (6).

Previous studies have suffered from methodological limitations. These include insufficient adjustment for important confounders such as tobacco smoke exposure. Also, important sources of bias were often not addressed, such as the possibility of reverse causation (12, 13) – early wheeze leading to prolongation of breastfeeding – which was addressed in one study only (7). None of the studies addressed the possible bias introduced by excluding cases with missing values from the analysis (14, 15). Furthermore, only two studies (6, 9) investigated in detail a possible effect modification by maternal history of asthma or atopy.

In this study, we investigated the association between breastfeeding and lung function at school-age in a population-based cohort of children, adjusting for important confounders and minimizing methodological limitations of previous studies. We determined if breastfeeding has differential effects on different lung function measures, assessed whether associations differed by any maternal history of asthma, and explored possible pathways (early infections and wheezing disorders/atopy) that could explain our findings (Figure 1). We hypothesized that longer duration of breastfeeding is associated with increased lung function values after appropriate adjustment for confounders and reverse causation, but there is no effect modification by maternal asthma for any outcome. Some of the results of this study have been previously reported in the form of an abstract (16).

METHODS

More details are provided in the online data supplement.

Study population and measurements

We analyzed data from a nested sample of 1458 children born 1993-97 from the Leicestershire cohorts, described in detail elsewhere (17, 18). In short, we recruited a random population-based sample of 6808 children of white and south Asian ethnic origin. Perinatal data were collected at birth, and data on growth and development were acquired prospectively during childhood. Respiratory morbidity and individual and family-related exposures were assessed by repeated questionnaires (1998, 2001, 2003, 2006, 2010). In 2006-2010, families who had returned two or more questionnaires (N=4125) were invited to the lab for assessment of lung function by spirometry and atopic status by skin prick tests.

We recorded FVC, FEV_1, PEF and forced mid-expiratory flow (FEF_{50}) before and 15 min after administering salbutamol 400 mcg by spacer. The main outcome was post-bronchodilator lung function, because it reflects structural lung development rather than reversible airway obstruction. Skin prick tests were performed for four allergens (cat hair, dog hair, 6-grass mix and house dust mite), a positive and a negative control.

Information on total duration of any breastfeeding, categorized as *not breastfed, ≤ 3 months, 4-6 months,* and *> 6 months,* was collected in 1998, when children were aged 1 year (N=979) or 2-4 years (N=479)**.** The question has excellent repeatability, Cohen's kappa=0.96 (19).

The study was approved by the local Area Health Authority Research Ethics Committee.

Data analysis

We investigated the association between breastfeeding and lung function and whether it might be explained by various pathways (Figure 1), using multivariable linear regression models. A complete data analysis that excludes children with missing data on any variable reduces the analyzable sample to half (N=773). To improve statistical power and minimize possible bias in estimating associations, we used multiple imputations (14, 15).

Each lung function measure was analyzed in three steps. First, we adjusted only for anthropometric data (age, height, weight and sex; *baseline model*). Second, we adjusted additionally, in the entire sample and stratified by maternal asthma, for potential confounders (perinatal data, ethnicity, socioeconomic factors, urban residence, parental history of asthma, exposure to infections, wheezing during breastfeeding and prenatal and postnatal tobacco smoke exposure) as described in the online supplement and in Table 1 (*adjusted model).* Third, we included an interaction term to test for effect modification by maternal asthma (*interaction model*).

We performed additional analyses to examine potential sources of bias: 1a) effect of missing data/multiple imputation, repeating the analyses for children with complete data; 1b) breastfeeding recall bias, excluding children with assessment of breastfeeding after age 1 year; 1c) reverse causation, separately excluding children with onset of wheeze during breastfeeding and during first year; and 1d) effect of reversible airway obstruction, by looking at pre-bronchodilator lung function. We also investigated possible causal pathways between breastfeeding and lung function: 2a) early respiratory infections in general and early lower respiratory tract infections in particular and 2b) development of atopy and/or asthma. We used Stata 11.2 for analysis (Stata Corporation, Austin, Texas).

RESULTS

Participants

Of the 4125 children invited for laboratory measurements, 1477 attended. Among those 19 had been born extreme preterm (birth weight <1500 g or gestational age <32 weeks) and were dropped from the analysis, resulting in a final sample of 1458. The mean age at lung function measurement was 12.2 years (range 8.5-14.0). Compared with children not attending the lab, participants with spirometry tended to have been breastfed for longer, to be white, have older and better educated parents and live in affluent areas. They were less likely to have attended a nursery, less likely to have had prenatal tobacco smoke exposure, but more likely to have been exposed postnatally (Table E3 in the online data supplement).

Breastfeeding prevalence

Overall, 471 children (32%) had not been breastfed at all, 438 (30%) had been breastfed for ≤3 months, 213 (15%) for 4-6 and 326 (22%) for >6 months[1]. Longer duration of breastfeeding was associated with higher birth weight, higher gestational age, older siblings, nursery use, wheezing with onset during the breastfeeding period, older mothers, south Asian ethnicity, better-educated parents, living in affluent area and less pre- and postnatal tobacco smoke exposure (Table 1).

Breastfeeding and lung function

The complete results of the three models (baseline, adjusted and with interaction) for all lung function measures are presented in Table E4 in the online data supplement, both for the entire sample and stratified by maternal asthma. The most pertinent findings are summarized in Table 2, Table 3 and Figure 2 and are discussed below.

FVC and FEV_1: In the entire sample we did not find evidence for an association between duration of breastfeeding and post-bronchodilator FVC or FEV_1, neither in the baseline model nor after adjustment for potential confounders (Table 2, Table E4). For FEV_1 for instance, the estimated difference compared to no breastfeeding in the adjusted model was 0.010 L (p=0.653) for breastfeeding $\leq$3 months, 0.012 L (p=0.674) for breastfeeding 4-6 months and 0.041 L (p=0.239) for breastfeeding >6 months (Table E4 – adjusted model – entire sample). When we stratified for maternal asthma, there was again no evidence for an association between breastfeeding and FVC or FEV_1 in children of non-asthmatic mothers (Table E4 – adjusted model – children of non-asthmatic mothers). Children of asthmatic mothers, however, had significantly higher FVC and FEV_1 if they had been breastfeed for 4 months or longer. For instance: the estimated difference for FEV_1 was 0.148 L (p=0.028) for breastfeeding 4-6 months and 0.183 L (p=0.019) for breastfeeding >6 months (Table E4 – adjusted model – children of asthmatic mothers).

Allowing for effect modification by maternal asthma (Table 3 and Figure 2), we found that, if not breastfed, children of asthmatic mothers tended to have a lower FVC (estimated difference -0.080 L, p=0.062) and FEV_1 (estimated difference -0.095 L, p=0.011) than children of non-asthmatic mothers. We found no evidence of association between breastfeeding and FVC or FEV_1 in children of non-asthmatic mothers. However, in children of asthmatic mothers, FEV_1 was higher if they had been breastfed: estimated differences 0.148 L (p=0.050, p-value for interaction between breastfeeding and maternal asthma =0.016) and 0.167 L (p=0.016, p-value for interaction =0.08) for breastfeeding 4-6 months and >6 months respectively. Results for FVC were essentially similar.

FEF_{50}: For forced mid-expiratory flows, results were somewhat different. Here, we found evidence for an increase of FEF_{50} with increasing duration of breastfeeding in the entire sample, with estimated differences in FEF_{50} of 0.130 L/sec (p=0.048) and 0.164 L/sec (p=0.041) for breastfeeding 4-6 months and >6 months respectively, compared to those not breastfed (Table 2 or Table E4 – adjusted model – entire sample). These increases were greater in children of asthmatic mothers (estimated differences 0.375 L/sec (p=0.015) and 0.468 L/sec (p=0.009) for breastfeeding 4-6 months and > 6 months compared to non-breastfed) (Table E4 – adjusted model – children of asthmatic mothers). The model including interaction terms showed again evidence for lower FEF_{50} (estimated difference -0.175 L, p=0.040) in non-breastfed children of asthmatic compared to non-breastfed children of non-asthmatic mothers. There was also evidence for higher FEF_{50} in children of asthmatic mothers breastfed for 4 months or longer, but limited evidence for an effect modification by maternal asthma (*p-interaction* 0.140 and 0.220 for breastfeeding 4-6 months and >6 months respectively) (Figure 2 and Table 3).

FEV_1/FVC and PEF: There was no evidence of association between breastfeeding and PEF or FEV_1/FVC. In children of asthmatic mothers, there was again a tendency for reduced values in non-breastfed children and higher values in breastfed children, however, p-values for associations and interaction terms did not reach conventional significance thresholds.

Additional analyses

Our results remained similar after (a) analyzing only children with complete data (no imputation; additional analysis 1a); (b) restricting the analysis to children in whom breastfeeding had been assessed at age 1 when recall is likely to be most accurate (additional analysis 1b); (c) excluding from analysis children who had wheeze onset during breastfeeding (first approach) and excluding all children with wheeze onset during the first year of life (second approach) to eliminate a possible bias due to reverse causation (additional analysis 1c) and (d) analyzing pre-bronchodilator lung function rather than post-bronchodilator outcomes (additional analysis 1d) (Table E5 to E7 in the online data supplement).

In a last step, we adjusted for alternative causal pathways, which could help to explain our findings , by (a) adjusting for frequency and severity of all respiratory infections in general and lower respiratory tract infections in particular during the first year of life, to assess whether the improved lung function in breastfed children might be explained by reduced number or severity of (lower) respiratory infections during infancy (additional analysis 2a) and (b) adjusting using separate variables for manifestations of atopy, measured through skin prick tests, and asthma history in the child, to assess whether the improved lung function in breastfed children might be explained by a reduced risk to develop atopy and/or asthma (additional analysis 2b). Results of these two analyses were again similar to those of the main analyses (Table E5 to E7 in the online data supplement).

DISCUSSION

Findings

This study investigated the relationship between duration of breastfeeding and lung function at school-age in a cohort study of children monitored since birth. Children breastfed for four months or longer had larger forced mid-expiratory flows (FEF_{50}) at school-age. Children of asthmatic mothers had larger FVC and FEV_1 if they had been breastfed, with evidence for a dose-response relationship with duration of breastfeeding. Most importantly, there was no evidence for a detrimental effect of breastfeeding in children whose mothers had asthma. Results were not changed by adjustment for confounders and remained robust in numerous additional analyses designed to evaluate potential biases related to study population, assessment of breastfeeding and lung function, statistical analysis and reverse causation.

Few studies have investigated the effect of breastfeeding on lung function at school-age (Tables E1, E2 in the online data supplement). Associations with FVC and FEV_1 have been reported by several authors. Guilbert found in the Tucson Respiratory Cohort a larger FVC (+103 ml, p=0.010) in children breastfed for longer than 4 months, but no evidence for an association with FEV_1 (6). Ogbuanu reported, from the Isle of Wight study, an increased FVC (+54ml, p=0.001) and FEV_1 (+39.5ml, p=0.050) in ten year olds who had been breastfed (9). From the same study, Soto-Ramirez reported, several years later, an increased FVC (+1.48mL/week of breastfeeding, p=0.01) and FEV_1 (+1.21mL/week of breastfeeding, p=0.03) (10). Similarly, a higher FEV_1 was reported for breastfed children from affluent countries in the ISAAC study (8), the Newcastle Thousand families study from the UK (11) and the BAMSE cohort from Sweden (7). Overall, these studies suggest a small but positive effect of breastfeeding.

Studies on PEF, FEF_{50} and FEV_1/FVC were more heterogeneous. Kull and Ogbuanu reported higher PEF in breastfed children (7, 9), two studies did not report on flows (8, 11) while Guilbert found a negative association between breastfeeding and FEV_1/FVC ratio and FEF_{25-75} (p=0.004 and 0.090, respectively) in the entire group, that was particularly evident in children of asthmatic mothers (6). In our cohort, in contrast, there was little evidence for an association between breastfeeding and PEF and FEV_1/FVC. However, we found a higher FEF_{50} in breastfed children in the entire group and in breastfed children of asthmatic mothers.

The question of an effect modification by maternal asthma remains controversial. Guilbert and colleagues concluded that "... longer breastfed children of mothers with asthma demonstrate no improved lung growth and significant decrease in airflows later in life" (6) (p.847), making breastfeeding a potential hazard for children of asthmatic mothers. As potential mechanisms, they suggested transmission of maternal IgE or other immunologically active substances through breast milk. If confirmed, these findings should lead to changes in feeding recommendations, making the topic highly relevant. However, the findings from Tucson were not supported by a test for interaction and were not replicated by other cohorts (7-9). Our results further help to remove concerns that breastfeeding might harm children of mothers with asthma. We found no evidence for an effect modification by maternal asthma on mid-expiratory flows, while FVC and FEV_1 were significantly higher rather than lower in breastfed children of asthmatic mothers. It is unclear why our results differ from those from Tucson. Possible explanations include chance, differences in confounders used in the analysis, or a bias such as reverse causation. They could, however, also reflect real differences between the two studies. For instance, if asthmatic mothers in Tucson had been treated with oral steroids or high-dose bronchodilators, these drugs, transmitted through breast milk, might have influenced fetal lung development and thus later airway function. Note also that the design of the Tucson study differed from ours; they looked at lung function at two points in time, at 11 and 16 years, using a longitudinal random-effects model. The Tucson study also reported an effect in children of atopic but not asthmatic mothers. We performed a separate analysis using maternal history of hayfever instead of asthma as predictor/effect modifier, but we did not find evidence for differences in the association between breastfeeding and lung function by maternal history of hayfever (results not reported). This suggests that maternal asthma rather than atopy is responsible for the differential effect in children of affected mothers.

Possible mechanisms or pathways

There are several mechanisms by which breastfeeding might influence lung function in children. These include: (a) reducing the frequency and severity of viral infections during infancy through transmission of maternal IgA or other immunological agents via breast milk (3,), resulting in less virus-induced lung damage (20), and (b) reducing the risk of atopy, asthma or reactive airway disease in the child (21). These two mechanisms might interact, although the literature on this issue is unclear (22). Finally, (c) breastfeeding might directly influence lung development by transmission of relevant cytokines or maternal hormones (23), which stimulate alveolarization (24-26) or airway growth or, as suggested by the researchers from the Isle of Wight study, by mechanical stimuli related to suckling (9, 10).

In our study, we examined whether these mechanisms account for the better lung function observed in breastfed children by including into our analysis a number of relevant variables related to these pathways. If the effect was mediated via one of these mechanisms, we would expect the effect of breastfeeding to decrease when the variables were included into the equation. This was not the case, suggesting, at least partially, a direct effect of breastfeeding on lung growth and structure. This is also supported by the fact that we found the association both in post-bronchodilator and pre-bronchodilator lung function. The ISAAC study also reported an effect of breastfeeding on lung function, but not on bronchial hyperresponsiveness (8).

When we stratified the analysis for maternal asthma, our findings were more complex. Children who had not been breastfed had lower FVC, FEV_1 and FEF_{50} if their mothers had asthma. Breastfeeding was associated with a better FVC and FEV_1 in children of asthmatic mothers and with a better FEF_{50} in all children (independent of maternal asthma).

It is not clear why an effect of breastfeeding should differ between children of asthmatic and children of non-asthmatic mothers; we can only speculate on the mechanisms. One possible explanation is that asthmatic mothers have more frequent or more severe respiratory infections which they could pass on to their infants (27, 28). If these infections are not tempered by breastfeeding, they could lead to poorer lung development and lung function. However, in the additional analysis we did not find a mediating effect of early infections. It is possible that the mechanisms are more complex so that their effect could not be captured in our model and/or that there are other possible explanations. For instance, children of asthmatic mothers might have a genetic or epigenetic susceptibility to poor lung growth that could interact with breastfeeding. The question remains open.

Strengths and limitations

This study has a number of strengths: it used data from a large representative cohort with short recall time for breastfeeding and prospective assessment of other exposures and respiratory outcomes. We included a large number of potential confounders in the analysis and we tested the robustness of our results with a number of additional analyses, looking at the effect of missing data, recall bias, and reverse causation. Limitations include the modest response rate for the laboratory examinations (36%), which has reduced power and could potentially have introduced bias. The most likely explanation for the low participation is that many potential participants were discouraged because they expected a lengthy and time-consuming procedure. The number of appointments that could be offered during school holiday times were limited and many parents are reluctant to take their children away from school. However, this response rate is not unusual for lab measurements in a population based cohort. The sample analysed might not be fully representative of the entire population of Leicestershire area. The results from the participants/non-participants comparison analysis (Table E3 in the online data supplement) suggest that the participants tended to come from a higher socio-economic class. Similarly, breastfeeding prevalence in our sample differed slightly from the prevalence in Leicestershire area (29), with proportionally more children being breastfed in our sample. This, however, should not affect the association between breastfeeding duration and lung function measurements. As in other studies (6, 9), we relied on self-reported duration of breastfeeding, maternal asthma, and infections during infancy. The repeatability of the question on duration of breastfeeding in this cohort was excellent (Cohen's kappa 0.96) suggesting high validity of this information (19). There was also a potential risk for recall bias for the age of wheezing onset. The sensitivity analysis in children who were 1 year old at recruitment yielded comparable results; therefore we are confident that our findings are robust.

Relevance of the findings

The mean differences in lung function detected in this study between breastfed and non-breastfed children are not very relevant, clinically, for healthy children. However, if we consider the number of children falling below a certain lung function threshold rather than a shift in mean values, our findings become relevant at population level. For instance, if we take as threshold the value of the 20th percentile of lung function (adjusted for age, sex, height, weight) among non-breastfed children of asthmatic mothers, and assuming that breastfeeding causes a shift in the Gaussian distribution of FVC (FEV_1) by 165mL (168mL), as estimated in our study, then the number of children falling below the threshold would decrease from 20% to 9%. These reductions are important at a population level. These children with lower FVC or FEV_1 as young adults might be more at risk of developing COPD later in life.

Conclusions

In conclusion, this study adds importantly to existing evidence against claims that breastfeeding could be harmful in children of asthmatic mothers. In contrast, it suggests a modest improvement in mid-expiratory flows in all children, and in FVC and FEV_1 in the offspring of asthmatic mothers. Our data suggest that, rather than acting via reduction of respiratory infections, asthma or allergy, breastfeeding might have a direct effect on lung growth, which should be investigated further. In the meantime, breastfeeding can remain strongly recommended for all infants, including those whose mothers have asthma.

ACKNOWLEDGEMENTS

We thank the parents of Leicestershire children for completing the questionnaires, Tony Davis (Specialist Community Child Health Services, Leicester City Primary Care Trust, Leicester, UK) for his assistance with the Child Health Database and Teresa McNally for laboratory measurements and data management.

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FIGURE LEGENDS

Figure 1

Model of the association between breastfeeding and lung function, including potential confounders and pathways

Notes: it is hypothesized that the variables in the model have an influence on lung growth and development which, in turn, impact lung function measurements at school-age

[*]skin prick test for cat, dog, grass, dust; history of severe wheeze

[†]frequency and duration of colds during first year; number of other respiratory infections during first year

[‡]sex, age, height, quadratic height, weight, quadratic weight, number of older siblings, nursery use, birth weight, gestational age, birth season (winter, spring, summer, autumn), wheeze onset during breastfeeding

[§]maternal age, maternal ethnicity, family education, maternal asthma, paternal asthma, Townsend deprivation score (25), residence area (urban or rural)

‖smoking exposure during pregnancy, smoking exposure during childhood

[**] wheezing during breastfeeding is a precursor of wheezing in later life which can lead to poor lung development and to poor lung function (arrow not shown). However, it could also play a role in reverse causation (when the outcome influences the exposure): poor lung function at school-age may be a direct result of poor lung development in infancy which may have caused wheezing which in turn may have influenced the duration of breastfeeding (the dashed line in the figure).

Figure 2

Adjusted mean values of lung function and 95% confidence intervals among children of non-asthmatic (N=1167) and asthmatic mothers (N=273), categorized by duration of breastfeeding

Note: this figure presents the results from the adjusted model with interaction term between breastfeeding and maternal asthma

Abbreviations: FVC=forced vital capacity; FEV_1=forced expiratory volume at 1 second; BF=breastfeeding; mo=months

Adjusted for birth weight, gestational age, birth season (winter, spring, summer, autumn), age, height, weight, sex, number of older siblings, nursery use, wheeze onset during breastfeeding, maternal age, maternal ethnicity, family education, maternal asthma, paternal asthma, Townsend deprivation score, residence area (urban or rural), smoking exposure during pregnancy, smoking exposure during childhood (see supplemental material for description of variables).

FOOTNOTES

[1]Descriptive statistics are based on original values, and not imputed ones; therefore, in all descriptive tables the frequencies do not add up to the total of 1458, due to missing values.

TABLES

Table 1. Characteristics of the study population, number (%) or mean (SD), by duration of breastfeeding (N=1458)

	complete data[*]	*no BF N=471*	*BF<3 mo N=438*	*BF=4-6 mo N=213*	*BF>6 mo N=326*	*p*
Child variables						
Birth weight[*] (grams)	1424	3315 (557)	3314 (516)	3401 (553)	3425 (491)	0.007
Gestational age[†] (weeks)	1422	39.2 (1.7)	39.3 (1.7)	39.5 (1.6)	39.5 (1.5)	0.019
Age at spirometry[†] (years)	1457	12.3 (1.2)	12.2 (1.2)	12.2 (1.2)	12.2 (1.2)	0.628
Height at spirometry[†] (cm)	1458	153 (9.7)	152 (10.3)	153 (10.0)	153 (10.0)	0.910
Weight at spirometry[†] (kg)	1458	47.3 (12.5)	45.8 (12.1)	45.4 (10.6)	45.6 (11.4)	0.093
Female[‡]	1458	214 (45.4)	217 (49.5)	106 (49.8)	145 (44.5)	0.539
Number of older siblings[†]	1421	0.97 (1.00)	0.81 (0.94)	0.90 (0.87)	1.04 (1.04)	0.008
Nursery use[‡]	1445	178 (37.8)	185 (42.2)	108 (50.7)	147 (45.1)	<0.001
Wheezing during breastfeeding[‡]	992	0 (0.0)	18 (4.3)	36 (14.5)	261 (20.2)	<0.001
Asthma history[†,§]	1448	2.2 (3.5)	1.4 (2.5)	1.5 (2.8)	1.7 (3.3)	0.001
Frequency of colds[†,‖]	1436	1.7 (0.8)	1.6 (0.7)	1.8 (0.8)	1.7 (0.8)	0.085
Duration of colds[†,**]	1427	0.9 (0.7)	0.8 (0.6)	0.8 (0.7)	0.8 (0.7)	0.098
Respiratory infections[†,††]	1438	1.0 (1.0)	0.9 (1.0)	1.0 (1.0)	0.9 (1.0)	0.238
Positive SPT[‡]	1458	173 (36.7)	173 (39.5)	88 (41.3)	130 (39.9)	0.707
Family variables						
Maternal age[†] (years)	1457	28.89 (4.81)	29.21 (4.71)	30.67 (4.86)	31.39 (4.61)	<0.001
South Asian mother[‡]	1458	65 (13.8)	117 (26.7)	42 (19.7)	68 (20.9)	<0.001
High family education[‡,‡‡]	1380	209 (44.4)	271 (61.9)	141 (66.2)	240 (73.6)	<0.001
Maternal asthma[‡]	1394	93 (19.7)	83 (18.9)	36 (16.9)	55 (16.9)	0.414
Paternal asthma[‡]	1355	96 (20.4)	72 (16.4)	43 (20.2)	64 (19.6)	0.030
Living in an affluent area[‡,§§]	1437	229 (48.6)	219 (50.0)	126 (59.2)	206 (63.2)	0.003
Urban residence[‡]	1458	246 (52.2)	244 (55.7)	106 (49.8)	154 (47.2)	0.062
Tobacco smoke exposures						
Smoking during pregnancy[‡]	1422	106 (22.5)	47 (10.7)	12 (5.6)	19 (5.8)	<0.001
Smoking during childhood[†,‖‖]	1458	1.34 (1.73)	1.02 (1.57)	0.73 (1.30)	0.69 (1.31)	<0.001

Abbreviations: BF=breastfeeding; mo=months; SPT=skin prick test; SD=standard deviation

[*] number of cases with complete data on each particular variable

[†] numeric covariates: values are Mean (SD); ANOVA test comparison

[‡] categorical covariates: values are N (%), column percentages; chi-square test comparison

[§] sum of four severity scores calculated at four data collection points as follows: 0=*no current wheeze*; 1=*current wheeze, no treatment*; 2=*current wheeze + treatment with short-acting beta agonists only;* 3=*current wheeze + treatment with ICS or montelukast*; and 4=*current wheeze + treatment with steroid tablets*.

[‖] based on a question from 1998 questionnaire: *"In the last 12 months, how many times has your child had a cold or flu? (never, 1-3 times, 4-6 times, 7 or more times)".* The variable was treated as numeric.

[**] based on a question from 1998 questionnaire: *"How long does a cold usually last in your child? (less than 1 week; 1-2 weeks; 2 to 4 weeks; more than 4 weeks)".* The variable was treated as numeric.

[††] includes pneumonia, whooping cough, bronchiolitis, croup, throat infections and other chest infections. The variable represents the sum.

[‡‡] higher educational level attained by either parent, based on the British educational system: *low*=none, GCSE/O or trade; *high*=A-levels, below degree, degree

[§§] above median value of Townsend deprivation score, an area-based deprivation score (1)

‖ each family returned between 2 and 4 questionnaires before attending for measurements; the number represents the mean number of occasions when maternal smoking was reported (see online supplement)

Table 2. Association between breastfeeding duration and lung function in the entire sample of children (baseline model and model adjusted for confounders)

	FVC, [L]: b (*p*)	FEV_1, [L]: b (*p*)	FEV_1/FVC: b (*p*)	PEF, [L/sec]: b (*p*)	FEF_{50}, [L/sec]: b (*p*)
Baseline model†					
no BF‡	2.838	2.531	0.891	5.587	3.402
BF≤3 mo	-0.039 (0.116)	-0.02 (0.356)	0.007 (0.064)	-0.01 (0.865)	0.034 (0.479)
BF=4-6 mo	-0.010 (0.758)	-0.002 (0.949)	0.003 (0.446)	0.015 (0.839)	0.112 (0.061)
BF>6 mo	0.024 (0.370)	0.025 (0.286)	0.002 (0.560)	0.077 (0.222)	0.116* (0.026)
Adjusted model§					
no BF‡	2.835	2.528	0.892	5.621	3.386
BF≤3mo	-0.001 (0.970)	0.010 (0.653)	0.005 (0.195)	-0.008 (0.889)	0.043 (0.395)
BF=4-6 mo	0.006 (0.849)	0.012 (0.674)	0.003 (0.503)	-0.016 (0.838)	0.130* (0.048)
BF>6 mo	0.035 (0.358)	0.041 (0.239)	0.004 (0.491)	0.004 (0.970)	0.164* (0.041)

Abbreviations: FVC=Forced Vital Capacity; FEV_1=Forced Expiratory Volume at 1 second; PEF=Peak Expiratory Flow; FEF_{50}=Forced mid-Expiratory Flow;

L=liters; L/sec= liters per second; *b*=unstandardized regression coefficient (represents difference from reference category); BF=breastfeeding; mo=months

*$p \leq 0.05$

†adjusted for age, height, weight, sex and quadratic terms for height and weight

‡ reference category (intercept); the values represents the average lung function values in that category

§adjusted for birth weight, gestational age, birth season (winter, spring, summer, autumn), age, height, weight, sex, number of older siblings, nursery use, wheeze onset during breastfeeding, maternal age, maternal ethnicity, family education, maternal asthma, paternal asthma, Townsend deprivation score, residence area (urban or rural), smoking exposure during pregnancy, smoking exposure during childhood

Table 3. Association between maternal asthma, breastfeeding duration and lung function (adjusted model with interaction[†])

	FVC, [L]: b (p)	FEV_1, [L]: b (p)	FEV_1/FVC: b (p)	PEF, [L/sec]: b (p)	FEF_{50}, [L/sec]: b (p)
Non-breastfed children					
no maternal asthma[‡]	2.851	2.547	0.894	5.639	3.421
maternal asthma	-0.080 (0.062)	-0.095* (0.011)	-0.010 (0.111)	-0.091 (0.374)	-0.175* (0.040)
Children of non-asthmatic mothers (N=1167)					
no BF[‡]	2.851	2.547	0.894	5.639	3.421
BF≤3 mo	-0.018 (0.520)	-0.001 (0.964)	0.005 (0.192)	-0.026 (0.703)	0.024 (0.664)
BF=4-6 mo	-0.022 (0.537)	-0.019 (0.534)	0.001 (0.828)	-0.055 (0.527)	0.086 (0.234)
BF>6 mo	0.003 (0.932)	0.010 (0.795)	0.003 (0.656)	-0.035 (0.723)	0.130 (0.125)
Children of asthmatic mothers (interaction terms) (N=273)					
no BF[‡]	2.770	2.451	0.884	5.547	3.246
BF≤3 mo	0.063 (0.417)	0.051 * (0.569)	0.002 (0.409)	0.056 (0.846)	0.111* (0.548)
interaction[§]	0.081 (0.187)	0.052 * (0.334)	-0.003 (0.728)	0.082 (0.576)	0.086* (0.482)
BF=4-6 mo	0.123 (0.177)	0.148** (0.050)	0.013 (0.477)	0.149 (0.550)	0.319* (0.049)
interaction[§]	0.145 *(0.064)	0.167** (0.016)	0.011 (0.313)	0.204 (0.283)	0.234* (0.141)
BF>6 mo	0.164* (0.040)	0.167** (0.016)	0.009 (0.645)	0.161 (0.490)	0.296* (0.061)
interaction[§]	0.161* (0.018)	0.158** (0.008)	0.006 (0.531)	0.196 (0.233)	0.166* (0.224)

Abbreviations: FVC=Forced Vital Capacity; FEV_1=Forced Expiratory Volume at 1 second; PEF=Peak Expiratory Flow; FEF_{50}=Forced mid-Expiratory Flow; *b*=unstandardized regression coefficient (represents difference from reference category); L=liters; L/ sec=liters per seconds; BF=breastfeeding; mo=months

*$p \leq 0.05$; **$p \leq 0.01$

[†]adjusted for age, height, weight, sex, quadratic terms for height and weight, birth weight, gestational age, birth season (winter, spring, summer, autumn), age, height, weight, sex, number of older siblings, nursery use, wheeze onset during breastfeeding, maternal age, maternal ethnicity, family education, maternal asthma, paternal asthma, Townsend deprivation score, residence area (urban or rural), smoking exposure during pregnancy, smoking exposure during childhood and interaction term between breastfeeding and maternal asthma

[‡]reference category (intercept); the values represents the average lung function values in that category

[§]the interaction term reflects the *additional* difference in children of asthmatic mothers compared with the corresponding difference in children of non-asthmatic mothers, for a particular level of breastfeeding. For example, the difference in FVC between *BF<3mo* and *no BF* in children of asthmatic mothers (0.063) equals the corresponding difference in children of non-asthmatic mothers (-0.018) *plus* the interaction term (0.081). A model without interaction terms assumes that the differences are equal in the two groups (children of asthmatic and non-asthmatic mother