Breastfeeding and Lung Function at School Age

Does Maternal Asthma Modify the Effect?

Cristian M. Dogaru[1], Marie-Pierre F. Strippoli[1], Ben D. Spycher[1,2], Urs Frey[3], Caroline S. Beardsmore[4], Michael Silverman[4], and Claudia E. Kuehni[1]

[1]Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland; [2]School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom; [3]Department of Paediatrics, University Children's Hospital of Basel, Basel, Switzerland; and [4]Department of Infection, Immunity, and Inflammation, University of Leicester, Leicester, United Kingdom

***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, peak expiratory flow (PEF), forced midexpiratory flow (FEF_{50}), and skin prick tests were measured at age 12 years. We performed multivariable linear regression and tested potential causal pathways (N = 1,458).**

***Measurements and Main Results*: In the entire sample, FEF_{50} was higher by 130 and 164 ml in children breastfed for 4 to 6 months and longer than 6 months, respectively, compared with 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 mothers with asthma (P for interaction, 0.018 and 0.008): FVC was increased by 123 and 164 ml for those breastfed 4 to 6 months or longer than 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 more than 4 months was associated with increased FEF_{50} and, in children of mothers with asthma, 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.**

Keywords: breastfeeding; lung function; epidemiology; maternal asthma; effect modification

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 mothers with asthma.

What This Study Adds to the Field

In this cohort, breastfed children of mothers with asthma had higher FVC, FEV_1, and FEF_{50} compared with nonbreastfed. Our data suggest a direct effect of breastfeeding on lung growth.

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 nonbreastfed peers and that these are less severe (3–5).

Few studies have investigated a possible effect of breastfeeding on lung function, with heterogeneous results (*see* Tables E1 and E2 in the online supplement) (6–11). Most found a higher FVC or 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), and Guilbert and coauthors 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

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Correspondence and requests for reprints should be addressed to Claudia E. Kuehni, Ph.D., Institute of Social and Preventive Medicine, University of Bern, Finkenhubelweg 11-3012 Bern, Switzerland. E-mail: kuehni@ispm.unibe.ch

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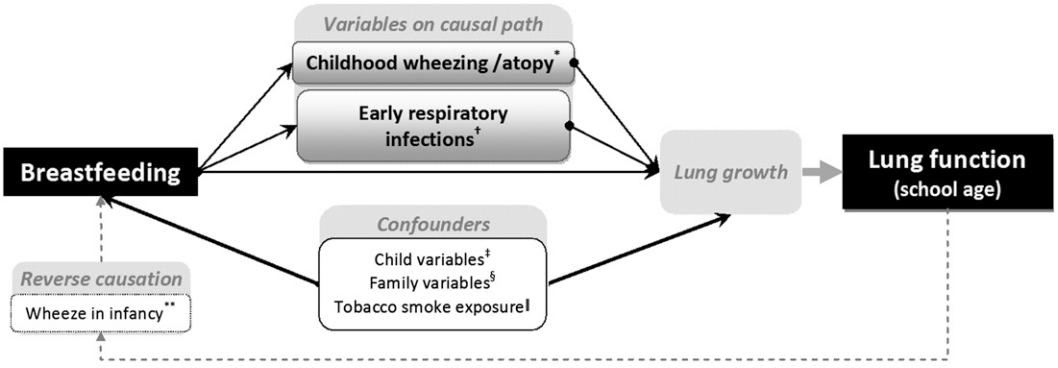

Figure 1. Model of the association between breastfeeding and lung function, including potential confounders and pathways. It is hypothesized that the variables in the model have an influence on lung growth and development, which, in turn, impact lung function measurements at school age. *Skin prick test 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 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 (*dashed line*).

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 supplement.

Study Population and Measurements

We analyzed data from a nested sample of 1,458 children born between 1993 and 1997 from the Leicestershire cohorts, described in detail elsewhere (17, 18). In short, we recruited a random population-based sample of 6,808 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 to 2010, families who had returned two or more questionnaires (n = 4,125) were invited to the laboratory for assessment of lung function by spirometry and atopic status by skin prick tests. We recorded FVC, FEV_1, PEF, and forced midexpiratory flow (FEF_{50}) before and 15 minutes after administering salbutamol 400 μg 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, six-grass mix, and house dust mite), a positive and a negative control.

Information on total duration of any breastfeeding, categorized as not breastfed, less than or equal to 3 months, 4 to 6 months, and more than 6 months, was collected in 1998, when children were aged 1 year (n = 979) or 2 to 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 prebronchodilator 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, TX).

RESULTS

Participants

Of the 4,125 children invited for laboratory measurements, 1,477 attended. Among those, 19 had been born extreme preterm (birth weight < 1,500 g or gestational age < 32 wk) and were dropped from the analysis, resulting in a final sample of 1,458. The mean age at lung function measurement was 12.2 years (range 8.5–14.0 yr). Compared with children not attending the laboratory, participants with spirometry tended to have been breastfed for longer, to be white, to have older and better-educated parents, and to live in affluent areas. They were less likely to have attended a nursery and less likely to have had prenatal tobacco smoke exposure but more likely to have been exposed postnatally (Table E3).

Breastfeeding Prevalence

Overall, 471 children (32%) had not been breastfed at all, 438 (30%) had been breastfed for 3 or fewer months, 213 (15%) for 4 to 6 months, and 326 (22%) for more than 6 months. (Descriptive statistics are based on original values, not imputed ones; therefore, in all descriptive tables the frequencies do not add up to the total of 1,458 due to missing values.) Longer duration of breastfeeding was associated with higher birth weight, higher

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION

	Complete Data*	No BF (*n* = 471)	BF ⩽ 3 mo (*n* = 438)	BF 4–6 mo (*n* = 213)	BF > 6 mo (*n* = 326)	*P* Value
Child variables						
Birth weight,† g	1,424	3,315 (557)	3,314 (516)	3,401 (553)	3,425 (491)	0.007
Gestational age,† wk	1,422	39.2 (1.7)	39.3 (1.7)	39.5 (1.6)	39.5 (1.5)	0.019
Age at spirometry,† yr	1,457	12.3 (1.2)	12.2 (1.2)	12.2 (1.2)	12.2 (1.2)	0.628
Height at spirometry,† cm	1,458	153 (9.7)	152 (10.3)	153 (10.0)	153 (10.0)	0.910
Weight at spirometry,† kg	1,458	47.3 (12.5)	45.8 (12.1)	45.4 (10.6)	45.6 (11.4)	0.093
Female‡	1,458	214 (45.4)	217 (49.5)	106 (49.8)	145 (44.5)	0.539
Number of older siblings†	1,421	0.97 (1.00)	0.81 (0.94)	0.90 (0.87)	1.04 (1.04)	0.008
Nursery use‡	1,445	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†,§	1,448	2.2 (3.5)	1.4 (2.5)	1.5 (2.8)	1.7 (3.3)	0.001
Frequency of colds†,‖	1,436	1.7 (0.8)	1.6 (0.7)	1.8 (0.8)	1.7 (0.8)	0.085
Duration of colds†,¶	1,427	0.9 (0.7)	0.8 (0.6)	0.8 (0.7)	0.8 (0.7)	0.098
Respiratory infections†,**	1,438	1.0 (1.0)	0.9 (1.0)	1.0 (1.0)	0.9 (1.0)	0.238
Positive SPT‡	1,458	173 (36.7)	173 (39.5)	88 (41.3)	130 (39.9)	0.707
Family variables						
Maternal age,† yr	1,457	28.89 (4.81)	29.21 (4.71)	30.67 (4.86)	31.39 (4.61)	<0.001
South Asian mother‡	1,458	65 (13.8)	117 (26.7)	42 (19.7)	68 (20.9)	<0.001
High family education‡,††	1,380	209 (44.4)	271 (61.9)	141 (66.2)	240 (73.6)	<0.001
Maternal asthma‡	1,394	93 (19.7)	83 (18.9)	36 (16.9)	55 (16.9)	0.414
Paternal asthma‡	1,355	96 (20.4)	72 (16.4)	43 (20.2)	64 (19.6)	0.030
Living in an affluent area‡,‡‡	1,437	229 (48.6)	219 (50.0)	126 (59.2)	206 (63.2)	0.003
Urban residence‡	1,458	246 (52.2)	244 (55.7)	106 (49.8)	154 (47.2)	0.062
Tobacco smoke exposures						
Smoking during pregnancy‡	1,422	106 (22.5)	47 (10.7)	12 (5.6)	19 (5.8)	<0.001
Smoking during childhood†,§§	1,458	1.34 (1.73)	1.02 (1.57)	0.73 (1.30)	0.69 (1.31)	<0.001

Definition of abbreviations: BF = breastfeeding; SD = standard deviation; SPT = skin prick test.

Data are presented as number (%) or mean (SD), by duration of breastfeeding (N = 1,458).

*Number of cases with complete data on each particular variable.

†Numeric covariates: values are mean (SD); analysis of variance 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 β-agonists only; 3 = current wheeze + treatment with inhaled corticosteroids 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; 2–4 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, General Certificate of Secondary Education (GCSE) or trade; high = A-levels, below degree, degree.

‡‡Above median value of Townsend deprivation score, an area-based deprivation score (30).

§§Each family returned between two and four questionnaires before attending for measurements; the number represents the mean number of occasions when maternal smoking was reported (*see* online supplement).

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, 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, either in the baseline model or after adjustment for potential confounders (Table 2, Table E4). For FEV_1 for instance, the estimated difference compared with no breastfeeding in the adjusted model was 0.010 L ($P = 0.653$) for breastfeeding 3 months or less, 0.012 L ($P = 0.674$) for breastfeeding 4 to 6 months, and 0.041 L ($P = 0.239$) for breastfeeding more than 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 mothers without asthma (Table E4, adjusted model, children of mothers without asthma). Children of mothers with asthma, however, had significantly higher FVC and FEV_1 if they had been breastfed for 4 months or longer. For instance: the estimated difference for FEV_1 was 0.148 L ($P = 0.028$) for breastfeeding 4 to 6 months and 0.183 L ($P = 0.019$) for breastfeeding more than 6 months (Table E4, adjusted model, children of mothers with asthma).

Allowing for effect modification by maternal asthma (Table 3, Figure 2), we found that, if not breastfed, children of mothers with asthma 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 mothers without asthma. We found no evidence of association between breastfeeding and FVC or FEV_1 in children of mothers without asthma. However, in children of mothers with asthma, 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 to 6 months and more than 6 months, respectively. Results for FVC were essentially similar.

TABLE 2. ASSOCIATION BETWEEN BREASTFEEDING DURATION AND LUNG FUNCTION IN THE ENTIRE SAMPLE OF CHILDREN: BASELINE MODEL AND MODEL ADJUSTED FOR CONFOUNDERS

	FVC, L	FEV_1, L	FEV_1/FVC	PEF, L/s	FEF_{50}, L/s
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 ⩽ 3 mo	−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)

Definition of abbreviations: BF = breastfeeding; FEF_{50} = forced midexpiratory flow; PEF = peak expiratory flow.

Data are presented as unstandardized regression coefficient representing difference from reference category (*P* value).

*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.

‡$P \leqslant 0.05$.

§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 (30), residence area (urban or rural), smoking exposure during pregnancy, smoking exposure during childhood.

FEF_{50}. For forced midexpiratory 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/s ($P = 0.048$) and 0.164 L/s ($P = 0.041$) for breastfeeding 4 to 6 months and longer than 6 months, respectively, compared with those not breastfed (Table 2 or Table E4, adjusted model, entire sample). These increases were greater in children of mothers with asthma (estimated differences, 0.375 L/s [$P = 0.015$] and 0.468 L/s [$P = 0.009$] for breastfeeding 4–6 months and >6 months compared with nonbreastfed) (Table E4, adjusted model, children of mothers with asthma). The model including interaction terms showed again evidence for lower FEF_{50} (estimated difference, −0.175 L; $P = 0.040$) in nonbreastfed children of mothers with asthma compared with nonbreastfed children of mothers without asthma. There was also evidence for higher FEF_{50} in children of mothers with asthma 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, Table 3).

FEV_1/FVC and PEF. There was no evidence of association between breastfeeding and PEF or FEV_1/FVC. In children of mothers with asthma, there was again a tendency for reduced values in nonbreastfed children and higher values in breastfed children; however, *P* values for associations and interaction terms did not reach conventional significance thresholds.

TABLE 3. ASSOCIATION BETWEEN MATERNAL ASTHMA, BREASTFEEDING DURATION, AND LUNG FUNCTION: ADJUSTED MODEL WITH INTERACTION

	FVC, L	FEV_1, L	FEV_1/FVC	PEF, L/s	FEF_{50}, L/s
Nonbreastfed 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 mothers without asthma (*n = 1,167*)					
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 mothers with asthma (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)

For definition of abbreviations, *see* Table 2.

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 (30), 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.

†$P \leqslant 0.05$.

‡The interaction term reflects the additional difference in children of mothers with asthma compared with the corresponding difference in children of mothers without asthma, for a particular level of breastfeeding. For example, the difference in FVC between BF < 3 mo and no BF in children of mothers with asthma (0.063) equals the corresponding difference in children of mothers without asthma (−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 mothers with asthma and mothers without asthma).

§$P \leqslant 0.01$.

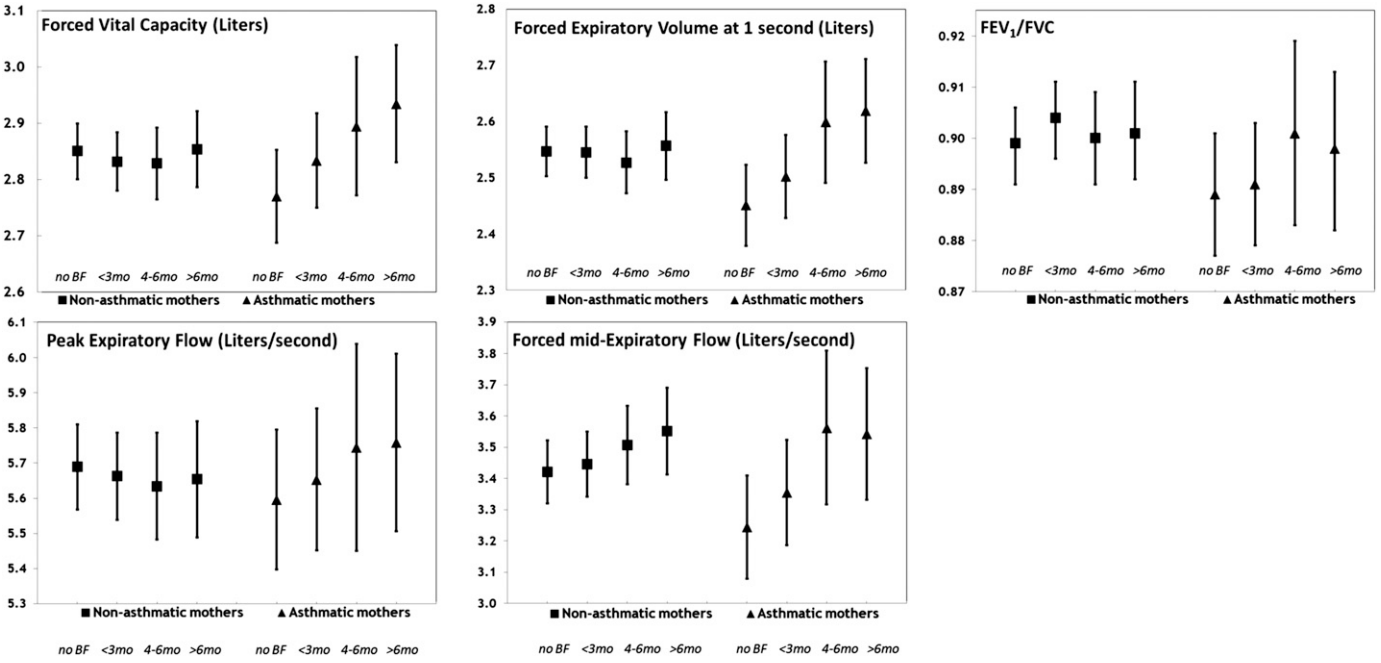

Figure 2. Adjusted mean values of lung function and 95% confidence intervals among children of mothers without asthma (n = 1,167) and mothers with asthma (n = 273), categorized by duration of breastfeeding. This figure presents the results from the adjusted model with interaction term between breastfeeding and maternal asthma. 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* online supplement for description of variables). BF = breastfeeding.

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 year, 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 prebronchodilator lung function rather than post-bronchodilator outcomes (additional analysis 1d) (Table E5–E7).

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–E7).

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 4 months or longer had larger FEF_{50} at school age. Children of mothers with asthma 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 and E2). Associations with FVC and FEV_1 have been reported by several authors. Guilbert and colleagues 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 and colleagues reported, from the Isle of Wight study, an increased FVC (+54 ml, $P = 0.001$) and FEV_1 (+39.5 ml, $P = 0.050$) in 10-year-olds who had been breastfed (9). From the same study, Soto-Ramírez and colleagues reported, several years later, an increased FVC (+1.48 ml/wk of breastfeeding, $P = 0.01$) and FEV_1 (+1.21 ml/wk 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 United Kingdom (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 colleagues and Ogbuanu and colleagues reported higher PEF in breastfed children (7, 9), two studies did not report on flows (8, 11), and Guilbert and colleagues found a negative association between breastfeeding and FEV_1/FVC ratio and forced expiratory flow between 25 and 75% of the FVC ($FEF_{25–75}$) ($P = 0.004$ and 0.090, respectively) in the entire group, which was particularly evident in children of mothers with asthma (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 mothers with asthma.

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), making breastfeeding a potential hazard for children of mothers with asthma. 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 midexpiratory flows, whereas FVC and FEV_1 were significantly higher rather than lower in breastfed children of mothers with asthma. 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 mothers with asthma 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 mothers who were atopic but did not have asthma. 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: (*1*) 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 (*2*) 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, (*3*) 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 prebronchodilator 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 mothers with asthma 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 mothers with asthma and children of mothers without asthma; we can only speculate on the mechanisms. One possible explanation is that mothers with asthma 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 mothers with asthma 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 laboratory measurements in a population-based cohort. The sample analyzed might not be fully representative of the entire population of the Leicestershire area. The results from the participants/nonparticipants comparison analysis (Table E3) suggest that the participants tended to come from a higher socioeconomic class. Similarly, breastfeeding prevalence in our sample differed slightly from the prevalence in the 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 nonbreastfed 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, and weight) among nonbreastfed children of mothers with asthma, and assuming that breastfeeding causes a shift in the Gaussian distribution of FVC (FEV_1) by 165 ml (168 ml), 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 chronic obstructive pulmonary disease later in life.

Conclusions

In conclusion, this study adds importantly to existing evidence against claims that breastfeeding could be harmful in children of mothers with asthma. In contrast, it suggests a modest improvement in midexpiratory flows in all children, and in FVC and FEV_1 in the offspring of mothers with asthma. 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.

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