Effect of breastfeeding duration on lung function at age 10 years: a prospective birth cohort study

I U Ogbonu, W Karmaus, S H Arshad, R J Kurukulaaratchy, S Ewart

ABSTRACT

Introduction: The protective effects of breastfeeding on early life respiratory infections are established, but there have been conflicting reports on protection from asthma in late childhood. The association of breastfeeding duration and lung function was assessed in 10-year-old children.

Methods: In the Isle of Wight birth cohort (n = 1456), breastfeeding practices and duration were prospectively assessed at birth and at subsequent follow-up visits (1 and 2 years). Breastfeeding duration was categorised as “not breastfed” (n = 196); “<2 months” (n = 243); “2 to <4 months” (n = 142) and “≥4 months” (n = 374).

Lung function was measured at age 10 years (n = 1033): forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), FEV1/FVC ratio and peak expiratory flow (PEF). Maternal history of asthma and allergy was assessed at birth. The effect of breastfeeding on lung function was analysed using general linear models, adjusting for birth weight, sex, current height and weight, family social status cluster and maternal education.

Results: Compared with those who were not breastfed, FVC was increased by 54.0 (SE 21.1) ml (p = 0.001), FEV1 by 39.5 (20.1) ml (p = 0.05) and PEF by 180.8 (68.1) ml/s (p = 0.006) in children who were breastfed for at least 4 months. In models for FEV1 and PEF that adjusted for FVC, the effect of breastfeeding was retained only for PEF (p = 0.04).

Conclusions: Breastfeeding for at least 4 months enhances lung volume in children. The effect on airflow appears to be mediated by lung volume changes. Future studies need to elucidate the mechanisms that drive this phenomenon.

Pulmonary function (lung volume and flow rate) could be altered in several physiological and pathological states. Lung volume measurements reflect the stiffness or elasticity of the lungs and rib cage as well as the strength of respiratory muscles. Flow rate measurements reflect the degree of narrowing or obstruction of the airways. Flow rate measurements are abnormal in obstructive disorders, such as chronic obstructive pulmonary disease and asthma. In this study, we used lung function as a measure of susceptibility to asthma.

METHODS

Study population

Between January 1989 and February 1990, children born on the Isle of Wight, UK, were recruited to participate in a longitudinal study (n = 1456). The local research ethics committee approved the study and informed written parental consent was obtained for all participants at recruitment and subsequently at each follow-up. This whole population birth cohort was largely Caucasian (99%) and living in a semi-rural environment with no heavy industry. The Isle of Wight birth cohort has been described in detail elsewhere.

Briefly, at birth, birth weight was measured and data from birth records and extensive questionnaires were collected, including information on asthma and family history of allergy, as well as maternal smoking habits. Breastfeeding practices and duration were prospectively assessed at birth and at subsequent follow-up visits (1 and 2 years). At ages 1, 2, 4 and 10 years, the original questionnaire based information was updated, a study physician performed physical examinations on the children and symptoms of asthma and allergic diseases were recorded. Skin prick tests to common food and aeroallergens were administered at the 4 and 10 year follow-up visits, and at age 10 years lung function tests were performed on all consenting children (n = 1033). To assess whether our analytic sample (children with pulmonary function test data available) was representative of the total cohort available at age 10 years, we compared the characteristics of these two subsets (table 1).

Lung function measurements

Lung function testing was performed using Koko spirometry software (PDS Instrumentation, Louisville, USA), according to American Thoracic Society guidelines. To perform spirometry, children were required to be free from respiratory infection for 14 days, and not be taking oral steroids; they must have abstained from any β agonist medication for 6 h and...
was recorded.

Exposures to environmental tobacco smoke (ETS) in the household and maternal smoking during pregnancy were combined and classified into three groups. When mothers did not smoke during pregnancy and there was no exposure to household ETS in children up to the age of 10 years, children were categorised as “ETS-0”. When mothers did not smoke during pregnancy but household members smoked within the home at some point up to the child’s age of 10 years, the exposure status was categorised as “ETS-1”. When mothers smoked during pregnancy and the children were also exposed to household ETS at some point up to the age of 10 years, the exposure was categorised as “ETS-2”. None of the children had mothers who smoked during pregnancy with no exposure to household tobacco smoke after birth.20

“Family social status cluster” is a composite variable that accounts for “socioeconomic status” broadly defined. The Isle of Wight population has been characterised as semi-rural, with most families (65%) residing in “owner occupied” homes that have been owned by their families for decades. In order to correctly classify them, we chose to cluster family social status using the following three variables: (a) the British socioeconomic classes (1–6) derived from parental occupation reported at birth; (b) the number of children in the index child’s bedroom (collected at age 4 years); and (c) family income at age 10 years. This composite variable captures the family social class across the entire study period.

The British Registrar General’s social classification grouping places professional occupations in group 1 and unskilled manual occupations in group 5, with two subgroups within group 3 (3.1 = non-manual and 3.2 = manual). Family income at age 10 years was recorded under six categories: class 1 = less than £12 000; 2 = £12 000 to £17 999; 3 = £18 000 to £29 999; 4 = £30 000 to £41 999; 5 = £42 000 and greater. The number of children who shared one bedroom ranged from 1 to 3. A cluster analysis of these three variables yielded six groups, one clearly “highest” and one clearly “lowest” status, and four “middle” clusters representing a diversity of middle class living conditions.

In addition, we also investigated the effect of the number of years of formal education completed by the mother, using the number of years of compulsory education as a metric. The maternal education variable was ascertained at the 10 year follow-up and classified into three groups: “less than compulsory” (<16 years of formal education), “compulsory” (16–18 years) and “more than compulsory” (≥19 years).

Statistical analyses

FVC, FEV1, FEV1/FVC ratio and PEF were approximately normally distributed at age 10 years. General linear models were used to assess mean differences in lung function (dependent variable) among the four levels of breastfeeding duration, as defined above, using those who were not breastfed as the referent group. Changes in lung function were presented as millilitres (SE). Separate models were run for each lung function variable. A backward selection approach was utilised to retain confounders in the final model if they changed the effect of breastfeeding categories by 10% or more (table 2).

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### Table 1 Baseline characteristics for children with lung function data at age 10 years compared with the total cohort available for the 10-year follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total cohort at age 10 years</th>
<th>Sample with PFT data</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1370</td>
<td>1033</td>
<td></td>
</tr>
<tr>
<td>Breastfeeding duration (% (n))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not breast fed</td>
<td>22.0 (270)</td>
<td>20.5 (196)</td>
<td>0.82</td>
</tr>
<tr>
<td>&lt;2 months</td>
<td>25.7 (316)</td>
<td>25.5 (243)</td>
<td></td>
</tr>
<tr>
<td>2 to &lt;4 months</td>
<td>14.7 (181)</td>
<td>14.9 (142)</td>
<td></td>
</tr>
<tr>
<td>&gt;4 months</td>
<td>37.5 (461)</td>
<td>39.2 (374)</td>
<td></td>
</tr>
<tr>
<td>Sex (% (n))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>50.8 (696)</td>
<td>49.8 (514)</td>
<td>0.61</td>
</tr>
<tr>
<td>Girls</td>
<td>49.2 (674)</td>
<td>50.2 (519)</td>
<td></td>
</tr>
<tr>
<td>Maternal smoking in pregnancy* (% (n))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETS-0</td>
<td>45.2 (616)</td>
<td>47.3 (487)</td>
<td>0.43</td>
</tr>
<tr>
<td>ETS-1</td>
<td>31.5 (429)</td>
<td>31.5 (324)</td>
<td></td>
</tr>
<tr>
<td>ETS-2</td>
<td>23.3 (318)</td>
<td>21.3 (219)</td>
<td></td>
</tr>
<tr>
<td>Maternal atopy (% (n))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>65.8 (902)</td>
<td>65.5 (677)</td>
<td>0.88</td>
</tr>
<tr>
<td>Yes</td>
<td>34.2 (468)</td>
<td>34.5 (356)</td>
<td></td>
</tr>
<tr>
<td>Maternal asthma (% (n))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>82.4 (1083)</td>
<td>81.3 (799)</td>
<td>0.51</td>
</tr>
<tr>
<td>Yes</td>
<td>17.6 (232)</td>
<td>18.7 (184)</td>
<td></td>
</tr>
<tr>
<td>Birth weight category (% (n))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>96.3 (1284)</td>
<td>96.6 (971)</td>
<td>0.70</td>
</tr>
<tr>
<td>Low</td>
<td>3.7 (49)</td>
<td>3.4 (34)</td>
<td></td>
</tr>
<tr>
<td>Family social status cluster†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>14.5 (188)</td>
<td>13.8 (141)</td>
<td>0.83</td>
</tr>
<tr>
<td>Middle</td>
<td>77.2 (1004)</td>
<td>78.2 (801)</td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td>8.3 (109)</td>
<td>8.0 (82)</td>
<td></td>
</tr>
<tr>
<td>Maternal education (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 16</td>
<td>10.3 (126)</td>
<td>10.3 (105)</td>
<td>0.82</td>
</tr>
<tr>
<td>16–18 (compulsory)</td>
<td>76.4 (937)</td>
<td>77.3 (786)</td>
<td></td>
</tr>
<tr>
<td>Greater than 18</td>
<td>13.3 (163)</td>
<td>12.4 (126)</td>
<td></td>
</tr>
</tbody>
</table>

*ETS-0, mother did not smoke during pregnancy and children not exposed to household ETS; ETS-1, mother did not smoke during pregnancy, but children were exposed to household ETS; ETS-2, mother smoked during pregnancy and children were exposed to household ETS.

†“Family social status cluster” is a composite variable derived from a combination of family income, parental occupation (socioeconomic status) and number of children in a child’s bedroom.

ETS, environmental tobacco smoke; PFT, pulmonary function test.

caffeine intake for at least 4 h. For consistency, the highest of three FEV1 measurements that were within 5% of each other was recorded.

### Variable definitions

Following the classification of the Tucson Children’s Respiratory Study, breastfeeding duration was categorised into four groups: “not breastfed” (n = 196; referent group); “breastfed for less than 2 months” (n = 245); “breastfed for more than 2 but less than 4 months” (n = 142) and “breastfed for at least 4 months” (n = 574).

Lung function assessment at age 10 years included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), FEV1/FVC ratio and peak expiratory flow (PEF).

### Covariates

Birth weight (continuous variable), sex (dichotomous variable), current height and weight (continuous variables), family social status cluster and maternal education were adjusted for in all explanatory models. Maternal history of asthma and allergy was assessed by questionnaire at birth as present or absent. Mothers were regarded as allergic if they reported one or more clinical allergic diseases.

Information on tobacco smoking by mothers (during pregnancy and later), fathers or any other individual inside the home was recorded at recruitment and updated at each follow-up. Exposures to environmental tobacco smoke (ETS) in the household and maternal smoking during pregnancy were combined and classified into three groups. When mothers did not smoke during pregnancy and there was no exposure to household ETS in children up to the age of 10 years, children were categorised as “ETS-0”. When mothers did not smoke during pregnancy but household members smoked within the home at some point up to the child’s age of 10 years, the exposure status was categorised as “ETS-1”. When mothers smoked during pregnancy and the children were also exposed to household ETS at some point up to the age of 10 years, the exposure was categorised as “ETS-2”. None of the children had mothers who smoked during pregnancy with no exposure to household tobacco smoke after birth.20

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In addition, we also investigated the effect of the number of years of formal education completed by the mother, using the number of years of compulsory education as a metric. The maternal education variable was ascertained at the 10 year follow-up and classified into three groups: “less than compulsory” (<16 years of formal education), “compulsory” (16–18 years) and “more than compulsory” (≥19 years).
Following our hypothesis that the effect of breastfeeding would differ across levels of maternal history of asthma and allergy, we assessed the interaction between breastfeeding duration and maternal asthma and allergy.

RESULTS

To test whether the sample we analysed differed from the total sample available at the 10 year follow-up, we compared these two subgroups using cross tabulation. There were no substantial differences between the total cohort at age 10 years and the sample that had lung function data available across the breastfeeding duration categories (primary exposure) and other variables of interest (table 1).

Compared with children who were not breastfed, those who were breastfed for at least 4 months had FVC values that were, on average, 54 ml larger than those who were not breastfed, after adjusting for current height and weight, birth weight, gender, family social status cluster and maternal education (54 (SE 21.1) ml; p = 0.01) (table 2, model 1). Similarly, children who were breastfed for 4 months or longer had significantly higher PEF (180.8 (66.1) ml/s; p = 0.006). FEV1 was marginally significant (39.5 (20.1); p = 0.05) while FEV1/FVC was not significantly associated with breastfeeding duration in this cohort of children. In all models, breastfeeding for less than 4 months did not show significant beneficial effects on lung function (table 2).

The lack of statistical significance seen with the FEV1/FVC ratio may suggest that adjustment for vital capacity diminishes the effect of breastfeeding on FEV1. In this regard, inclusion of FVC as a covariate in the explanatory model for FEV1 also led to a significant reduction of the effect on FEV1 from 39.5 ml to −1.6 ml (table 2, model 2).

To further investigate whether vital capacity was the major driver of the changes found for PEF, we re-ran the PEF explanatory model also controlling for FVC (table 2, model 2). Comparing model 1 with model 2 showed that controlling for FVC reduced the effect of breastfeeding duration on PEF from 180.8 to 131.7 ml/s. However, even after controlling for FVC, breastfeeding duration maintained its statistically significant effect on PEF, in contrast with the effect of controlling for FVC on the association of breastfeeding with FEV1.

In addition to test whether the association of breastfeeding and lung function parameters varied with history of maternal asthma and maternal atopy, we included two interaction terms in the models. These did not gain statistical significance, showing that in this cohort of children, the effect of breastfeeding duration on lung function measurements was not modified by maternal history of asthma or allergy.

DISCUSSION

This study assessed the relationship between duration of breastfeeding and lung function in a well characterised whole population birth cohort at the Isle of Wight, UK. Children who were breastfed for at least 4 months were found to have a significantly better lung function profile at age 10 years compared with those who were not breastfed. Although there was a trend of higher FEV1 and higher PEF with increasing duration of breastfeeding, a statistically significant increase in lung volume was not seen in children who were breastfed for shorter durations (less than 4 months). Our data also showed no evidence of effect modification by maternal history of asthma and allergy.

The likelihood that our results are caused by selection bias is minimised by the fact that all births were eligible, and 1556 eligible children (94.8%) agreed to participate. In addition, 94.1% (1570/1656) of the birth cohort participated at the 10 year follow-up. We compared our analytic sample with the total cohort available at age 10 years for evidence of selection bias but found no such evidence (table 1). The prospective nature of the data collection (breastfeeding information was ascertained at ages 1 and 2 years) and the fact that the primary outcome variable was assessed instrumentally at the clinic at the 10 year visit, combine to reduce information bias (reporting bias). These factors increase both the internal and external validity of this study.

When testing for interaction, we used maternal history of asthma and allergy from standard questionnaires. We did not find any effect modification of breastfeeding by maternal history of asthma or allergy. This finding is in contrast with that of Guilbert and colleagues. Although there was no information on the test for interaction effect in their report, Guilbert et al stratified their sample by maternal asthma and atopy and found a differential effect of the relation of breastfeeding to lung function depending on maternal asthmatic background. Of note, however, we classified maternal asthma and allergy using historical questionnaire information, because of the absence of clinical testing in the mothers. While this approach may not completely capture the effect of maternal asthma and atopy, the internal validity of the study is maintained. This approach limits the interpretation of our findings to historical ascertainment of asthma and allergy from questionnaire data, and not necessarily to parental atopy.

Our results showed a significant increase in FVC in children who were breastfed for longer than 4 months (table 2, model 1). Including FVC in the explanatory model for FEV1 is comparable to the division of FEV1 by FVC (table 2, model 1). The method of adjustment we used in model 2 has been applied in other studies and was shown to produce consistent results with

| Table 2 | Adjusted linear regression models for lung function at age 10 years and breastfeeding duration |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Breastfeeding duration** | **FVC (ml)** | **p Value** | **FEV1 (ml)** | **p Value** | **FEV1/FVC (%)** | **p Value** | **PEF (ml/sec)** | **p Value** | **Model 1** | **Model 2** | **Model 1** | **Model 2** |
| Not breastfed | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| >2 months | 9.6 (22.4) | 0.67 | 14.3 (21.3) | 0.50 | 0.28 (0.57) | 0.62 | 114.7 (70.2) | 0.10 | 7.16 (12.1) | 0.90 | 131.7 (63.5) | 0.04 |
| 2 to <4 months | 6.9 (25.7) | 0.79 | 16.8 (24.5) | 0.49 | 0.57 (0.65) | 0.38 | 143.4 (80.6) | 0.08 | 137.1 (77.2) | 0.08 |
| >4 months | 54.0 (21.1) | 0.01 | 39.5 (20.1) | 0.05 | −0.40 (0.53) | 0.45 | 180.8 (66.1) | 0.006 | 137.1 (63.5) | 0.08 |

Number of children included in the analysis for the FVC model was 929.

1*Model 1 was adjusted for height, weight and birth weight (as continuous variables) and for gender, family social status cluster, maternal education (as categorical variables).

2†For model 2, in addition to all the variables in model 1, we also adjusted for FVC.

3Model coefficient (SE).

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF peak expiratory flow; Ref, reference group.

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Paediatrics

minimal bias. The loss of statistical significance for breastfeeding duration on FEV1 after adjustment for FVC supports the notion that FVC may play a mediating role (breastfeeding → increased lung capacity → increased FEV1). Thus the association of breastfeeding with FVC seems to explain the increase in FEV1. Therefore, we believe that the effect of breastfeeding in our data is because of an increase in lung volume. Nevertheless, even after including FVC in the model, duration of breastfeeding was still associated with PEF, suggesting that breastfeeding may have some protective effect against airflow obstruction.

Unlike Guilbert and colleagues we did not find any effect of breastfeeding duration on the FEV1/FVC ratio. This may be due to the fact that an effect of similar strength acted on both FEV1 and FVC in our population. In other words, the primary effect is on lung capacity and secondarily on FEV1. If so, the use of a ratio would nullify the effect of breastfeeding. As the FEV1/FVC ratio was not affected, our findings support an effect of prolonged breastfeeding on increased lung volumes, but no effect of breastfeeding duration on airway obstruction.

The results of previous studies suggest that factors in human breast milk, such as cytokines and chemokines, are responsible for the beneficial effects of breastfeeding on asthma and other allergic disorders. This view is supported by a recent report by Snijders et al who found that longer duration of breastfeeding was associated with a reduced risk for eczema when the mothers were non-allergic and non-asthmatic. They concluded that maternal allergic status was the major driver of this protective effect. Similar immune mechanisms may act by remodelling the airways and may explain the protective effect of breastfeeding duration on PEF.

While immunomodulatory factors are important, the effect of breastfeeding on the respiratory system may be a result of complex and interlinked mechanisms that may be accounted for by several variables. It has been demonstrated that during breastfeeding, for the 75 s prior to milk ejection, there is a negative pressure of up to 98 mm Hg, which is about three times higher than the pressure developed during bottle feeding. Sucking exercises during breastfeeding (an average of 8 min) is nearly twice as long as bottle feeding duration (4.4 min). In addition, bottle feeding has a higher rate of swallowing, more frequent interruption of breathing and decreased ventilatory efforts. Hence mechanical factors related to sucking may explain the differences in lung volume seen in breastfed infants compared with those who were not breastfed. For lung function, it may be that the physical exercise caused by sucking at the breast, about six times daily on average (for more than 4 months), may result in increased elasticity and efficiency of the lung parenchyma, resulting in increased lung capacity and increased airflow in breastfed children compared with bottle-fed children. This interpretation is supported by our finding that FVC (and only indirectly FEV1) was higher in breastfed children.

Hence two explanatory mechanisms may compete. Firstly, prolonged sucking at the breast compared with the bottle may convey a mechanical stimulus that results in improved mechanics of ventilation (due to physical training). Secondly, the presence of protective immunomodulatory factors in breast milk may reduce allergic susceptibility of the lung tissue. This differentiation is relevant for future efforts to promote better lung growth. Pumping and subsequently bottle-feeding (indirect feeding) may eliminate the protective effects of breastfeeding, thus explaining the negative findings in some studies, especially in countries with minimal maternity leave periods. This mechanical explanation necessitates the collection of data on the method of breast milk administration employed in different studies. In addition, if suckling is essential and the newborn cannot be breastfed, then the design of the feeding bottle is important. For instance, an artificial increase of flow “resistance” from infant feeding bottles may be beneficial. On the other hand, if immune factors are essential, it would be important to investigate which constituents of breast milk provide the most protection.

In conclusion, this paper adds to the evidence supporting the promotion of prolonged breastfeeding for the improvement of lung volume in late childhood. In addition to repeating this analysis in other populations, future studies should assess the biological mechanisms that drive this phenomenon, in order to promote normal lung growth and development.

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Competing interests: None.

Ethics approval: The local research ethics committee approved the study.

REFERENCES

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