Effect of Breastfeeding on Lung Function in Childhood and Modulation by Maternal Asthma and Atopy

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Rationale: The protective effect of breastfeeding on early respiratory infections is well established, but its relationship to the development of subsequent asthma remains controversial.

Objectives: To clarify these complex issues, we examined the association between lung function and infant-feeding practices.

Methods: In the Tucson Children's Respiratory Study, feeding practices were assessed prospectively based on questionnaires completed at enrollment and well-child visits. Formula introduction was categorized as having occurred before 2 months ($n = 143$, "early formula introduction"), from 2 and before 4 months ($n = 336$), or at 4 months and older ($n = 200$, "longer breastfed"). Lung function was measured at age 11 and 16 years. A random-effects model was used to assess the relationship of infant-feeding practices to measures of lung function.

Measurements and Main Results: FVC by age 16 was increased by 103 ± 40.0 ml ($P = 0.01$), and the FEV_1/FVC ratio was lower ($-1.9 \pm 0.6\%$, $P = 0.004$) in the longer breastfed children compared with children with early formula introduction. This effect was modified after stratifying by maternal asthma. Compared with children with early formula introduction, longer breastfed children with asthmatic mothers had an FVC that was not increased ($P = 0.7$) and an FEV_1/FVC ratio ($-5.7 \pm 2.4\%$, $P = 0.02$) that was significantly decreased by age 16. Longer breastfed children with nonatopic, nonasthmatic mothers demonstrated an increased FVC (142 ± 71.1 ml, $P = 0.047$) and no decrease in FEV_1/FVC ($P = 0.7$) compared with children with early formula introduction.

Conclusions: Longer duration of breastfeeding favorably influences lung growth in children. However, in the presence of maternal asthma, longer breastfeeding is associated with decreased airflows.

Keywords: breastfeeding; formula feeding; lung function; epidemiology; lower respiratory tract infections; asthma

It is well established that breastfeeding is associated with reduced incidence and severity of lower respiratory tract illness (LRI) (1–5), a major cause of morbidity in infancy, and in the developing world, of infant death. Several lines of evidence suggest that breast milk is an immunoactive substance that plays a role in the maturation of antimicrobial responses. Indeed, numerous factors in human milk, including bioactive enzymes, hormones, growth factors, and immunologic agents, appear to augment and stimulate the development of immature host defense (6–10). However, the role of breastfeeding as a protective factor against the development of asthma is less clear

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The protective effect of breastfeeding on early respiratory infections is well established, but its relationship to the development of subsequent asthma remains controversial.

What This Study Adds to the Field

Lung function is reduced in children with prolonged breastfeeding with mothers with asthma and atopy compared with offspring of nonasthmatic, nonatopic mothers.

(11). Our previous studies have found that atopic children who have mothers with asthma are more likely to develop asthma if they are breastfed (12).

The mechanisms by which breastfeeding may be associated with an increase in risk of asthma in offspring of mothers with asthma are not understood. Recent experimental evidence in mice suggests that these mechanisms are independent of atopy, and may be mediated by substances present in milk that make the lungs more susceptible to the development of airway obstruction (13). Human milk contains substances that can have biological effects on the maturation of the child's lung (14–16). We have shown, for example, that the level of transforming growth factor (TGF)- β in breast milk is inversely associated with the risk of having wheezing episodes during the first year of life (17). Infants with narrower airways are known to be more prone to wheeze during viral infections (18), and we thus hypothesized that TGF- β in milk could enhance lung and airway growth. However, children with asthma have, as a group, evidence of chronic airway obstruction, as shown by their lower mean values for FEV_1 and FEV_1/FVC ratio (19, 20), and the level of airway obstruction is strongly and directly associated with severity and persistence of the disease (20, 21). We thus reasoned that breastfeeding could have differential effects on lung and airway growth, depending on the asthma status of the mother, and that these effects could persist until the school years.

To test this hypothesis, we studied the association between feeding practices during infancy and level of lung function up to adolescence in a cohort of children enrolled at birth. Some of the results of these studies have been previously reported in the form of an abstract (22).

METHODS

A population-based cohort of healthy infants was enrolled at birth in the Children's Respiratory Study in Tucson, Arizona ($n = 1,246$), and monitored prospectively through adolescence; more information on the study has been published elsewhere (23, 24).

Subjects

This analysis is limited to the 679 study participants that performed lung function testing at ages 11 and/or 16 years and provided data regarding infant-feeding practices.

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Feeding Practices

Feeding practices were assessed prospectively based on forms completed by the child's pediatrician at well-child visits at ages 2, 4, 6, and 9 months. Infant-feeding information gathered from the well-child visit forms was categorized into three groups: breastfeeding for less than or equal to 1 month ($n = 143$, "early formula introduction"), breastfeeding for 2 to less than 4 months ($n = 336$), and breastfeeding for 4 or more months ($n = 200$, "longer breastfed").

Wheezing History and Parental Asthma

Detailed respiratory questionnaires were completed by the caregiver for the child at age 6, 11, and 16 years. The prevalence of wheeze at ages 11 and 16 was obtained by asking if the child had "ever wheezed" and "how often during the past year?" the child had wheezed. Current wheeze in children was defined as being "infrequent" (one to three episodes of wheeze) or "frequent" (more than three episodes of wheeze) in the previous 12 months, regardless of a diagnosis of asthma. Wheezing LRIs were ascertained prospectively during the first 3 years of life based on physician report. The pediatrician completed a form when a study child was seen for signs or symptoms of LRIs (deep or wet cough, wheezing, hoarseness, stridor, shortness of breath). Children were classified as having a wheezing LRI if wheeze was observed on physical examination. Parental asthma was determined by asking the parent on the enrollment questionnaire if they had ever had physician-diagnosed asthma. "Severity of maternal asthma" was further defined with reference to frequency of wheeze in the past year as being inactive (wheezed but not in the past year) or active (one or more episodes of wheeze in the past year).

Lung Function Tests

Lung function testing was performed at 11 years of age ("Yr11" survey: mean age [SD], 10.9 ± 0.7 yr, $n = 616$) and 16 years of age ("Yr16" survey: 16.7 ± 0.6 yr, $n = 479$). Pulmonary function tests at age 11 were completed with a custom-built pneumotach-based system running software on a portable computer (25). Pulmonary function tests at age 16 were completed with a portable Schiller Spirovit SP-1 spirometer (Schiller AG, Baar, Switzerland) using standardized spirometric techniques (26). Both systems were calibrated with a Jones syringe (Jones Medical Instrument Co., Oak Brook, IL). FVC (ml), FEV₁ (ml), and the forced expiratory flow between 25 and 75% of the FVC (FEF₂₅₋₇₅, ml/s) were measured. Children were asked not to use short-acting bronchodilators within 4 hours of the test, or long-acting bronchodilators in the previous 12 hours. To assess response to bronchodilator at ages 11 and 16, 180 μ g inhaled albuterol was administered via metered dose inhaler and a spacer. Spirometry was performed before and 15 minutes after the albuterol dose, and a response was calculated (27). The child's height, weight, and age at the time of the test were recorded by the study nurses.

Atopy

When the children were 6 years old, the children and their parents were skin-prick tested to allergenic extracts (house dust mite mix, *Alternaria alternata*, Bermuda grass [*Cynodon dactylon*], carelessnessweed [*Amaranthus palmeri*], olive [*Olea europaea*], mesquite [*Prosopis glandulosa*], and mulberry tree [*Morus alba*]) (Hollister-Stier Laboratories, Everett, WA) (28). Wheal sizes of 3 mm or larger after subtraction of the control value were considered positive (29). Total serum IgE (IU/ml) was measured at ages 11 and 16 years in duplicate using the Pharmacia Diagnostics AUTOCAP system (Kalamazoo, MI). Eczema during the first 2 years of life was determined based on parental report of a physician diagnosis of eczema.

Possible Confounders

Information on potential confounders was collected on parents shortly after the child's birth, including the following: ethnicity, history of physician-diagnosed asthma, years of education, age, and smoking history at the child's birth. The child's sex was also recorded.

Statistical Analyses

FVC, FEV₁, FEV₁/FVC ratio, FEF₂₅₋₇₅, FEF₂₅₋₇₅/FVC, and height were all approximately normally distributed at ages 11 and 16; t tests and

contingency tables with χ^2 were used to test differences in means and frequencies between groups, respectively. A random-effects model (REM) was used to assess longitudinal differences in FVC, FEV₁, FEV₁/FVC ratio, FEF₂₅₋₇₅, and FEF₂₅₋₇₅/FVC ratio at ages 11 and 16 between infant-feeding practice groups. An REM can be compared with a multiple regression in that it provides the coefficients for a predictive equation while adjusting for the correlation within subjects. Initially, a marginal analysis was performed at ages 11 and 16 to assess the significance of covariates believed to influence the relation of infant-feeding practices to lung function, either from the literature or from previous analyses. At each age, the base model included current weight, height, age, sex, and feeding practices. Covariates that had a significance of less than or equal to 0.1 or that were considered important based on the literature were retained for the longitudinal REMs. From these longitudinal models, covariates that had a significance level of less than 0.1 were again retained to create a best-fitting longitudinal model for each lung function outcome. If one category of a categorical variable had a significance of 0.1 or less, all parts of the categorical variable were retained in the best-fitting model. All best-fitting models included height, weight, age, sex, and maternal education and feeding practices (base model) plus any remaining significant covariates.

SPSS for Windows, version 14 (SPSS, Inc., Chicago, IL), and STATA, version 9.0 (StataCorp, College Station, TX), were used for statistical analyses. A two-sided P value of 0.05 was considered significant for all tests.

This research was approved by the Institutional Review Board of the University of Arizona. Parents signed consent forms for initial enrollment and, separately, for testing at each age.

RESULTS

Children with complete information on infant feeding and lung function testing were more likely to have formula introduced at 2 months or later, at least one white parent, parents with more than 12 years of education, nonsmoking parents, and atopic mothers compared with those who had incomplete data (Table 1). There were no differences in FVC, FEV₁/FVC ratio, parental asthma, child atopy, sex, or wheezing history between groups. Children with longer breastfeeding were more likely to have non-Hispanic white parents, a mother older than 28 years, non-smoking parents, and more educated parents, compared with those who introduced formula earlier than 4 months (Table E1

TABLE 1. BASELINE CHARACTERISTICS FOR CHILDREN WITH INFANT-FEEDING PRACTICE INFORMATION AND LUNG FUNCTION DATA AT AGES 11 AND/OR 16 YEARS, COMPARED WITH THOSE WITH INCOMPLETE DATA

Characteristic	Complete Data	Incomplete Data	P Value
Infant-feeding practices, n	679	467	
Early formula introduction, %	21.1	17.3	0.03
Formula 2 to less than 4 mo, %	49.5	57.6	
Longer breastfeeding, %	29.5	25.1	
Girls, % (n)	50.5 (679)	51.1 (567)	0.9
Ethnicity, n	679	567	
Non-Hispanic white, %	59.7	57.9	<0.001
Hispanic white, %	12.2	9.0	
Mixed white, %	13.5	6.5	
Other/missing, %	14.6	26.6	
Wheezing LRI by age 3, % (n)	35.0 (588)	29.8 (238)	0.2
Atopy at age 6 yr, % (n)	39.3 (613)	33.1 (148)	0.2
Maternal smoking, % (n)	15.6 (679)	20.2 (564)	0.03
Maternal education > 12 yr, % (n)	71.2 (679)	64.6 (562)	0.01
Maternal age > 28 yr, % (n)	38.6 (679)	38.4 (567)	0.9
Maternal atopy, % (n)	62.4 (633)	53.2 (169)	0.03
Maternal history of asthma, % (n)	10.6 (669)	11.5 (486)	0.6
Paternal smoking, % (n)	28.9 (671)	34.6 (555)	0.03
Paternal education > 12 yr, % (n)	73.0 (664)	67.1 (553)	0.02
Paternal atopy, % (n)	65.7 (533)	60.8 (120)	0.3
Paternal history of asthma, % (n)	12.7 (635)	11.1 (45.9)	0.4

Definition of abbreviation: LRI = lower respiratory tract infection.

of the online supplement). Although the feeding groups did not differ in sex, paternal asthma, parental atopy, or wheezing history, infants with early formula introduction were less likely to have a maternal history of asthma.

Longer breastfeeding was associated with significantly increased FVC (118 ml [48.1, 188], $P = 0.001$) and decreased FEV₁/FVC ratio (-1.9% [$-3.3, -0.6$], $P = 0.006$) and FEF₂₅₋₇₅/FVC ratio (-8.1% [$-13.4, -2.9$], $P = 0.002$) at age 11, and similarly, albeit less significantly, altered FVC at age 16 (116 ml [$-1.2, 234$], $P = 0.052$), relative to early formula introduction, after adjusting for current height, weight, age, and sex (Tables E2a and E2b). On average, FVC was increased 4.5% at age 11 for participants with longer breastfeeding compared with those with early formula introduction (mean $\pm$ SE: 2,734 $\pm$ 23.1 vs. 2,616 $\pm$ 27.2 ml), and 2.7% at age 16 (4,376 $\pm$ 37.5 vs. 4,260 $\pm$ 46.5 ml). Children who received formula from 2 to before 4 months had values intermediate to the other two groups for FVC at age 11. Administration of a bronchodilator did not change the relationships of feeding with FVC, FEV₁, FEV₁/FVC ratio, or FEF₂₅₋₇₅ (data not shown). Tables E2a and E2b also demonstrate other covariates that were found to be significant when added to the base model of current weight, height, child age, and sex.

In the longitudinal REM through age 16, children in the longer breastfed group had FVCs that were 103 $\pm$ 40 ml higher than those of children in the early formula group ($P = 0.01$), after controlling for current height, weight, child age, maternal atopy, current wheeze, sex, and maternal education (Table 2). When feeding practice was considered as an ordinal variable in three categories as previously defined, FVC increased by 52 $\pm$ 20 ml, $P = 0.008$, for each categorical increase in exclusive breastfeeding.

There was no relation between infant feeding and FEV₁ through age 16 ($P = 0.9$, Table 2). Compared with the early formula introduction group, the FEV₁/FVC ratio was lower in the longer breastfed children ($-1.9 \pm 0.65\%$, $P = 0.004$) due to the increase in FVC and lack of change in FEV₁. The FEF₂₅₋₇₅/FVC ratio is also significantly lower for the longer breastfed group compared with the early formula introduction group of infants. Stratifying by sex did not significantly change the relationships of FVC, FEV₁, FEV₁/FVC ratio, FEF₂₅₋₇₅, and FEF₂₅₋₇₅/FVC ratio (data not shown). The relationship of infant feeding and lung function also did not change after administration of a bronchodilator.

However, these relations were different when the analysis was stratified by maternal asthma and atopy (Table 3). Among longer breastfed children with mothers with asthma, FVC was not increased and FEV₁/FVC and FEF₂₅₋₇₅/FVC ratios were significantly decreased by age 16 (Table 3). The observed decrease in FEV₁/FVC ratio with maternal asthma did not change when stratified by the severity of maternal asthma, although the sample size was small, or when adjusted by eczema in the child (data not shown).

Longer breastfed children with atopic, nonasthmatic mothers had an FVC that was significantly higher (119 $\pm$ 55.5 ml, $P = 0.03$) and FEV₁/FVC ($-2.1 \pm 0.85\%$, $P = 0.01$) and FEF₂₅₋₇₅/FVC ratios ($-9.3 \pm 3.2\%$, $P = 0.004$; Table 3) that were significantly lower by age 16 compared with those with early formula introduction. Finally, longer breastfed children with nonatopic, nonasthmatic mothers demonstrated an increased FVC and no decrease in FEV₁/FVC or FEF₂₅₋₇₅/FVC ratios (Table 3) by age 16 compared with children in the early formula group. These associations did not change after adjusting for both early (LRI) and current wheeze. The relationships of lung function and infant feeding for mothers with both atopy and asthma remained the same after a bronchodilator was given (Table E3). Relationships for children with nonasthmatic, non-atopic mothers were similar to those shown for the group as a whole in that longer breastfeeding was associated with greater FVC and no reduction in FEV₁/FVC ratio, suggesting that the slightly reduced FEV₁/FVC ratio shown for the whole population is likely attributed to the subgroup with mothers with atopy or asthma.

DISCUSSION

This study has investigated relationships between infant-feeding practices in early life and lung function at ages 11 and 16 years in a population of healthy children monitored since birth. Children with early introduction of formula had decreased FVC when compared with the children with longer breastfeeding, suggesting that breastfeeding may positively influence lung growth. These findings were significant at age 11 and are of borderline significance at age 16, suggesting that early life influences on lung function attenuate as children age. However, breastfeeding was not associated with a proportionate improvement in airflow, resulting in a slightly decreased FEV₁/FVC ratio and FEF₂₅₋₇₅. Finally, the relation of breastfeeding to lung function was influenced by maternal characteristics, specifically atopy and asthma.

What we see appears to be a differential effect of the relation of breastfeeding to lung function based on the asthmatic background of the mother. Breastfed children with nonatopic, nonasthmatic mothers had an increased FVC and no decrease in their airflows. However, children of mothers with asthma with longer breastfeeding did not demonstrate any improvement in FVC but had a significant reduction in the FEV₁/FVC and FEF₂₅₋₇₅/FVC ratios, suggesting that the risk for increased asthma in this group (12) may be partly due to altered lung growth. These relationships did not change after administration of bronchodilator at doses typically used in a clinical setting and, therefore, are not likely explained by increased airway tone. Children with longer breastfeeding who had atopic but nonasthmatic mothers showed a similar increase in FVC compared

TABLE 2. BEST-FITTING LONGITUDINAL RANDOM-EFFECTS MODELS* FOR LUNG FUNCTION THROUGH AGE 16 AND INFANT-FEEDING PRACTICES

Infant Feeding Practices	FVC (ml)		FEV ₁ (ml)		FEV ₁ /FVC Ratio (%)		FEF ₂₅₋₇₅ (ml/s)		FEF ₂₅₋₇₅ /FVC Ratio (%)	
	$\beta^{\dagger}$ (SE)	P	$\beta^{\dagger}$ (SE)	P	$\beta^{\dagger}$ (SE)	P	$\beta^{\dagger}$ (SE)	P	$\beta^{\dagger}$ (SE)	P
Early formula	Ref		Ref		Ref		Ref		Ref	
Formula at 2 to less than 4 mo	43 (36)	0.2	20 (31)	0.5	-0.7 (0.6)	0.2	-2.9 (66)	0.9	-2.7 (2.1)	0.2
Longer breastfeeding	103 (40)	0.01	27 (35)	0.4	-1.9 (0.6)	0.004	-124 (73)	0.09	-7.6 (2.3)	0.001

Definition of abbreviation: Ref = reference group in the model.

* All best-fitting models included height, weight, age, sex, maternal education, and feeding practices (base model) plus any remaining significant covariates; covariates with $P > 0.1$ were not retained in the final models. Number of observations for FVC model was 1,092, number of individuals included in the analysis was 677, with an average number of observations per individual of 1.6.

[†] Model coefficient.

TABLE 3. BEST-FITTING LONGITUDINAL RANDOM-EFFECTS MODELS* FOR LUNG FUNCTION THROUGH AGE 16 AND INFANT-FEEDING PRACTICES STRATIFIED BY MATERNAL ASTHMA AND ATOPY

Maternal			FVC (ml)		FEV ₁ (ml)		FEV ₁ /FVC Ratio (%)		FEF _{25–75} (ml/s)		FEF _{25–75} /FVC Ratio (%)	
Asthma	Atopy	Infant-Feeding Practices	β [†] (SE)	P	β [†] (SE)	P	β [†] (SE)	P	β [†] (SE)	P	β [†] (SE)	P
No	No	Early formula	Ref		Ref		Ref		Ref		Ref	
		Formula at 2 to <4 mo	98 (65)	0.14	115 (56)	0.038	0.5 (1.1)	0.6	119 (117)	0.3	−1.0 (3.8)	0.8
		Longer breastfeeding	142 (71)	0.047	98 (60)	0.1	−0.4 (1.2)	0.7	40 (127)	0.8	−3.1 (4.1)	0.4
No	Yes	Early formula	Ref		Ref		Ref		Ref		Ref	
		Formula at 2 to <4 mo	83 (49)	0.09	21 (41)	0.6	−1.6 (0.8)	0.03	−67 (84)	0.4	−4.3 (2.8)	0.1
		Longer breastfeeding	119 (55)	0.03	41 (46)	0.4	−2.1 (0.9)	0.016	−180 (96)	0.06	−9.3 (3.2)	0.004
Yes	+/-	Early formula	Ref		Ref		Ref		Ref		Ref	
		Formula at 2 to <4 mo	−88 (124)	0.5	−95 (118)	0.4	−1.8 (2.1)	0.4	−348 (233)	0.1	−9.0 (6.8)	0.2
		Longer breastfeeding	52 (140)	0.7	−125 (131)	0.3	−5.7 (2.4)	0.018	−614 (260)	0.018	−21 (7.5)	0.005

Definition of abbreviation: Ref = reference group in the model.

* All best-fitting models included height, weight, age, sex, maternal education, and feeding practices (base model) plus any remaining significant covariates. Number of observations in the FVC models for children with nonatopic, nonasthmatic mothers was 359, number of individuals included in the analysis was 223; number with atopic, nonasthmatic mothers was 543, number of individuals included in the analysis was 333; and number for children with asthmatic mothers, with or without atopy, was 117; number of individuals was 70.

[†] Model coefficient.

with those with nonatopic, nonasthmatic mothers, but a decrease in FEV₁/FVC and FEF_{25–75}/FVC ratios similar to children with mothers with asthma. Thus, they had findings that were intermediate to the findings in the children of nonatopic, nonasthmatic mothers and those with mothers with asthma. These findings were unchanged when we controlled for other possible determinants of lung function (parental smoking habits, family history of asthma, parental and personal atopy, and social status) that could confound the relationship with feeding practices.

Several caveats should be noted. In this analysis, formula introduction was analyzed as a categorical variable instead of a continuous one because it was obtained prospectively during well-child visits. In addition, formula introduction is not identical to duration of breastfeeding, although formula introduction was associated with cessation of breastfeeding in this cohort, similar to the findings of other studies (30, 31). In addition, our results can only be generalized to children fed cow's milk-based formula, as only a minority of infants in this cohort (10%) used soy-based formulas during the first year of life.

One explanation for the increased FVC associated with longer breastfeeding in children of nonasthmatic mothers may be the presence of factors in human milk that may favorably modify lung development, leading to increase in total lung capacity due to growth or a reduction in residual volume secondary to increased respiratory muscle strength. Because alveoli continue to develop after birth, the effects on FVC may also be explained by positive influence on alveolar development. Potential candidates include several cytokines, such as IL-1β, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-α, TGF-α and TGF-β2, granulocyte and macrophage-colony stimulating factor, IFN-γ, epithelial growth factor, and prostaglandin E2 (16, 17, 32). It is unclear if these factors interact with receptors in the intestinal wall or if they cross into systemic circulation. Another possible candidate is TGF-β1, one of the most abundant cytokines found in human milk. TGF-β1 appears to play a role in lung morphogenesis (33) and development (34–37), particularly in elastin production (14, 15). Elastin, an important structural protein of the pulmonary alveolar interstitium, is important to the normal structure and function of the lung parenchyma. It appears to be deposited in the airways early in life and elastin content of the lung remains static throughout life (38). It is possible that infants who receive more TGF-β1 through longer breastfeeding may increase the elastin content in the lung and this may improve its function (14, 15). Oddy and colleagues (17)

demonstrated that the dose of TGF-β1 received from breast milk was inversely associated with infant wheeze. These findings suggest that growth factors in milk have the potential to modify lung development, which might account for some of the protective effect of breastfeeding against wheeze (5, 39–41).

Other candidate components of milk that might be responsible for differences in lung growth in relation to duration of exclusive breastfeeding are maternal hormones. Estrogen and prolactin in human milk may act on infant lung tissue in a fashion similar to that in the breast, where they increase the number of ducts and alveoli, and foster their development. These hormones are present in human milk in concentrations higher than maternal serum (9) and there is evidence that they are absorbed by the newborn.

The analysis presented here demonstrates a more pronounced effect of longer breastfeeding on the FEV₁/FVC ratio in children with mothers with asthma and atopy (compared with offspring of nonasthmatic, nonatopic mothers). This finding is consistent with the speculation that the milk of mothers with atopy or asthma may differ with regard to immunologically active substances, and thus breastfeeding in these groups may have a different effect on growth and/or development of the airways. We have shown (42) that maternal IgE is associated with IgE in the child only if the child is breastfed, and further, that longer breastfeeding among children whose mothers had high IgE was associated with high IgE in the child. Our results are strongly supported by a recent study (13), which demonstrated that mice pups born to normal mothers that are then breastfed by asthmatic foster mothers develop increased airway hyperresponsiveness and eosinophilic airway inflammation. Several studies (11, 12) have found that longer breastfeeding by mothers with asthma is associated with asthma in the child, at least among children who were themselves atopic; our findings may provide one possible explanation for this observation. However, the link between longer breastfeeding and asthma for children of mothers with asthma has not been replicated in other studies (41, 43–45), although it should be noted that only Burgess and colleagues (44) stratified the analysis by maternal asthma as was done here. The majority of mothers with asthma (>70%) in the Children's Respiratory Study were diagnosed with asthma as older children and required asthma-related medications as adults, and therefore, they would not likely be transient wheezers. These medications were presumably mostly bronchodilators given the pattern of asthma treatment in the 1980s. It should also be noted that the number of mothers

reporting physician diagnosis of asthma was relatively small and thus these subgroup analyses should be interpreted with caution.

It is important to emphasize that the clinical significance of these findings is unknown. Human milk is uniquely suited to the feeding of infants, having been subjected to selective pressures for millennia. There are multiple well-documented benefits of breastfeeding, such as improved neural development (46, 47) and reduced number of infections (1, 3, 4, 39, 48). For children of nonasthmatic mothers, this analysis demonstrates a further benefit of breastfeeding—that is, that longer breastfeeding is associated with enhanced lung growth. For children of mothers with asthma, it is premature to suggest any change in recommendations to breastfeed their infants given the previously mentioned benefits. Further study is needed to confirm our findings and to determine a biological basis for the relationships observed.

In conclusion, this analysis suggests that longer breastfeeding is associated with improved lung growth in later childhood, with minimal effects on airflow in children of nonasthmatic mothers. However, longer breastfed children of mothers with asthma demonstrate no improved lung growth and significant decrease in airflows later in life.

Conflict of Interest Statement: T.W.G. received \$5,500 in 2007, \$9,500 in 2006, \$8,000 in 2005, and \$4,500 in 2004, for serving on an advisory board, consulting on designing clinical trials, and speaking at conferences sponsored by GlaxoSmithKline; she received \$15,000 in 2005 for speaking engagements sponsored by Novartis; she served as a subinvestigator on a study sponsored by Altus Pharmaceuticals but did not receive any reimbursement; she received \$12,000 in 2003 from Genentech as a research grant for participating in a multicenter epidemiology trial; she received \$9,000 in 2004 from the Exchange program for consulting in the design of CME courses and for asthma; and she has participated as a speaker in CME-accredited courses sponsored by the following companies: SOMA Medical Education, and Antidote. D.A.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. W.J.M. received \$5,000 to \$7,000 per annum from 1993 to 2006 as Chair of the Epidemiology Study on Cystic Fibrosis funded by Genentech. F.D.M. has in the last 3 years served on a Merck advisory board; acted as a consultant for Genentech and Pfizer; and has received symposium reimbursement and honoraria from Merck. A.L.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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