

Mechanisms of allergy

Breast-feeding, maternal IgE, and total serum IgE in childhood

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Background: There is controversy regarding the relationship of the effect of breast-feeding on markers of allergy such as total serum IgE in childhood.

Objective: This study, using longitudinal data, tested the hypothesis that the relation of breast-feeding to IgE in childhood differs depending on maternal total IgE level.

Methods: Total serum IgE was assessed with the paper radioimmunosorbent test at 4 ages in nonselected children enrolled at birth into the prospective Tucson Children's Respiratory Study. Children were classified as never breast-fed, breast-fed less than 4 months, or breast-fed 4 months or longer, on the basis of physician report or questionnaires completed by parents by the time the child was 18 months old. A longitudinal random effects model was used to test for group differences and temporal trends in IgE for children classified with reference to maternal IgE (high tertile vs all others) and breast-feeding history. A total of 664 children with 1457 observations were included.

Results: Among children whose mothers were in the 2 lower tertiles of IgE, breast-feeding was associated with lower total serum IgE at age 6 years (24.2 vs 44.3 IU/mL for never breast-fed children; $P < .02$); similar trends existed at age 11 years. In contrast, for children whose mothers were in the highest tertile of IgE, breast-feeding of 4 months or longer was associated with higher IgE levels in the child compared with those never breast-fed or breast-fed less than 4 months (97.0 vs 38.9 IU/mL; $P < .005$). These cross-sectional analyses were confirmed with the longitudinal random effects model, which also showed no effect of confounders. Paternal IgE showed no similar relation with child IgE.

Conclusion: Breast-feeding appears to have paradoxical relations with IgE in childhood, depending on maternal IgE level. These findings may help explain the contradictory results found in other investigations of the relation of breast-feeding to allergic symptoms and markers. (*J Allergy Clin Immunol* 1999;104:589-94.)

Key words: IgE, breast-feeding, childhood, allergy, infant feeding, longitudinal studies, asthma

The relationship between infant feeding and the development of allergic response in childhood has not been clearly established; some studies find a protective effect of breast-feeding,^{1,2} although others find no relation.^{3,4} This lack of consensus is not surprising, given the fact that a range of outcomes of diverse cause have been considered, that varied definitions of breast-feeding have been used, and that studies have sometimes failed to adjust for confounders.⁵ In addition, reports of allergic symptoms may be variably biased by parental allergic status, depending on how symptom data are collected.

One way to avoid parental recall bias is to assess the potential effect of infant feeding practices with the use of biologic markers of allergic predisposition that can be measured objectively. Total serum IgE level is one such marker of allergic response, being clearly associated with allergic symptoms in childhood,⁶ atopy (as indicated by a positive reaction to allergy skin prick tests),⁶⁻⁸ asthma,^{9,10} and bronchial hyperresponsiveness.^{11,12} Additionally, IgE is implicated in the pathogenesis of allergic disease, including asthma.^{13,14}

A second strategy that may clarify the potential role of breast-feeding is to assess relations after stratification by maternal rather than parental allergic status. Some studies have found that the development of allergic outcomes in the child is more strongly related to maternal than paternal atopic status,^{15,16} raising the possibility that the mechanisms underlying maternal influences may differ from those for paternal influences. In addition, human milk varies substantially with regard to virus-specific antibodies¹⁷ and other factors related to maternal characteristics. If milk also varied with maternal atopic status, these effects on risk of allergy in the child would be obscured by lumping maternal and paternal history.

This investigation used epidemiologic data from the Tucson Children's Respiratory Study to test the hypothesis that the relation of breast-feeding to IgE levels in the child differs depending on maternal total IgE level. Because IgE levels track from birth, with levels later in life being strongly correlated with levels early in life, longitudinal approaches were used to assess these relations at multiple points in time.

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TABLE I. Characteristics of children by infant feeding history

	Percent never breast-fed (n = 170)	Percent breast-fed <4 mo (n = 377)	Percent breast-fed ≥4 mo (n = 567)
Ethnicity*			
Hispanic parents (n = 184)	28.3	41.3	30.4
≥1 Non-Hispanic parent (n = 930)	12.7	32.4	54.9
Maternal schooling*			
≤15 y (n = 907)	17.8	35.2	47.1
≥16 y (n = 205)	4.4	27.3	68.3
Maternal physician- diagnosed asthma†			
Yes (n = 117)	10.3	28.2	61.5
No (n = 964)	16.0	33.4	50.6
Maternal physician-diagnosed allergic rhinitis‡			
Yes (n = 404)	11.6	29.0	54.4
No (n = 673)	18.0	34.6	47.4

*P = .00001 for relation with feeding history.

†P < .10 for relation with feeding history.

‡P < .0005 for relation with feeding history.

METHODS

Data for this analysis came from the Tucson Children's Respiratory Study, a prospective longitudinal study of the risk factors for the development of asthma in childhood. A total of 1246 healthy newborns and their families who obtained care from the pediatricians at the largest health maintenance organization in Tucson (78% of those eligible) were enrolled at birth between 1980 and 1984; more detailed descriptions are available elsewhere.^{18,19} Infants were not selected with reference to allergic history or feeding plans. Most enrolled families had at least one employed member (85%) and were non-Hispanic white (80%).

Measurements of total serum IgE were made 4 times (at birth with umbilical cord blood and at the mean ages of 9 months, 6 years, and 11 years). Sera were frozen at -70°C until assayed, and IgE levels were determined by the paper radioimmunosorbent test with commercially available kits (Pharmacia Diagnostics, Piscataway, NJ). As previously described,²⁰ the assay threshold was regarded as 0.1 IU/mL. Samples were assayed in duplicate, and the mean of the 2 IgE values was used in the analyses. Raw IgE values were log₁₀ transformed, and results were expressed as mean log₁₀ (IgE). Parental total serum IgE level was assessed similarly, when the child was 6 years old.

Infant feeding data came from 1 of 2 sources,²¹ with prospective data given priority. The health maintenance organization physicians completed a standardized form on current feeding practices at each well-child visit in the first year of life (prospective data). In addition, a questionnaire was completed by parents in the child's second year of life (mean age ± SD, 1.6 ± 0.3 years). Based on these data, children were categorized into one of the following feeding groups: never breast-fed, breast-fed up to 4 months, and breast-fed for 4 or more months. Analyses were also conducted with reference to duration of exclusive breast-feeding (never exclusively breast-fed, exclusive breast-feeding 3 months or less, exclusive breast-feeding more than 3 months). Background information on potential confounders (parental ethnicity, level of education, and physician diagnosis of either asthma or allergic rhinitis) was obtained by questionnaire at birth. Whether the mother smoked during pregnancy was ascertained when the retrospective feeding data was obtained (age, 1.6 years).

TABLE II. Total serum IgE in mother and in child in relation to feeding status*

	Never breast-fed		Breast-fed <4 mo		Breast-fed ≥4 mo	
	n	IU/mL	n	IU/mL	n	IU/mL
Maternal IgE	112	118.3	208	113.5	376	103.4
IgE level in the child						
Birth	152	0.10	327	0.12	503	0.12
9 mo	126	3.5	231	3.8	410	3.8
6 y	83	38.4	145	27.5	291	40.4
11 y	99	74.1	166	58.3	319	59.5

*There were no significant differences in relation to feeding status.

The relations between maternal IgE level, feeding history, and IgE level in the child were first assessed cross-sectionally. Standard statistical procedures such as *t* tests, one-way analysis of variance, and the chi-squared distribution were used to assess differences between groups in bivariate and stratified analyses.

Longitudinal analyses used repeated measures analysis. Because there were missing observations, a random effects model was used.²²⁻²⁴ The model estimated mean total IgE level at 3 times in the first decade of life for children in 6 subgroups based on 2 categories of maternal IgE (high tertile vs all others) and on 3 categories of infant feeding (never breast-fed, breast-fed less than 4 months, and breast-fed 4 months or longer). This procedure tests for group differences and temporal trends with the use of the likelihood ratio test. Subsequent models assessed whether results were altered by the addition of potential confounders.

All components of the study were approved by the University of Arizona Institutional Review Board. Informed consent was obtained from parents both at the birth of the child and when blood was drawn.

RESULTS

Sample characteristics

Measures of total serum IgE levels were available for 1047, 790, 534, and 599 children at birth, 9 months, 6 years, and 11 years, respectively. Total serum IgE level was measured on 717 mothers and 548 fathers.

Table I shows the characteristics of children with reference to infant feeding practices. Mothers were significantly more likely to breast-feed for 4 months or longer if they had completed college, were non-Hispanic, or had been diagnosed by a doctor as having allergic rhinitis; mothers with asthma tended to be more likely to breast-feed. Infant feeding was unrelated to sex or paternal history of either physician-diagnosed asthma or allergic rhinitis. There was no significant relation between feeding status and either maternal IgE level or IgE level in the child at any age, when assessed for the group as a whole (Table II).

Cross-sectional analyses of the relation of infant feeding to IgE level in the child and as stratified by parental IgE level

Table III displays the geometric mean total IgE in the child at different ages, in relation to infant feeding status,

TABLE III. Child's geometric mean total serum IgE level at different ages by feeding history and maternal tertile of IgE

	Birth			9 mo			6 y			11 y		
	n	IU/mL	±95% CI	n	IU/mL	±95% CI	n	IU/mL	±95% CI	n	IU/mL	±95% CI
Lower maternal IgE tertiles												
Never breast-fed	65	0.08	0.07-0.10	61	3.0	2.2-4.0	49	44.3	29.4-66.7	57	68.4	43.6-107.3
Breast-fed <4 mo	118	0.11	0.09-0.13	94	3.0	2.4-3.9	76	21.4*	14.8-30.5	91	45.6	30.3-68.6
Breast-fed ≥4 mo	222	0.10	0.09-0.12	190	3.5	2.9-4.2	159	25.8*	19.8-33.5	173	40.8	31.2-53.5
High maternal IgE tertile												
Never breast-fed	36	0.18	0.13-0.26	25	4.2	2.6-6.9	24	36.2	21.9-59.8	28	100.1	49.9-200.6
Breast-fed <4 mo	67	0.15	0.12-0.19	51	5.1	3.5-7.3	50	41.8	24.7-70.9	56	92.3	60.6-140.8
Breast-fed ≥4 mo	120	0.15	0.03-0.93	89	5.2	4.0-6.8	88	97.0†	65.8-142.9	96	122.0	81.8-182.1

* $P < .05$ for difference from never breast-fed within the same maternal IgE strata (using analysis of variance with Duncan's multiple range test); 95% confidence interval (CI) are asymmetric because of $\log_{10}$ distribution.

† $P < .01$ for difference from never breast-fed within the same maternal IgE strata (using analysis of variance with Duncan's multiple range test); 95% confidence interval (CI) are asymmetric because of $\log_{10}$ distribution.

and stratified by maternal tertile of IgE. Among children whose mothers were in the 2 lower tertiles of IgE, those who were breast-fed any length of time had significantly lower IgE levels compared with children who were never breast-fed. Total serum IgE level at age 6 was 24.2 IU/mL for children who were breast-fed versus 44.3 IU/mL for children who were never breast-fed ($P < .02$). At age 11 years, total IgE level was 42.4 IU/mL for children who were breast-fed versus 68.4 IU/mL for children who were never breast-fed, a trend of borderline significance ($P < .08$).

For children whose mothers were in the highest tertile of IgE, breast-feeding tended to be associated with higher IgE levels in the child at all ages after birth. In this group, breast-feeding for 4 months or longer was associated with significantly higher IgE levels at age 6 years relative to those breast-fed less than 4 months or never breast-fed (97.0 IU/mL vs 38.9 IU/mL; $P < .005$). Similar trends were observed at age 11 years, although differences were not significant. Patterns were virtually identical when assessed with reference to duration of exclusive breast-feeding (data not shown).

There was no systematic relation between breast-feeding and total IgE level in the child when stratified by paternal IgE (data not shown).

Longitudinal relations of total serum IgE in the mother and the child and as altered by infant feeding practices

Total IgE levels in the first decade of life were assessed longitudinally for relation with maternal IgE and feeding status, as described earlier, with the use of a random effects model. Children were classified with reference to maternal tertile of IgE (highest vs all others)

and feeding status. A total of 664 children with 1457 observations were included. These children did not differ with regard to ethnicity, sex, maternal education, or parental asthma from those originally enrolled but lacking sufficient data for the longitudinal analyses.

Fig 1 plots both the actual geometric mean total serum IgE levels at 3 ages and the modeled mean values with the use of the random effects model. For the modeled data, only the IgE levels of the groups that differed significantly from the reference group (children who were never breast-fed) are shown. Thus although there are 6 groups of children defined with reference to maternal tertile of IgE and feeding status, only 3 groups were distinguishable from the reference group with the use of the model. IgE values at birth were not included in the model because of the large number of specimens with undetectable levels.

The model confirms the cross-sectional analyses, indicating that the relation of maternal IgE level to IgE level in the child differs depending on feeding status. Children of mothers with high IgE levels who were breast-fed for 4 months or more had significantly higher IgE levels at 6 and 11 years than children in the reference group. IgE levels for children of mothers with high IgE levels who breast-fed for less than 4 months did not differ significantly from the reference group and therefore do not appear as a separate line.

In contrast, among children whose mothers were in the 2 lower tertiles of IgE, breast-feeding of any duration was associated with significantly lower total IgE at age 6 and 11 years. IgE levels at 9 months did not differ in relation to feeding status. Patterns were similar when assessed with relation to the duration of exclusive breast-feeding.

Ethnicity, maternal asthma, and maternal allergic

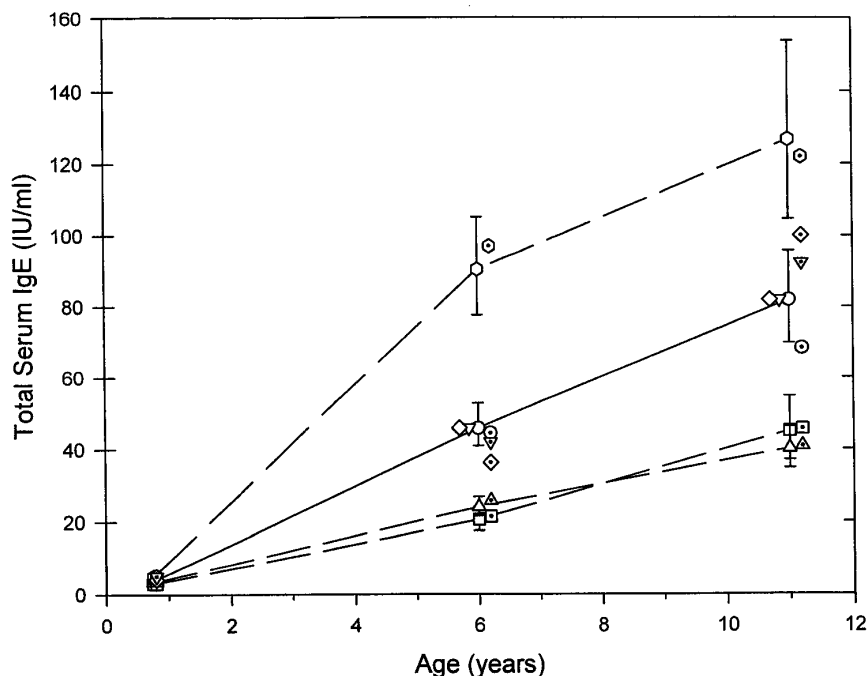


FIG 1. Geometric mean total serum IgE levels ($\pm$ SE) by age. Observed cross-sectional values are indicated by symbols enclosing a dot; comparable predicted means with repeated measures analyses are shown as open symbols (see key below). The 95% confidence intervals for observed values are shown in Table III. The solid line reflects values for the reference group; the dashed lines show values that differ significantly from the reference group. Circles, Lower maternal IgE level, never breast-fed (reference group); squares, lower maternal IgE level, breast-fed <4 months; triangles, lower maternal IgE level, breast-fed $\geq$ 4 months; diamonds, higher maternal IgE level, never breast-fed; inverted triangles, higher maternal IgE level, breast-fed <4 months; hexagons, higher maternal IgE level, breast-fed $\geq$ 4 months.

rhinitis were related to IgE level in the child at some ages and thus were possible confounders. However, the relations shown earlier were not altered when these factors were included into subsequent random effects models (data not shown); the addition of maternal education or smoking during pregnancy to the model also did not alter results.

DISCUSSION

This study suggests that the relation of breast-feeding to one allergic marker in childhood is complex and may differ depending on maternal status for this marker. Among children of mothers with lower IgE levels, breast-feeding was associated with diminished IgE levels in the child; whereas among children of mothers with high IgE levels, breast-feeding was associated with elevated IgE levels relative to never breast-fed children in that maternal IgE strata. These observations were not attributable to either confounding factors or differences in IgE levels at birth. No similar relations with feeding practices were evident with regard to paternal IgE level and IgE level in the child.

The relations shown here are consistent with other findings regarding IgE. Although IgE is at least partially inherited,²⁵ environmental exposures in the first year of

life appear to influence total serum IgE levels later in childhood.²⁶ Foods are the first allergens to evoke detectable specific IgE responses in most children,²⁷ and early production of food-specific IgE is associated with an elevated risk for allergic outcomes.¹⁴ Thus it is logical that characteristics of infant feeding practices (which provide immediate, continuing, and high-volume exposure to antigens, including bacteria and allergens) might alter inherited predisposition toward IgE production.

Previous findings on the relation between breast-feeding and IgE levels in early childhood have been contradictory. Saarinen et al²⁸ found that total IgE level was significantly lower in infants who were breast-fed compared with infants who were formula fed, but only before the introduction of solid foods. In contrast, Juto and Bjorksten²⁹ found no feeding-related differences in IgE level in the first 6 months of life but showed significantly higher IgE levels at 12 months for infants weaned from breast milk after 6 months compared with those weaned before that time. These 2 studies differed in definitions of and proportions with family history of allergy, in the composition of the alternate feeding regimens, and in the percent of mothers following a hypoallergenic diet. Another study³⁰ at 4 days postpartum found that IgE levels increased more slowly in infants who were exclusively breast-fed relative to those infants receiving formula.

However, none of these studies assessed whether relations were altered depending on maternal (as compared with familial) allergic history or IgE level.

There were several possible explanations for the finding that breast-feeding has paradoxical relations with IgE level in the child depending on maternal IgE level. First, it is possible that some aspect of the shared environment of both mothers with high IgE levels and their children might swamp the beneficial effects of breast-feeding seen in the low maternal IgE group. However, in Tucson, sensitization is most commonly seen to aeroallergens and ubiquitous molds rather than indoor or other localized allergens.⁸

A second possibility is that the milk produced by allergic mothers might differ from that of nonallergic mothers. Little is known regarding the effect of maternal atopy on characteristics of the milk, although one study³¹ has found significant differences in long-chain fatty acids in milk related to maternal allergic status. It is known that human milk contains only small amounts of IgE³²⁻³⁴ and thus IgE in milk is unlikely to account for the findings reported here. Although one small study³² found no correlation between IgE in the mother's serum and in her milk, a larger study³³ found an association between total IgE in maternal serum and milk.

Because cytokines play a crucial role in the regulation of IgE synthesis,³⁵ these substances might both differ by maternal atopic status and potentially affect subsequent development of immune system markers of allergy in the child. Recent studies have demonstrated that cells in human milk produce a variety of cytokines,^{36,37} often in amounts that would be physiologically significant,³⁸ although the fate of both cells and cytokines in the intestinal track is unknown. To our knowledge, however, neither IL-4 nor other cytokines that might enhance IgE production have been detected in human milk. Nevertheless, Allardice and Wilson³⁹ showed that cord blood lymphocytes stimulated with supernatants from cultured breast milk cells of atopic mothers were significantly more likely to produce IgE than were lymphocytes stimulated with supernatants from milk of nonatopic mothers.

An alternate explanation for the findings reported here is that breast-feeding may alter some other outcome that affects IgE production. It has been hypothesized that infections in early life may stimulate the infant immune system toward an antimicrobial (T_{H1}) rather than an allergic (T_{H2}) response.⁴⁰ Because breast-feeding is clearly associated with lower rates of infant illness,⁴¹⁻⁴⁴ this protection might be associated with a higher risk of the development of allergic symptoms. In addition, it has been hypothesized⁴⁵ that intestinal colonization in infancy may play a critical role in development of the T_{H1} response. The enteric flora of breast-fed infants differs substantially from that of formula-fed infants^{46,47} and is associated with reduced morbidity as the result of diarrheal illnesses.⁴⁸ However, this normal, healthy enteric flora associated with breast-feeding may also either delay or decrease the T_{H1} response and encourage persistence of the T_{H2} immunity characteristic of early postnatal life, particularly in the context of a

genetic predisposition toward IgE production. The current finding that IgE levels did not differ at 9 months in relation to feeding status, despite the fact that the bulk of milk had been consumed by that time, lends credence to this hypothesis by suggesting that it takes time for the effect to manifest.

Our findings suggest that certain analytic strategies might be particularly useful in future research into the relations of infant feeding and the development of allergy in childhood. First, use of biologic indicators of allergic predisposition will provide an empiric outcome that can bolster assessments that focus on symptom history. In addition, maternal and paternal influences on the development of allergy should be differentiated in future research, based on our finding of a different relationship of paternal versus maternal influence on the child's IgE level.

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