

Breast-feeding and the prevalence of asthma and wheeze in children: Analyses from the Third National Health and Nutrition Examination Survey, 1988-1994

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Background: Asthma prevalence has increased dramatically in recent years, especially among children. Breast-feeding might protect children against asthma and related conditions (recurrent wheeze), and this protective effect might depend on the duration and exclusivity of the breast-feeding regimen.

Objective: We sought to determine whether there is an association between breast-feeding and asthma, recurrent wheeze, or both in children up to 72 months of age and whether the duration and exclusivity of breast-feeding affect this association.

Methods: Data were from the third National Health and Nutrition Examination Survey, a nationally representative cross-sectional survey conducted from 1988 to 1994. We tested for significant associations between breast-feeding and physician-diagnosed asthma and recurrent wheeze (≥ 3 episodes in the past 12 months) before and after adjusting for potential confounders.

Results: Crude analyses showed that breast-feeding was associated with significantly reduced risks for asthma and recurrent wheeze in children 2 to 71 months of age, but after adjusting for potential confounders, these overall protective associations attenuated and were no longer statistically significant. However, 2 new and important associations were revealed after adjusting for confounders: (1) compared with never breast-fed children, ever breast-fed children had significantly reduced odds of being diagnosed with asthma and of having recurrent wheeze before 24 months of age, and (2) among children 2 to 71 months of age who had been exposed to environmental tobacco smoke, those who had ever been breast-fed had significantly reduced risks of asthma and wheeze compared with those who had never been breast-fed.

Conclusions: Breast-feeding might delay the onset of or actively protect children less than 24 months of age against asthma and recurrent wheeze. Breast-feeding might reduce the prevalence of asthma and recurrent wheeze in children exposed to environmental tobacco smoke. (*J Allergy Clin Immunol* 2003;111:328-36.)

Key words: Asthma, recurrent wheeze, breast-feeding, atopy, environmental tobacco smoke, National Health and Nutrition Examination Survey III

According to the National Center for Health Statistics, the national rates for self-reported asthma prevalence have increased significantly in recent years, especially among children. From 1980 to 1995, the prevalence of asthma increased by 74% in the overall US population but increased by 163% in 0- to 4-year-old children and 81% in 5- to 14-year-old children.¹ Morbidity indices for asthma have also increased faster in children. While overall rates of asthma-related hospitalizations and emergency department visits increased by about 50% to 60% from 1975 to 1995, these rates more than doubled in those less than 14 years of age.² Currently, asthma affects almost 5 million children in the United States under the age of 18 years³ and is the leading cause of emergency department admissions and school absenteeism, the third leading cause for hospitalizations, and a major cause for interrupted sleep, limited activity, and disruption to family and care giver routines.^{3,4}

Asthma etiology is highly complex, involving genetic, environmental, and socioeconomic factors. Bronchial hyperresponsiveness and elevated total serum IgE levels, 2 hallmarks of asthma, have been shown to have a strong genetic component.^{5,6} Environmentally, asthma can be triggered by exercise, abrupt weather changes, and exposure to allergens, infectious agents, and airway irritants.⁷ The effect of environmental tobacco smoke (ETS) on the prevalence and severity of asthma is especially striking. In children 2 to 24 months of age examined in the third National Health and Nutrition Examination Survey (NHANES III; conducted from 1988-1994), 40% to 60% of the cases of asthma, chronic bronchitis, and recurrent wheeze (≥ 3 episodes per the last 12 months) were attributed to ETS.⁸ In older children 24 to 71 months of age, ETS was still associated with increased prevalences of all 3 conditions, but only the association with asthma remained significant. Other risk factors for asthma include having a parental history of atopic disease and male gender, African American ethnicity, low socioeconomic status, and residence in an urban area.⁹⁻¹³

Conversely, protective factors for asthma might include early exposure to respiratory viral infections through contact with older siblings or by attending day-

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Abbreviations used

ETS: Environmental tobacco smoke
HR: Hazard ratio
NHANES III: Third National Health and Nutrition
Examination Survey
OR: Odds ratio

care centers,^{14,15} living on a farm,^{16,17} and breast-feeding.^{18,19} In this study we focus on the latter, a possible protective association between breast-feeding and asthma or recurrent wheeze. Previous studies of such associations have yielded conflicting results. Most have shown that breast-feeding protects children against respiratory illnesses, such as bronchitis and recurrent or persistent wheeze, but does not protect children against asthma.^{10,20-25} For example, in the NHANES II (conducted from 1976-1980) breast-feeding was associated with lower prevalences of asthma and wheeze, but only the association with wheeze was significant.¹⁰ In the Tucson Children's Respiratory Study, a prospective study of children up to 6 years of age, exclusive breast-feeding reduced the rates of general wheeze respiratory tract illnesses in children up to 1 year of age and recurrent wheeze in children up to 3 years of age.^{21,22} While asthma was examined as a dependent variable, no significant association with breast-feeding was observed.

Because persistent and recurrent wheeze are purportedly indicative of an asthmatic predisposition, one would expect to observe a similar protective association between breast-feeding and asthma, but such an association has been reported in only 2 studies to date. In the Western Australian Pregnancy Cohort Study, another prospective study of children up to 6 years of age, those who had been breast-fed exclusively had significantly lower risks of both asthma and persistent wheeze.^{18,26} In a large population-based study conducted in Canada, breast-feeding reduced the risks for both asthma and wheeze in children 12 to 24 months of age.¹⁹

These conflicting reports highlight the need for more in-depth study concerning the associations between breast-feeding, asthma, and wheeze. To help resolve these issues, we used data from the NHANES III to re-examine these relationships and also to determine whether the duration and exclusivity of breast-feeding are contributing factors.

METHODS

Study population

Data for this study were obtained from children 2 to 71 months of age ($n = 8261$) who were sampled in the NHANES III. This survey was conducted by the National Center for Health Statistics and designed to provide estimates of the health status of the US population. A complex cross-sectional design was used to sample the total civilian, noninstitutionalized population 2 months of age or older. The NHANES III was conducted in 2 discrete phases.²⁷ Phase 1 was conducted from 1988 through 1991, and phase 2 was conducted from 1991 through 1994. Each of the 2 NHANES III phases comprised a national probability sample, such that unbiased estimates

(from the point of view of sample selection) of the health and nutrition characteristics could be independently produced for either phase 1 or phase 2, as well as for both phases combined. Data used in this study were taken from the Household Youth Questionnaire in the NHANES III, which was administered to a family reference person, usually the child's parent or guardian. A complete description of the plan and operations of the NHANES III can be found elsewhere.²⁸

Exposure variable

Breast-feeding regimens were classified in 3 ways: (1) ever breast-fed; (2) breast-feeding duration based on the age (in months) that the child completely stopped breast-feeding or being fed breast milk; and (3) exclusive breast-feeding duration based on the age (in months) that the child was first fed something other than breast milk or water. Durations for breast-feeding and exclusive breast-feeding were dichotomized by using a threshold of 4 months, and only children at least 4 months of age at the time of the interview were used in the analyses concerning duration. The 4-month threshold was chosen because it is the median (50th percentile) duration of nonexclusive breast-feeding. Furthermore, 4 months was used as the threshold in most earlier studies^{18,20-23} and is bioclinically significant.²⁰

Outcomes

The 2 respiratory outcomes examined in this study were physician-diagnosed asthma and recurrent wheeze, as assessed with a questionnaire. Recurrent wheeze was defined as having had 3 or more episodes of wheeze within the last 12 months. This was done to discriminate from children with transient or early infectious wheeze (0-2 episodes in the past 12 months). Both outcomes were based on retrospective recall of the family reference person.

Covariates

Potential confounders and effect modifiers used as covariates in the multivariate analyses included the sex, birth weight, and race-ethnicity of the child and the educational level of the family reference person. Other covariates included whether the child attended daycare before 4 years of age (yes or no), had a parental history of asthma or hay fever (mother, father, or both), was exposed to ETS from a household member (0 vs ≥ 1 smoker), and had a mother who smoked while pregnant (yes or no).

Statistical methods

Crude associations between the study variables and physician-diagnosed asthma and recurrent wheeze were assessed with χ^2 tests. For physician-diagnosed asthma, Cox regression was used to estimate both the crude and adjusted hazard ratios (HRs) and 95% CIs for each breast-feeding variable within the different breast-feeding classifications.²⁹ The time to diagnosis of asthma in months was modeled by using survival analyses. Children who were not diagnosed with asthma were censored at their age at the time of interview. For recurrent wheeze, the age at onset was not assessed in the NHANES III. Therefore logistic regression was used to estimate both the crude and adjusted odds ratios (ORs) and 95% CIs for each breast-feeding variable.

For both physician-diagnosed asthma and recurrent wheeze, covariates were retained in the model regardless of their statistical significance. Two-way and some 3-way interaction terms between breast-feeding and the covariates were tested separately in fully adjusted models and retained if they achieved statistical significance ($P < .05$). Preliminary survival analyses indicated that the HRs for the breast-feeding variables were not constant over time. Therefore an interaction term between the breast-feeding variables and survival time (age at asthma diagnosis dichotomized at <24

TABLE I. Bivariate distribution of children by study variables and outcomes

Population characteristics	% of total population	Asthma,* % (SE)	Recurrent wheeze,† % (SE)
Sex			
Male	50.5%	6.7% (0.53)	8.6% (0.72)
Female	49.5%	5.0% (0.57)	6.5% (0.53)
		<i>P</i> = .026	<i>P</i> = .008
Race-ethnicity			
Non-Hispanic white	37.3%	5.0% (0.55)	7.4% (0.77)
Non-Hispanic black	26.5%	8.9% (0.75)	7.8% (0.71)
Mexican American	30.2%	6.0% (0.65)	8.1% (0.79)
Other	6.0%	6.6% (1.38)	7.8% (1.68)
		<i>P</i> = .001	<i>P</i> = .921
Education of reference person			
<12 y	35.4%	7.6% (0.77)	9.7% (1.05)
12 y	33.5%	6.6% (0.87)	8.0% (0.88)
>12 y	31.1%	4.5% (0.62)	6.9% (0.81)
		<i>P</i> = .002	<i>P</i> = .042
Parental history of asthma/hay fever			
Father	7.8%	8.3% (0.95)	8.5% (1.61)
Mother	9.3%	10.7% (1.51)	8.6% (1.92)
Both	2.1%	21.2% (4.52)	15.6% (3.69)
Neither	80.8%	4.4% (0.40)	7.0% (0.60)
		<i>P</i> < .001	<i>P</i> = .206
Birth weight			
<2500 g	8.4%	7.1% (1.48)	11.3% (2.13)
2500-4100 g	84.1%	6.1% (1.43)	7.5% (0.51)
>4100 g	7.5%	3.3% (1.12)	4.5% (1.27)
		<i>P</i> = .05	<i>P</i> = .017
Household smokers			
0 smokers	62.1%	4.9% (0.47)	6.3% (0.65)
≥1 smoker	37.9%	7.6% (0.68)	9.7% (0.74)
		<i>P</i> = .002	<i>P</i> = .001
Pregnant mother smoke			
No	80.2%	5.0% (0.43)	6.5% (0.55)
Yes	19.8%	9.1% (0.93)	11.1% (1.09)
		<i>P</i> < .001	<i>P</i> < .001
Attend daycare <4 y of age			
Yes	29.3%	7.2% (0.77)	8.7% (0.89)
No	70.7%	5.1% (0.45)	6.8% (0.56)
		<i>P</i> = .028	<i>P</i> = .071

*Physician-diagnosed asthma as reported by the proxy respondent.

†Three or more episodes of wheeze during the previous 12 months.

months and ≥24 months) were included in the asthma models. Similarly, preliminary logistic models for wheeze indicated a significant interaction between the breast-feeding variables and the age at interview in months. Therefore an interaction term between the breast-feeding variables and the age at interview were included in the recurrent wheeze models.

NHANES III was based on a complex multistage probability sample design, and therefore special statistical considerations were required in analyzing the NHANES III data. SUDAAN (RTI, Research Triangle Park, NC) statistical software was used to adjust for weighting and clustering of subjects. Statistical significance was set a priori at the .05 level.

RESULTS

Characteristics of children with asthma and recurrent wheeze

Data regarding both ever having been breast-fed and asthma were available on most of the children 2 to 71

months of age sampled in phase 1 and phase 2 of the NHANES III (8246/8261). Of these, 7766 children had accompanying data for breast-feeding duration, recurrent wheeze, and all study covariates. The prevalences of physician-diagnosed asthma and recurrent wheeze among this population (*n* = 7766) were 5.9% and 7.6%, respectively. The key characteristics of the study population are listed in Table I. All variables listed were significantly associated with asthma. Children with asthma were more likely to be male, be non-Hispanic black, be born with a low birth weight (<2500 g), have a family reference person with less than 12 years of education, and attend daycare before 4 years of age. Children with asthma were also more likely to come from households with 1 or more smokers, have a mother who smoked while pregnant, or both. A parental history of asthma or hay fever was a particularly strong risk factor for asthma: 21.2% of children born of 2 affected parents were diagnosed with asthma

TABLE II. Relationship between breast-feeding and respiratory outcomes before and after adjusting for study covariates

	Asthma (HRs)		Recurrent wheeze (ORs)	
	Crude	Adjusted	Crude	Adjusted
Breast-feeding regimen				
Ever breast-fed*				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	0.68 (0.51-0.90)‡	0.85 (0.64-1.13)	0.70 (0.51-0.95)†	0.81 (0.57-1.14)
Duration of breast-feeding§				
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<4 mo	0.77 (0.51-1.15)	0.89 (0.59-1.34)	0.81 (0.54-1.21)	0.87 (0.57-1.33)
≥4 mo	0.61 (0.43-0.86)†	0.82 (0.58-1.17)	0.65 (0.43-0.97)†	0.80 (0.51-1.23)
Duration of exclusive breast-feeding				
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<4 mo	0.74 (0.44-1.24)	0.97 (0.57-1.65)	0.76 (0.45-1.30)	0.84 (0.46-1.55)
≥4 mo	0.35 (0.20-0.64)‡	0.56 (0.29-1.11)	0.61 (0.23-1.60)	0.82 (0.34-1.98)

*Includes all phase 1 and phase 2 children, 2 to 72 months of age.

† $P < .05$.

‡ $P < .01$.

§Includes all phase 1 and phase 2 children, 4 to 72 months of age.

||Includes only phase 2 children 4 to 72 months of age.

before their sixth birthday compared with 4.4% if neither parent was affected. Children born of only one affected parent had higher rates as well. Children with recurrent wheeze had many but not all of the same characteristics as children with asthma. Having a parental history of asthma or hay fever was associated with higher prevalences of recurrent wheeze, but this was not statistically significant. In addition, recurrent wheeze was not associated with race-ethnicity or daycare attendance.

Characteristics of children ever breast-fed

Approximately half of the children (3602/7766) were reported to have ever been breast-fed. Non-Hispanic white children were most likely to have been breast-fed (60.3%) compared with other racial-ethnic groups (26.2% for non-Hispanic black, 55.9% for Mexican Americans, and 53.5% for other). Children from households in which the family reference person had a higher level of education were more likely to have been breast-fed (70.8% for reference persons with >12 years of education vs 45.8% and 35.7% for those with 12 and <12 years of education, respectively). Children were less likely to have been breast-fed if their mothers smoked while pregnant (40.9%) or they lived in households with one or more smokers (36.8%).

Just over half of the ever breast-fed children (1864/3602) were breast-fed for 4 months or longer. The 25th, 50th, and 75th percentiles for breast-feeding duration were 1.7, 4.0, and 7.2 months, respectively. Exclusive breast-feeding durations were typically shorter; the 25th, 50th, and 75th percentiles for exclusive duration were 0.6, 2.0, and 3.76 months, respectively. Data on breast-feeding duration (the age that the child completely stopped being breast-fed or fed breast milk) were collected during both phase 1 and phase 2 of the NHANES III. From these data, however, we could not determine the exact breast-feeding regimen the children underwent during this time. Some might have been breast-fed exclu-

sively (only breast milk and water) or fed some combination of breast milk and other types of food (formula, solids). Others might have been breast-fed exclusively for some initial period and then gradually allowed formula or other types of food over time. Data on exclusive breast-feeding duration (age that the child was first fed something other than breast milk or water) were only collected during phase 2. About 30% of the phase 2 children ever breast-fed (524/1725) were exclusively breast-fed for 4 months or longer.

Multivariate analyses

The unadjusted hazard and regression models showed that children who had ever been breast-fed were less likely to be diagnosed with asthma or have recurrent wheeze compared with children who had never been breast-fed (Table II). Children breast-fed for the longer duration (≥4 months), regardless of exclusivity, were less likely to be diagnosed with asthma than those breast-fed the shorter duration. A longer breast-feeding duration was also associated with a lower odds for recurrent wheeze, but this was only significant for children nonexclusively breast-fed the longer duration. After adjusting for potential confounding factors, all protective associations between breast-feeding, asthma, and recurrent wheeze attenuated and were no longer statistically significant. This was in spite of an almost 2-fold protection (HR = 0.56) against asthma in children exclusively breast-fed for 4 months or longer.

Interactions with age and ETS exposure

Two interesting interactions were observed with regard to asthma and recurrent wheeze and other study covariates. First, we noted an interaction between age and ever having been breast-fed. For asthma, this was the age of diagnosis ($P < .01$), and for recurrent wheeze, this was the age at the time of the interview ($P < .05$). In both cases ever having been breast-fed appeared to significantly reduce the likelihood of each outcome before 24

Asthma, rhinitis,
other respiratory
diseases

TABLE III. Relationship between breast-feeding, age, and respiratory outcomes before and after adjusting for study covariates: Asthma

Breast-feeding regimen	Asthma (HRs)			
	Diagnosed <24 mo of age		Diagnosed ≥24 mo of age	
	Crude	Adjusted	Crude	Adjusted
Ever breast-fed*				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	0.56 (0.42-0.75)‡	0.72 (0.54-0.95)†	1.06 (0.61-1.83)	1.27 (0.71-2.28)
Duration of breast-feeding§				
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<4 mo	0.61 (0.40-0.91)†	0.77 (0.52-1.16)	1.14 (0.54-2.41)	1.24 (0.59-2.61)
≥4 mo	0.54 (0.35-0.86)	0.69 (0.44-1.09)	0.89 (0.48-1.67)	1.18 (0.59-2.34)
Duration of exclusive breast-feeding				
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<4 mo	0.79 (0.43-1.43)	1.04 (0.61-1.78)	0.79 (0.31-2.00)	0.95 (0.33-2.70)
≥4 mo	0.34 (0.16-0.72)‡	0.60 (0.29-1.22)	0.43 (0.17-1.12)	0.71 (0.23-2.20)

*Includes all phase 1 and phase 2 children, 2 to 72 months of age.

† $P < .05$.‡ $P < .01$.

§Includes all phase 1 and phase 2 children, 4 to 72 months of age.

||Includes only phase 2 children 4 to 72 months of age.

TABLE IV. Relationship between breast-feeding, age, and respiratory outcomes before and after adjusting for study covariates: Recurrent wheeze

Breast-feeding regimen	Recurrent wheeze (ORs)			
	Interviewed <24 mo of age		Interviewed ≥24 mo of age	
	Crude	Adjusted	Crude	Adjusted
Ever breast-fed*				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	0.47 (0.30-0.74)	0.52 (0.34-0.81)	0.84 (0.57-1.23)	0.98 (0.65-1.50)
Duration of breast-feeding§				
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<4 mo	0.46 (0.25-0.84)	0.44 (0.25-0.78)	1.02 (0.61-1.69)	1.10 (0.65-1.86)
≥4 mo	0.52 (0.34-0.81)	0.63 (0.38-1.03)	0.71 (0.43-1.19)	0.88 (0.51-1.52)
Duration of exclusive breast-feeding				
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<4 mo	0.33 (0.16-0.70)	0.37 (0.16-0.87)	1.0 (0.53-1.86)	1.10 (0.55-2.19)
≥4 mo	0.57 (0.23-1.43)	0.73 (0.29-1.83)	0.64 (0.18-2.21)	0.86 (0.27-2.78)

*Includes all phase 1 and phase 2 children, 2 to 72 months of age.

† $P < .05$.‡ $P < .01$.

§Includes all phase 1 and phase 2 children, 4 to 72 months of age.

||Includes only phase 2 children 4 to 72 months of age.

months of age (Tables III and IV). These protective relationships were no longer evident in ever breast-fed children who were diagnosed with asthma or had recurrent wheeze after 24 months of age. When duration was considered, statistically significant results were observed in relation to the child's age at asthma diagnosis only before adjusting for the study covariates. The protective effect was quite strong in children less than 24 months of age who were breast-fed exclusively for 4 months or longer (HR = 0.34; 95% CI, 0.16-0.72). Breast-feeding duration

had the opposite effect on recurrent wheeze in children interviewed at less than 24 months of age; those breast-fed the shorter duration were less likely to have recurrent wheeze than those breast-fed for the longer duration.

The second interaction we observed in this study was between having been exposed to ETS and ever having been breast-fed ($P < .05$). Many of the children in this study were from households with one or more smokers (37.9%), and these children had significantly higher prevalences of asthma and recurrent wheeze than chil-

TABLE V. Relationship between breast-feeding, ETS, and respiratory outcomes before and after adjusting for study covariates: Asthma

Breast-feeding regimen	Asthma (HRs)			
	0 Household smokers		≥1 Household smoker	
	Crude	Adjusted	Crude	Adjusted
Ever breast-fed*				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	0.9 (0.64-1.26)	1.12 (0.81-1.56)	0.56 (0.38-0.82)‡	0.61 (0.39-0.93)†
Duration of breast-feeding†				
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<4 mo	1.03 (0.64-1.66)	1.21 (0.74-1.97)	0.57 (0.36-0.90)†	0.59 (0.37-0.94)†
≥4 mo	0.81 (0.56-1.19)	1.08 (0.75-1.57)	0.45 (0.30-0.68)‡	0.53 (0.33-0.86)‡
Duration of exclusive breast-feeding‡				
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<4 mo	0.84 (0.44-1.60)	1.18 (0.62-2.25)	0.68 (0.31-1.46)	0.72 (0.35-1.50)
≥4 mo	0.42 (0.25-0.72)‡	0.64 (0.35-1.19)	0.27 (0.07-0.99)†	0.47 (0.11-1.94)

*Includes all phase 1 and phase 2 children, 2 to 72 months of age.

†Includes all phase 1 and phase 2 children, 4 to 72 months of age.

‡Includes only phase 2 children 4 to 72 months of age.

Asthma, rhinitis,
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TABLE VI. Relationship between breast-feeding, ETS, and respiratory outcomes before and after adjusting for study covariates: Recurrent wheeze

Breast-feeding regimen	Recurrent wheeze (ORs)			
	0 Household smokers		≥1 Household smoker	
	Crude	Adjusted	Crude	Adjusted
Ever breast-fed*				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	0.87 (0.54-1.39)	0.95 (0.57-1.58)	0.66 (0.43-0.99)†	0.66 (0.44-0.98)†
Duration of breast-feeding†				
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<4 mo	1.02 (0.60-1.75)	1.04 (0.59-1.86)	0.72 (0.42-1.22)	0.71 (0.42-1.19)
≥4 mo	0.81 (0.46-1.45)	0.94 (0.51-1.72)	0.62 (0.35-1.10)	0.63 (0.34-1.17)
Duration of exclusive breast-feeding‡				
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<4 mo	0.77 (0.39-1.54)	0.88 (0.39-1.98)	0.85 (0.4-1.78)	0.82 (0.41-1.64)
≥4 mo	0.74 (0.25-2.18)	0.93 (0.33-2.61)	0.32 (0.08-1.26)	0.46 (0.10-2.12)

*Includes all phase 1 and phase 2 children, 2 to 72 months of age.

†Includes all phase 1 and phase 2 children, 4 to 72 months of age.

‡Includes only phase 2 children 4 to 72 months of age.

dren from nonsmoking households (Table I). Ever having been breast-fed significantly lowered the likelihoods of asthma and recurrent wheeze in the children from smoking households compared with ever breast-fed children from nonsmoking households (Tables V and VI). When duration was considered, this protective effect was quite striking in children exclusively breast-fed for 4 months or longer (crude HR = 0.27; 95% CI, 0.07-0.99). Although longer breast-feeding durations were associated with lower odds for recurrent wheeze, and these were

quite dramatic for the exclusively breast-fed children (unadjusted OR = 0.32, adjusted OR = 0.46), these associations were not statistically significant. Finally, we observed a significant 3-way interaction among breast-feeding, age, and ETS exposure ($P = .02$). Ever breast-fed children from households with one or more smokers had significantly lower hazards for being diagnosed with asthma (unadjusted HR = 0.45 [95% CI, 0.29-0.71], adjusted HR = 0.48 [95% CI, 0.29-0.79]) or having recurrent wheeze (unadjusted OR = 0.50 [95% CI, 0.26-

0.98], adjusted OR = 0.49 [95% CI, 0.25-0.96]) before 24 months of age.

DISCUSSION

This study resulted in 2 new and important findings concerning the protective effects of breast-feeding on childhood asthma and recurrent wheeze. First, we found that ever having been breast-fed might reduce the chances of being diagnosed with asthma, having recurrent wheeze in children less than 24 months of age, or both. Second, breast-feeding might protect children against ETS-related asthma and recurrent wheeze. The protective effect against ETS-related outcomes was significant in children up to 72 months of age (Tables V and VI) but stronger in children less than 24 months of age.

The exact mechanisms by which breast-feeding protects against asthma and recurrent wheeze are unknown. It is likely that breast-feeding both delays and actively protects against allergic sensitization; both mechanisms are consistent with the short protection period (up to 24 months of age) observed in our study. Breast-feeding might delay allergic sensitization by delaying a child's exposure to foreign formula or food proteins. Bottle-fed children have increased immune responses (higher baseline activation and proliferative response of blood lymphocytes) compared with breast-fed children.³⁰ Breast milk also contains a myriad of immunomodulatory and anti-inflammatory factors, such as lactoferrin, IgM, IgG, and IgA antibodies, macrophages, neutrophils, B and T lymphocytes, cytokines, and growth factors that likely protect against allergic sensitization during the breast-feeding period and for a short time after breast-feeding termination.³¹ Furthermore, these compounds and others are important for the development and maturation of the infant's immune system after birth.³²

The second finding of this study, that breast-feeding might protect children against ETS-related outcomes, has never been reported in spite of the known toxic effects of ETS on the respiratory systems in children.³³⁻³⁷ Previously, in these same NHANES III children, 40% to 60% of the cases of asthma, recurrent wheeze, and chronic bronchitis in those less than 24 months of age were attributed to ETS, as were a significant percentage of the cases of asthma in the older children.⁸ Although the pathogenesis of ETS-induced asthma is unknown, it is known that ETS does not increase blood levels of IgE or change a child's atopic status.³⁶ Therefore ETS probably does not directly cause asthma but might sensitize predisposed (atopic) individuals to triggers of asthma, such as viral infections.³⁷ ETS might also sensitize latent asthmatics to triggers of wheeze attacks and thus increase their probability of being diagnosed or of being diagnosed at an earlier age. For example, in one Canadian study, only children with atopic dermatitis who had been exposed to ETS had asthma, whereas nonatopic children who had been exposed to ETS did not.³⁸ In another study conducted in Oslo, children with a history of parental atopy and ETS exposures had higher risks of bronchial

obstruction and asthma than children with nonatopic parents who had been exposed to ETS.³⁹ Similar increased trends of asthma and recurrent wheeze were observed in NHANES III children who had been exposed to ETS and had a parental history of hay fever or asthma. It is possible that breast-feeding might reduce ETS-related asthma and recurrent wheeze by interfering with a gene-environment interaction (atopic predisposition-ETS), at least during the first few years of life. Unfortunately, we were precluded from testing for a protective breast-feeding effect in atopic and ETS-exposed NHANES III children because breast-feeding data were collected only from children less than 6 years of age, and sensitivity testing was done only on children 6 years of age and older. Future studies designed to examine such a relationship should take both the mother and child's atopic status into consideration. While maternal asthma did not diminish the protective effect observed in the Western Australian Pregnancy Cohort Study,²⁶ exclusive breast-feeding by asthmatic mothers in the Tucson Children's Respiratory Study actually increased the rates of asthma and wheeze in atopic children 6 to 13 years of age.²¹

About 20% (n = 1619) of the NHANES III children had mothers who smoked while pregnant, and these children also had higher prevalences of asthma ($P < .01$) and wheeze ($P < .01$) compared with children whose mothers did not smoke while pregnant. Breast-feeding did not appear to protect these children against respiratory outcomes related to prenatal exposure. Because in utero exposure is not associated with atopic disease, we were not surprised with this finding. In utero exposure to tobacco products more likely interferes with prenatal lung development and might lead to more permanent lung function deficits at birth.^{40,41}

While asthma is the most common chronic disorder in children, diagnosis of asthma in infants up to 1 year of age is controversial. In older children the association between asthma and atopy, allergic inflammation, or bronchial hyperreactivity is clear. Diagnosis is based on definitive clinical tests and findings (spirometry, methacholine bronchoprovocation studies, positive skin testing, elevated serum IgE levels, and eosinophilia).⁷ Asthma diagnosis in infants, however, is far more subjective and based on the child's family history, food intolerances and symptoms, and wheeze patterns, as reported by the parents.⁴² Therefore some of the NHANES III children might have been misclassified (wheezy infants as asthmatic and vice versa). If misclassification was nondifferential with respect to breast-feeding, this would dilute the HRs and ORs, bringing them closer to 1. We have no reason to believe that asthma misdiagnosis would be differential with respect to breast-feeding in this study. Furthermore, in secondary analyses we used logistic regression analyses to examine the effects of breast-feeding in children who have both been diagnosed with asthma and had at least one episode of wheeze in the past 12 months. Similar trends of breast-feeding protection were observed in these combined outcome models as were observed in the models using the individual outcomes. For example, chil-

dren less than 24 months of age who had been breast-fed had significantly lower odds of the combined outcome both before (OR = 0.51; 95% CI, 0.25-0.68) and after (OR = 0.51; 95% CI, 0.29-0.89) adjusting for study covariates. Breast-feeding reduced the risk of the combined outcome in ETS-exposed children as well (unadjusted OR = 0.67 [95% CI, 0.39-1.14], adjusted OR = 0.69 [95% CI, 0.39-1.23]). Although the ORs for the combined outcome were similar to those for the individual outcomes, the CIs were wider because of the smaller number of children with the combined outcome. Protective trends against the combined outcome were similar for breast-feeding duration and exclusivity as well.

In conducting these analyses, we recognized the difficulties associated with classifying breast-feeding as an exposure variable. Ideally, random assignment into several well-defined breast-feeding regimens would represent the best study design, but this is both unrealistic and unethical. In the United States breast-feeding regimens are far from standardized; women most typically breast-feed exclusively for a short initial period and gradually introduce formula or solid foods into the infant's diet over time. The NHANES III data allowed us to stratify by duration and exclusivity, but only duration (not exclusivity) could be assessed from phase 1 children. Limiting the analysis for exclusive breast-feeding duration to only phase 2 children, which reduced the study population by approximately 50%, reduced our statistical power for those analyses. Despite these limitations, this study had considerable strengths. Because of the large number of subjects and variables, NHANES III data allowed us to overcome the problems associated with previous studies, such as small sample sizes, restricted focus on a geographic location, specific age groups and socioeconomic status, and inadequate data on potential confounding factors. Furthermore, the unique NHANES III sampling methodology with its clustering and weighting renders these results generalizable to the US population.

The first finding of this study, that breast-feeding might reduce asthma in children less than 24 months of age, is highly consequential because of the difficulties associated with treating such young children. Bronchodilation therapies, the mainstay of asthma therapies, are difficult to administer to the young and, although well tolerated by most, can cause adverse effects.^{7,42} β_2 -adrenergics can increase airway obstruction and aggravate hypoxia. Corticosteroids, often given in combination with β_2 -adrenergics, can interfere with normal lung growth and development.⁴³ Thus breast-feeding can beneficially impact health care by reducing the need to treat young children for asthma. The second finding of this study, that breast-feeding reduces the risks of ETS-related asthma and recurrent wheeze is also highly consequential, simply because of the large number of children who are exposed to ETS and develop related illnesses. These findings, in combination with the dramatic rise in asthma morbidity and mortality in the United States, reinforce the need for broad-based public health strategies to better educate individuals in the preventative effects of breast-feeding and reducing ETS exposures.

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