

Prospective study of breast-feeding in relation to wheeze, atopy, and bronchial hyperresponsiveness in the Avon Longitudinal Study of Parents and Children (ALSPAC)

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Background: Breast-feeding clearly protects against early wheezing, but recent data suggest that it might increase later risk of atopic disease and asthma.

Objective: We sought to examine the relationship between breast-feeding and later asthma and allergy outcomes by using data from the Avon Longitudinal Study of Parents and Children, a large birth cohort in the United Kingdom.

Methods: We used adjusted logistic regression models to evaluate the association between breast-feeding and atopy at age 7 years, bronchial responsiveness to methacholine at age 8 years, and wheeze at ages 3 and 7½ years. Bayesian methods were used to assess the possibility of bias caused by an influence of early wheezing on the duration of breast-feeding, as well as selection bias.

Results: Breast-feeding was protective for wheeze in the first 3 years of life (odds ratio [OR] of 0.80 [95% CI, 0.70-0.90] for ≥6 months relative to never) but not wheeze (OR, 0.98; 95% CI, 0.79-1.22), atopy (OR, 1.12; 95% CI, 0.92-1.35), or bronchial hyperresponsiveness (OR, 1.07; 95% CI, 0.82-1.40) at ages 7 to 8 years. Bayesian models adjusting for the longer duration of breast-feeding among children with wheezing in early infancy produced virtually identical results.

Conclusions: We did not find consistent evidence for either a deleterious effect or a protective effect of breast-feeding on later risk of allergic disease in a large prospective birth cohort of children with objective outcome measures and extensive data on potential confounders and effect modifiers. Neither reverse causation nor loss to follow-up appears to have materially biased our results. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, atopy, breast-feeding, bronchial hyperresponsiveness, allergy

Breast-feeding protects offspring from a variety of adverse health conditions,¹⁻³ but controversy remains regarding its role in the development of asthma and allergy. A substantial body of prospective studies supports a modest protective effect of breast-feeding against wheeze and asthma in infancy and early childhood.^{4,5} However, the protective effect of breast-feeding on asthma in later childhood (age 6 years and above) is less evident,⁵ and some recent studies suggest that breast-feeding actually increases the risk of asthma, wheeze, or atopy to aeroallergens at older ages.⁶⁻¹¹ In one study breast-feeding was associated with increased risk of asthma only in children with a family history of atopic illness.⁶ Recent data suggesting that breast-feeding might enhance the risk of asthma phenotypes conflict with public health guidelines encouraging breast-feeding¹ and have raised concern among pregnant women and their physicians.^{12,13}

Systematic reviews have highlighted methodological issues that contribute to the complexity of studying the association between breast-feeding and allergic disease.^{2-5,13,14} A key issue is recall bias in feeding history; this is eliminated by prospective data collection. Other important issues include lack of data on breast-feeding duration and degree of exclusivity; measurement and control for potential confounding factors, including family allergic history; and the lack of objective or uniform classification of allergic outcomes.¹⁵ More recently, it has been suggested that measuring the effects of breast-feeding on allergic disease can also be complicated by reverse causation if mothers prolong breast-feeding because they note early symptoms of asthma or allergy in their children.¹⁶⁻¹⁸ Only recently have studies attempted to examine this possible source of bias in a quantitative manner.^{7,17}

Given the recent controversy generated by new data on adverse effects of breast-feeding related to asthma phenotypes, we examined prospective data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based birth cohort study that enrolled more than 14,000 pregnant women and followed their children through late childhood. We also evaluated potential reverse causation by using prospective information on breast-feeding and early wheeze analyzed with Bayesian methods.¹⁹ These methods also account for the possibility of selection bias caused by loss to follow-up.

METHODS

ALSPAC study

We used data from the ALSPAC study (<http://www.alspac.bris.ac.uk>), which has been described in detail elsewhere.¹⁴ Additional information is

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Abbreviations used

ALSPAC: Avon Longitudinal Study of Parents and Children
 BHR: Bronchial hyperresponsiveness
 OR: Odds ratio

available in the Online Repository at www.jacionline.org. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees. The core ALSPAC sample consists of 14,541 pregnancies resulting in a cohort of 14,062 live births. Of these, 13,988 children were alive at 1 year of age. For reasons of confidentiality, data on the triplet and quadruplet children were not available, leaving 13,978 study children alive at age 1 year.

Breast-feeding

Data on breast-feeding were obtained from questions about dietary and feeding habits included in 6 questionnaires sent to mothers during the first 4 years of the child's life. (See the Online Repository for detailed information on breast-feeding.) We used data on breast-feeding from all questionnaires in which it was queried to minimize exclusion of subjects for missing data. We were able to assign breast-feeding duration (never, <1 month, 1 to <3 months, 3 to <6 months, and ≥ 6 months) to 90.3% ($n = 12,623$) of the cohort and exclusive breast-feeding to 90.9% ($n = 12,706$) of the cohort.

Self-reported health outcomes

Our primary self-reported outcomes were wheeze in the first 3 years of life and wheeze at 7½ years between the measurements of the 2 objective outcomes (atopy and bronchial hyperresponsiveness [BHR]). (See the Online Repository for additional details on wheeze.) We were able to classify 78.9% of the cohort with respect to wheezing status in the first 3 years, and we had data on wheeze at 7½ years on 8200 children.

Although asthma is subject to diagnostic bias based on factors that can be related to breast-feeding, whereas wheeze, a symptom, is not, we examined asthma at the 7½-year questionnaire for comparison with stratified analyses similar to those of Wright et al.⁶ We defined current asthma as a report on the questionnaire of a doctor's diagnosis of asthma plus either wheeze or the use of asthma medications within the previous 12 months. The question about a doctor's diagnosis of asthma read as follows: "Has a doctor ever actually said that your study child has asthma?" We had questionnaire data on asthma at 7½ years on 8131 children.

Objective outcome measures

Atopy. At the age of approximately 7 years, 7245 ALSPAC participants (of 12,715 invited children) underwent skin prick testing to a core panel of common allergens (cat, mixed grass pollen, peanut, egg white, *Dermaphagoides pteronyssinus*, and mixed nuts; ALK-Abelló, Hørshølm, Denmark). (See the Online Repository for more details on skin prick tests.) A positive skin test response for a given allergen was defined as a mean wheal diameter of 2 mm or greater with a zero response to the negative control.

We defined atopy as a positive test response to at least 1 of the aeroallergens included in the core panel (cat, mixed grass, and house dust mite). We have previously reported that positive responses to these 3 core aeroallergens predicted 95% of reactivity to any of 29 allergens that were tested in 3 panels on separate thirds of the children.²⁰ We were able to classify atopy to aeroallergens for 6512 children.

Lung function and BHR. At the age of approximately 8 years, 7081 ALSPAC participants (56.7% of 12,478 children invited) visited the research clinic ("Focus @ 8") for tests of lung function. We used American Thoracic Society²¹ criteria to select lung function measurements acceptable for analysis. (See the Online Repository for more details on lung function and BHR).

Of the 6997 children with acceptable lung function measurements, 6.4% ($n = 446$) had FEV₁ values of less than 70% and thus were not invited to

participate in assessments of BHR by using the rapid methacholine inhalation test.²² Approximately 67% ($n = 4364$) of the 6551 children with FEV₁ values of 70% or greater completed bronchial challenges. The challenge was stopped when the FEV₁ decreased by more than 20% from the postsaline value, with a cumulative dose of 1.2 mg of methacholine or greater.

Confounders. Variables were considered potential confounders if they were known to be associated with breast-feeding and each outcome of interest. Questionnaire data were used for all variables evaluated as confounders. For variables with the potential to change over time (eg, environmental tobacco smoke exposure and crowding), we used the highest value reported on questionnaires administered during the first 4 years of life.

Statistical analyses

We used logistic regression to evaluate the relationship between each measure of breast-feeding and each health outcome. Breast-feeding measures included ever versus never breast-fed, duration of breast-feeding (never, <1 month, 1 to <3 months, 3 to <6 months, and ≥ 6 months), and duration of exclusive breast-feeding (never breast-fed, exclusive breast-feeding <4 months, and exclusive breast-feeding ≥ 4 months). Sample sizes for analyses of different outcomes varied because of differences in available information (see Table E1 in the Online Repository at www.jacionline.org). As expected, more children were included in analyses of wheezing because this was ascertained by means of questionnaire rather than clinic visits.

We used a change-in-estimate method to evaluate variables as confounders of the relationship between breast-feeding (ever vs never) and each outcome.²³ For each logistic model, our cutoff criterion was a 10% change in the β coefficient for breast-feeding in relation to the outcome. (See the Online Repository for details on potential confounders.) Final models were adjusted for sex, maternal age (continuous), maternal smoking in the last 2 months of pregnancy (yes or no), environmental tobacco smoke in the first 4 years of life (none, low, or moderate/high), maternal asthma, maternal allergy, and older siblings (yes or no). We also evaluated each of the variables included as confounders as potential effect modifiers in stratified analyses.

To examine the potential for reverse causation, we used life table analysis and Kaplan-Meier survival curves²⁴ to describe the temporal relationship between wheezing and cessation of breast-feeding. We examined breast-feeding duration stratified by early wheezing status, including children who never wheezed and those who wheezed before cessation of breast-feeding. There were 9166 children with information on both early wheezing and breast-feeding. (See the Online Repository for additional information on breast-feeding and wheeze among these children.)

To model the potential for reverse causation in more detail, we used Bayesian analysis to fit a joint model designed to incorporate the potential for early wheezing to modify the duration of breast-feeding in assessing the relationship between breast-feeding and the later health outcomes.¹⁹ (See the Online Repository for information about Bayesian analysis.) The Bayesian analysis also adjusts for possible selection bias caused by loss to follow-up for the ascertainment of outcomes at ages 7 and 8 years. Models were adjusted for the confounders identified in previous logistic regression models.

We used SAS version 9.1 software (SAS Institute, Cary, NC) to conduct all analyses except for joint modeling. Models were fitted jointly by using WinBUGS (Windows version of Bayesian inference Using Gibbs Sampling), a freely available software package for Bayesian inference (available at <http://www.mrc-bsu.cam.ac.uk/bugs/>).

RESULTS

Approximately 25% of the children in the ALSPAC cohort were never breast-fed, 25% were breast-fed for at least 6 months, and approximately 8.5% were exclusively breast-fed for at least 4 months (see Table E1). Participation in the clinic visits at age 7 years for skin prick testing and age 8 years for bronchial responsiveness testing was higher among children who had been breast-fed, had older siblings, had less postnatal exposure to environmental tobacco smoke, or had mothers who were older,

had asthma, had allergy, or had not smoked during the last 2 months of pregnancy (see Table E1).

Wheezing in the first 3 years of life was reported for 4721 children (51.9% of questionnaire respondents with breast-feeding and covariate data), and wheezing at 7½ years was reported for 781 (10.5%) children. Skin prick tests at age 7 years revealed atopy in 1235 children (21.3% of those tested with breast-feeding and covariate data), and methacholine challenge indicated BHR for 615 (15.7%) children at age 8 years (Table I).

In crude analyses breast-feeding had a modest inverse association with wheeze in the first 3 years of life (eg, odds ratio [OR] for ≥6 months relative to never breast-fed, 0.64 [95% CI, 0.57-0.71]), and atopy was weakly positively related to breast-feeding (OR for ≥6 months relative to never breast-fed, 1.20 [95% CI, 1.00-1.44]; Table I). After adjustment for confounders, breast-feeding remained protective for early wheeze (OR for ≥6 months relative to never breast-fed, 0.80 [95% CI, 0.70-0.90]), but the weak relation with atopy was further attenuated and not statistically significant (OR, 1.11 [95% CI, 0.92-1.35]; Table I). Maternal age and maternal history of allergy were the most important confounders of the slight relationship between breast-feeding and atopy (data not shown). When the 70 children reporting antihistamine use were excluded from analyses, the results were not materially different. There was no appreciable association with BHR or current wheezing in either crude or adjusted analyses.

We found no clear evidence of effect modification of the association between breast-feeding and any of the outcomes by any of the factors that were included as confounders: sex, maternal age (dichotomized at the median), maternal smoking in the last 2 months of pregnancy (yes or no), environmental tobacco smoke in the first 4 years of life (none or some), maternal asthma, maternal allergy, and older siblings (yes or no; data not shown). Based on the findings of Wright et al⁶ that exclusive breast-feeding for at least 4 months led to a very high increased risk of later asthma in the subgroup of children who were both atopic and had an asthmatic mother, we also calculated ORs for each of our breast-feeding metrics (ever/never, duration, and exclusivity) in relation to the comparable outcome of current asthma at 7½ years (defined as a doctor's diagnosis plus either wheeze or medication use in the past 12 months) stratified by the 4 combined categories of child's atopy (based on skin prick testing) and mother's history of asthma. The analysis comparing exclusive breast-feeding for 4 or more months with exclusive breast-feeding for less than 4 months does not suggest an increased risk of asthma among atopic children with asthmatic mothers (crude OR for asthma, 0.55 [95% CI, 0.20-1.55]; OR for BHR, 0.67 [95% CI, 0.12-3.65]). Although our study is much larger than that of Wright et al,⁶ subset analyses remain limited by small numbers; for example, there were only 6 asthmatic children among the 198 who were exclusively breast-fed for more than 4 months and were both atopic and had asthmatic mothers and only 2 children with BHR among the 98 children with BHR data who had asthmatic mothers and were atopic. Based on a recent suggestion that the association between breast-feeding and atopy might depend jointly on parental atopy and the sex of the child,²⁵ we also examined possible effect modification by the combination of child sex and parental atopy. We found no evidence for this 3-way interaction: ORs for atopy in relation to ever/never breast-feeding were close to 1.0 for all combinations of child sex and parental atopy.

Children with wheeze reported by 3 months of age appeared to be breast-fed for longer periods than children without early wheeze (Fig 1). The mean duration of breast-feeding for children who did not wheeze in the first 3 months of life was 6.6 months (SE, 0.10) compared with 8.9 months (SE, 0.24) for children with wheeze (log-rank test for homogeneity, $P < .0001$).

The Bayesian joint model included a random-effects variable that suggested that children with susceptibility to wheeze were more likely to be breast-fed longer and to have allergic outcomes. However, results from this Bayesian analysis were virtually identical to those from logistic regression models. The Bayesian joint model also adjusted for possible effects of selection bias because of the loss of subjects for the visits at ages 7 and 8 years, when atopy and BHR were determined. In the Bayesian joint model breast-feeding remained protective against early wheeze, was slightly positively but not statistically significantly associated with atopy (relative to never breast-fed: OR = 0.95 for <3 months, 1.10 for 3-6 months, and 1.18 [95% CI, 0.93-1.48] for ≥6 months of breast-feeding), and was not associated with BHR (relative to never breast-fed: OR = 1.10 for <3 months, 1.08 for 3-6 months, and 1.03 [95% CI, 0.78-1.39] for ≥6 months of breast-feeding) for later wheeze.

DISCUSSION

In this large prospective study with objective outcome measures at ages 7 and 8 years and extensive data on potential confounders and effect modifiers, we found no evidence that breast-feeding increased the risk of later wheeze, asthma diagnosis, atopy, or BHR. We found no evidence of deleterious effects of breast-feeding either in the dataset as a whole or in subsets defined by parental atopy, child atopy, sex, family size, various combinations of these factors, or other risk factors in these data.

As in most previous prospective studies, we found evidence for a modest protective effect of breast-feeding on wheezing in the first few years of life.^{5,26,27} At this age, wheezing is predominantly associated with viral illnesses, and breast-feeding protects by reducing respiratory infections. Although we did not ask about asthma in the first few years of life, because of the uncertainty of this diagnosis in young children, the finding of a protective effect of early wheezing is consistent with results from studies that examined early asthma.²⁸⁻³⁰ In our data the protective effect of breast-feeding on wheeze in early life did not extend into later childhood (7½ years), which is consistent with most other studies.^{4,5} This is not surprising, however, because asthma phenotypes in later childhood are more likely to be atopic and would only be associated if breast-feeding modulates atopy. In contrast to our findings, a few prospective studies have reported adverse effects of breast-feeding on later wheeze or asthma risk.^{7,8} In another study breast-feeding was related to increased risk of asthma in later childhood only among the subgroup of 99 children of asthmatic mothers,⁶ whereas breast-feeding was not related to atopy to aeroallergens. For atopy, in unadjusted analyses we found a very slight increased risk of borderline statistical significance for 6 or more months of breast-feeding. However, after adjustment for confounders, especially maternal history of allergy and maternal age, breast-feeding was no longer associated with atopy. In 3 much smaller studies with measures of atopy to aeroallergens at age 5 years or after, breast-feeding was a modest risk factor,^{7,8,10} but there was no increased risk in another study.⁶

TABLE I. Breast-feeding in relation to wheeze, atopy, and bronchial BHR in the ALSPAC cohort

	Outcome present				Prevalence	OR, crude	95% CI		OR, adjusted*	95% CI		
	No		Yes				Lower	Upper		Lower	Upper	
	N	Percent	N	Percent								
Wheezing in first 3 y												
Ever breast-fed												
No	907	20.7	1254	26.6	58.0	1.00			1.00			
Yes	3472	79.3	3467	73.4	50.0	0.72	0.66	0.80	0.88	0.79	0.97	
Breast-feeding duration												
Never	907	20.7	1254	26.6	58.0	1.00			1.00			
<3 mo	1356	31.0	1534	32.6	53.1	0.82	0.73	0.92	0.94	0.83	1.05	
3-<6 mo	596	13.6	591	12.5	49.8	0.72	0.62	0.83	0.88	0.75	1.02	
≥6 mo	1519	34.7	1334	28.3	46.8	0.64	0.57	0.71	0.80	0.70	0.90	
Exclusive breast-feeding												
Never breast-fed	907	20.7	1254	26.6	58.0	1.00			1.00			
<4 mo	2995	68.4	3035	64.4	50.3	0.73	0.66	0.81	0.88	0.79	0.97	
≥4 mo	475	10.9	421	8.9	47.0	0.64	0.55	0.75	0.83	0.70	0.98	
Wheeze at 7.5 y												
Ever breast-fed												
No	1420	21.4	173	22.2	10.9	1.00			1.00			
Yes	5231	78.7	608	77.9	10.4	0.95	0.80	1.14	0.96	0.79	1.16	
Breast-feeding duration												
Never	1420	21.4	173	22.2	10.9	1.00			1.00			
<3 mo	2084	31.4	231	29.6	10.0	0.91	0.74	1.12	0.93	0.75	1.15	
3-<6 mo	906	13.7	107	13.7	10.6	0.97	0.75	1.25	0.99	0.76	1.29	
≥6 mo	2226	33.5	269	34.5	10.8	0.99	0.81	1.21	0.98	0.79	1.22	
Exclusive breast-feeding												
Never	1420	21.4	173	22.2	10.9	1.00			1.00			
<4 mo	4491	67.7	534	68.5	10.6	0.98	0.81	1.17	0.98	0.81	1.18	
≥4 mo	726	10.9	73	9.4	9.1	0.83	0.62	1.10	0.83	0.61	1.12	
Atopy at 7 y (7834 attended clinic visit, of which 7245 entered allergy session)												
Ever breast-fed												
No	888	19.5	217	17.6	19.6	1.00			1.00			
Yes	3656	80.4	1018	82.4	21.8	1.14	0.97	1.34	1.07	0.90	1.27	
Breast-feeding duration												
Never	888	19.6	217	17.6	19.6	1.00			1.00			
<3 mo	1411	31.1	358	29.1	20.2	1.04	0.86	1.25	1.00	0.83	1.22	
3-<6 mo	639	14.1	189	15.3	22.8	1.21	0.97	1.51	1.14	0.91	1.43	
≥6 mo	1596	35.2	468	38.0	22.7	1.20	1.00	1.44	1.11	0.92	1.35	
Exclusive breast-feeding												
Never	888	19.6	217	17.6	19.6	1.00			1.00			
<4 mo	3122	68.9	868	70.5	21.8	1.14	0.96	1.34	1.07	0.90	1.27	
≥4 mo	524	11.6	146	11.9	21.8	1.14	0.90	1.44	1.07	0.84	1.38	
BHR at 8 y (7171 attended clinic visit, of which 6551 had FEV ₁ >70% and 3920 had methacholine challenge)												
Ever breast-fed												
No	614	18.6	105	17.1	14.6	1.00			1.00			
Yes	2691	81.4	510	82.9	15.9	1.11	0.88	1.39	1.14	0.90	1.44	
Breast-feeding duration												
Never	614	18.6	105	17.2	14.6	1.00			1.00			
<3 mo	992	30.1	197	32.1	16.6	1.16	0.90	1.50	1.16	0.89	1.50	
3-<6 mo	493	15.0	100	16.3	16.9	1.19	0.88	1.60	1.21	0.90	1.65	
≥6 mo	1199	36.4	211	34.4	15.0	1.03	0.80	1.33	1.07	0.82	1.40	
Exclusive breast-feeding												
Never	614	18.6	105	17.1	14.6	1.00			1.00			
<4 mo	2293	69.6	454	73.9	16.5	1.16	0.92	1.46	1.17	0.93	1.49	
≥4 mo	388	11.8	55	9.0	12.4	0.83	0.58	1.18	0.87	0.61	1.26	

*Models adjusted for sex, older siblings, maternal age, maternal allergy, maternal smoking in the last 2 months of pregnancy, and exposure to environmental tobacco smoke in the first 4 years of life.

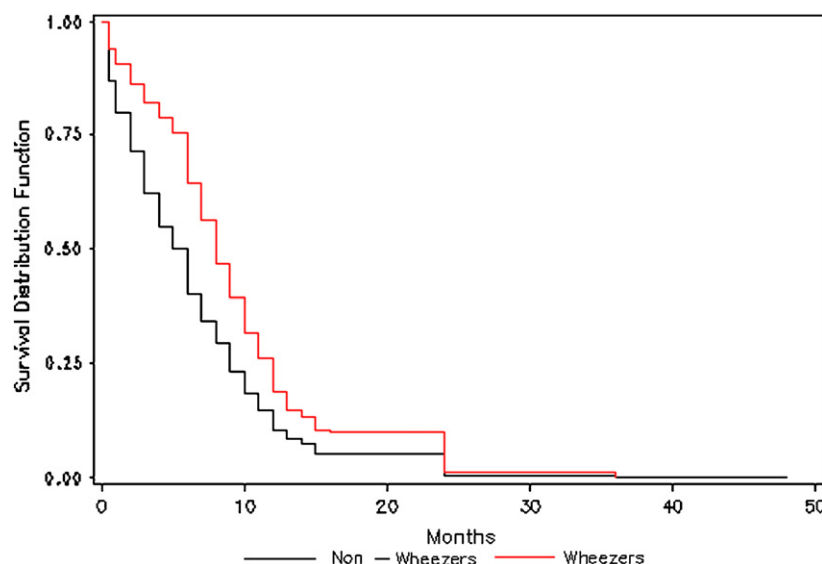


FIG 1. Kaplan-Meier curves for breast-feeding duration in children with and without early wheeze.

The divergent findings on effects of breast-feeding across studies might result by chance from small numbers, especially in subset analysis. Differences in breast-feeding practices across time and place, variability in ages at which children are studied, or methodological issues, including recall bias of feeding history, divergent criteria for allergic outcomes, and confounding, might also contribute to discrepancies in the literature. By using data on breast-feeding and a wide array of potential confounders collected prospectively from the large ALSPAC birth cohort, in whom objective measures of atopy and BHR were obtained in later childhood, we were able to address many of the major methodological issues.

Divergent findings across studies might also be related to differences in environmental exposures for different populations. For example, increased microbial loads have been associated with increased risk of wheeze from lower respiratory tract infections in children but in decreased risk of asthma and allergy in later childhood and adolescence.³¹ In the ALSPAC cohort 53% had older siblings, 11% attended daycare in the first 2 years of life, 70% had exposure to pets in the first 2 years, and at least 54% had used antibiotics in the first 15 months of life.

Although not well explored in the previous literature, reverse causation could contribute to positive associations between breast-feeding and allergic outcomes if the duration of breast-feeding is influenced by early manifestations of atopic or asthmatic phenotypes.¹⁶⁻¹⁸ To our knowledge, only one study has evaluated reverse causation in a quantitative manner. In the Melbourne Atopy Cohort study Lowe et al¹⁷ found that early signs of atopic disease led to prolongation of exclusive breast-feeding. Mihrshahi et al¹⁰ attempted to examine reverse causation with respect to itchy rash in the first 4 weeks or 3 months of life. Although limited by small numbers, they reported that “there were trends indicating a tendency to prolong breast-feeding and delay the introduction of solid foods among children with early features of eczema.” Although we did not collect data on itchy rash with sufficient time-course detail to allow assessment of reverse causation by this phenotype, we found that mothers breast-fed babies who wheezed in the first 3 months of life for a slightly longer time than nonwheezy babies, suggesting that early manifestations of asthma phenotypes might play a part in a

mother’s decision to continue breast-feeding. However, results from a joint model using Bayesian methods indicated that this modest difference in duration of breast-feeding based on early infant wheezing was not sufficient to bias the relationships between breast-feeding and the health outcomes examined.

As in virtually all previous birth cohorts, we experienced substantive loss to follow-up for outcome assessment in later childhood, although the attrition occurred steadily over the time course of the study. Children who were breast-fed were more likely to participate in the later clinic visits when atopy and BHR were measured (Table I). However, for selection bias to occur, loss to follow-up must be jointly dependent on the exposure of interest and the outcomes under study with sufficient strength to influence the association.³² Therefore we evaluated the possibility of informative missingness of later childhood outcomes, contingent on breast-feeding and risk factors for developing the conditions under study, using Bayesian methods. We did not find evidence that the pattern of missing data in this study appreciably influenced our findings.

The major benefits of this study for examination of the possible effects of breast-feeding on later development of atopy and asthma phenotypes include its large size and the use of objective outcome measures. For example, almost 7000 children underwent skin prick testing, and more than 4000 children had measures of BHR. This compares with approximately 700 children with skin prick testing and approximately 800 with BHR testing in the largest study with objective outcomes to report a deleterious effect of breast-feeding on these outcomes.⁷ In addition, our study is one of the largest prospective studies with questionnaire-based assessment of symptoms and diagnoses in later childhood. Thus we had improved power to investigate any potential effect modification with a reduced possibility of random variations in associations between breast-feeding and respiratory or allergic outcomes within small strata. For example, unusually large positive ORs of 8.7 have been reported for exclusive breast-feeding in relation to asthma among children of asthmatic mothers.⁶ Among the 99 children with an asthmatic mother in that study, there was only 1 asthmatic subject in the never breast-fed group, limiting the ability to reliably estimate associations. In contrast, our comparable analysis included 728

asthmatic children with an asthmatic mother. Likewise, Mandhane et al,²⁵ in follow-up of the findings of Wright et al⁶ regarding interaction with maternal asthma, found no such interaction but on additional stratification by child sex found some strong increased risks (OR, 7.4) for breast-feeding in relation to atopy among the subgroup of 55 boys with atopic fathers. Although multiway interaction analyses are often interesting to contemplate, they require sample sizes that are far larger than any published study of breast-feeding and respiratory outcomes.³³ Very large birth cohorts (approximately 100,000 children each) currently being assembled in the United States, Norway, Denmark, and other countries might have sufficient power to examine properly these higher-order interactions that could be of relevance to the study of breast-feeding and allergy or asthma.

A trial in which women are randomized to breast-feeding or not and children are examined in later childhood without loss of follow-up could answer definitively the question of whether breast-feeding leads to later risk of atopy or asthma. However, such a trial is not feasible. A recent study randomized communities in Belarus to receive or not receive a hospital and clinic-based breast-feeding promotion intervention.¹¹ The intervention successfully increased the duration of breast-feeding; for example, at 3 months, the prevalence of breast-feeding was 72.7% in intervention communities compared with 60.0% for control communities, with much greater differences for exclusive breast-feeding (43.3% vs 6.4%). Being in an intervention community had no significant effect on skin test positivity (OR for atopy to any of 5 common antigens, 1.2 [95% CI 0.5-2.6]). An increased risk of atopy (OR, 2.0 [95% CI, 1.1-3.4]) appeared only in a sensitivity analysis removing the 6 of 31 clinics with suspiciously high rates of atopy, resulting in exclusion of 26.1% of the intervention subjects versus 12.3% of the control group. Notably, no increased risks of wheezing, asthma, or eczema were found.

Our study supports the body of evidence that breast-feeding does not adversely affect children with regard to asthma and other allergic outcomes. Even if breast-feeding does not protect against atopy or asthma in later childhood, the protection against wheezing illness in the first few years of life is a benefit for respiratory health. Given some recent findings from smaller studies or subset analyses suggesting deleterious effects, these results should provide reassurance to expectant mothers, including those with atopy, regarding current public health guidelines that encourage breast-feeding.

We thank all of the mothers who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC study team, which comprises interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

Clinical implications: Breast-feeding does not increase the risk of asthma or atopy in children, even when their mothers are asthmatic.

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METHODS

ALSPAC study

Briefly, ALSPAC is a longitudinal birth cohort study recruiting subjects in pregnancy and designed to investigate the effects of early-life exposures on health and developmental outcomes of childhood. ALSPAC enrolled 14,541 pregnant women residing in Avon, United Kingdom, with expected delivery dates between April 1, 1991, and December 31, 1992. Comprehensive data about the participating women, their partners, and their children were collected from self-completed questionnaires mailed to participants from the time of enrollment (approximately 8 weeks' gestation) through their child's approximate age of 91 months. All participating children from age 7 years with known addresses were invited to attend annual research clinics for detailed physical tests.

Breast-feeding

Data on breast-feeding were obtained from questions about dietary and feeding habits included in 6 questionnaires sent to mothers during the first 4 years of the child's life. The first questionnaire, completed when the child was 4 weeks of age, included detailed questions about breast-feeding and bottle feeding for each week in the first month of life. Questionnaires sent at ages 6 and 15 months asked about current feeding, age at cessation of breast-feeding, and age at introduction of formula, milk, or solids. Questionnaires sent at ages 2, 3, and 4 years asked about current feeding, including whether the child had received breast milk since the previous questionnaire.

We used responses to the 6-month questionnaire to categorize early breast-feeding duration as never, less than 1 month, 1 to less than 3 months, 3 to less than 6 months, and 6 or more months. For children with missing values for this variable at 6 months ($n = 916$ of 13,978), we assigned breast-feeding duration based on responses to the 15-month questionnaire. For children with missing information on both the 6- and 15-month questionnaires ($n = 1921$), we used the data collected at 4 weeks and at 2, 3, and 4 years to classify breast-feeding exposure for 566 additional children. The 3 earliest questionnaires (4 weeks, 6 months, and 15 months) also included information about the specific age at breast-feeding cessation, which we used as a continuous variable in some analyses. We were able to assign breast-feeding duration to 90.3% ($n = 12,623$) of the cohort.

For 251 children missing information on the duration of breast-feeding, we assigned them to categories of ever or never breast-fed based on items from the 6- and 15-month questionnaires. Thus we were able to assign this dichotomous exposure to 92.1% ($n = 12,874$) of the cohort. We defined the duration of exclusive breast-feeding as the minimum age at which formulas, milks, or solid foods were introduced. We were able to assign exclusive breast-feeding duration to 90.9% ($n = 12,706$) of the cohort.

Self-reported outcomes

Our primary self-reported outcome was wheeze. We defined wheeze in the first 3 years of life as a positive response to either of the following questions asked at 6, 18, 30, and 42 months: "Has your child wheezed?" and "Has your child had wheezing or whistling in his chest when he breathed?"

For children with reported wheeze, we assigned age at onset by using information from the 6- and 18-month questionnaires ("How old was (s)he at first wheeze attack?"). For the 1198 children with missing information about age at onset of wheeze, we assigned a value midway between the age at first reported wheeze and the previous questionnaire. For example, children with missing data for age of onset who reported wheeze at 6 months were assigned age at onset of 3 months; those with first reported wheeze at 18 months were assigned age at onset of 12 months. Questions about age at onset were not included on the 30- and 42-month questionnaires; thus the 925 children with first reported wheeze at these later dates were assigned ages at onset of 24 and 36 months, respectively. We were able to classify 78.9% of the cohort with respect to wheezing status in the first 3 years.

Missing data on wheeze are primarily due to missing questionnaires rather than failure to answer questions regarding wheeze. For example, information on wheeze was missing for less than 1% of participants in the first 2 years and for approximately 3% on the 30-month questionnaire. For a large cohort study,

response rates were relatively high in the first 3 years (eg, from 87% at 4 weeks to 74% at 30 months), and the attrition rate was gradual.

We also considered wheezing at the questionnaire administered at 7½ years between the measurements of the 2 objective outcomes (atopy and BHR). Wheeze at age 7½ years was defined by a positive response to the following question: "Has your child had wheezing in the past 12 months?" We had data on wheeze at 7½ years on 8200 children.

Objective outcome measures

Atopy. Drops of each allergen, positive control (histamine, 10 mg/mL), and negative control (saline) were placed on the forearm and pricked with separate sterile lancets. After 5 minutes, the drops were blotted off to avoid contamination. After a further 10 minutes, the maximum diameters of wheals and flares were measured and recorded.

Children were considered nonatopic if they had negative test responses for all 3 core aeroallergens. We excluded the 559 children missing data on one of the 3 core skin tests and children who reacted to the negative control ($n = 15$) or did not react to the positive control ($n = 143$).

Parents were asked to withhold antihistamines from children for 48 hours before the visit. Of 70 children with reported antihistamine use, 55 had taken them within 48 hours of their visit. We repeated analyses excluding the 70 children having antihistamine use.

Lung function and BHR. Children were instructed to blow at least 3 times to produce a maximal expiratory maneuver, for a total of 3 reliable and reproducible maneuvers. A reliable maneuver was a maximal exhalation for more than 1 second, with a clear plateau of flow. Reproducibility criteria were set to 3 maneuvers within 200 mL for forced vital capacity. A respiratory pediatrician inspected all flow-volume curves to ensure that reproducibility criteria had been met and that the best of 3 curves was selected for analysis.

Each participant inhaled 3 breaths of normal saline from a hand-operated bulb nebulizer (DeVilbiss Co, Hanover, Pa), and the FEV₁ measurement repeated 1 minute later was taken as the baseline for the challenge. This was followed at 1-minute intervals by inhalation of 8 doubling doses of methacholine from 0.03 to 6.1 μ mol. FEV₁ was measured 1 minute after each dose and followed immediately by the next dose. The challenge was stopped when the FEV₁ decreased by more than 20% from the postsaline value (defined as BHR = yes) or when the maximum dose (6.1 μ mol) was reached (defined as BHR = no).

Children were not tested if, within the previous 3 weeks, they had been treated with medications for acute asthma or chest infections or had an upper respiratory tract infection or cold.

Statistical analysis

Using a change-in-estimate method, we assessed the following potential confounders: sex, preterm birth, daycare in the first 2 years of life, maternal age, older siblings (defined as maternal parity >0 during this pregnancy), pet exposure in the first 2 years of life, maternal smoking in the last 2 months of pregnancy, environmental tobacco smoke exposure in the first 4 years of life, maternal asthma, maternal allergy, and crowding (defined as >1 resident per room of the family home).

Subjects with missing data on any of the covariates were excluded, resulting in the exclusion of the following numbers of subjects with data on breast-feeding: 1062 (10.4%) for wheeze by 3 years, 704 (8.7%) for wheeze by 7½ years, 638 (9.9%) for atopy, and 397 (9.2%) for BHR. Thus the numbers of subjects included in the adjusted analyses were 9100 for wheeze by 3 years, 7432 for wheeze at 7½ years, 5779 for atopy, and 3920 for BHR. Crude logistic regression results did not differ materially between the entire population versus the subset with nonmissing data on any covariates (data not shown).

To examine the potential for reverse causation, we used life table analysis and Kaplan-Meier survival curves^{E1} to describe the temporal relationship between wheezing and cessation of breast-feeding. We examined breast-feeding duration stratified by early wheezing status, including children who never wheezed and those who wheezed before cessation of breast-feeding. There were 9166 children with information on both early wheezing and breast-feeding. Approximately 84% ($n = 7672$) of these children were breast-fed, of whom 47% ($n = 3605$) never wheezed and 21% ($n = 1630$) wheezed before

breast-feeding was stopped. The remaining breast-fed children ($n = 2437$) first wheezed after cessation of breast-feeding and were not included in the life table or Kaplan-Meier analysis.

Bayesian analysis

The joint model comprised 6 separate mixed-effects logistic models, each including a shared random-effects variable measuring each child's susceptibility to wheeze and the risk of development of each allergic outcome (asthma, atopy, and BHR). The first component modeled the relationship between breast-feeding duration and wheeze; the second component modeled the probability of continuing to breast-feed with increasing age; the next 4 components modeled the probability of having wheeze, asthma, atopy, and BHR in later childhood, given breast-feeding duration; and the final component modeled whether the child missed the atopy examination. Joint models with shared random effects have been increasingly used in investigating causal effects, accounting for reverse causation, informative missingness that can lead to selection bias, and other complications.^{E2,E3} The Bayesian approach

implemented in WinBUGS provides a convenient approach for fitting joint models, which allows prior distributions for the random effect and other parameters to be updated with all the data available for a child. The updating of prior values resulted in a posterior distribution for the random effect, which was dependent on the child's wheeze history and whether the child missed the atopy examination, hence automatically adjusting the models for the dependence between wheeze and breast-feeding duration and for informative missingness.

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TABLE E1. Characteristics of the study population at baseline and with outcome data at ages 7 to 8 years*

	Alive at 1 y (n = 13,978)	Skin prick test (n = 6512)	BHR (n = 4364)	Wheeze at 7½ y (n = 8200)
Breast-fed ever	9364 (67.0)	5133 (78.8)	3501 (80.2)	6339 (77.3)
Missing	1104 (7.9)	95 (1.5)	47 (1.1)	64 (0.8)
Breast-fed				
Never	3510 (25.1)	1284 (19.7)	816 (18.7)	1797 (21.9)
<3 mo	4062 (29.1)	1986 (30.5)	1327 (30.4)	2554 (31.2)
3-<6 mo	1554 (11.1)	901 (13.8)	641 (14.7)	1097 (13.4)
≥6 mo	3497 (25.0)	2193 (33.7)	1503 (34.4)	2647 (32.3)
Missing	1355 (9.7)	148 (2.3)	77 (1.8)	105 (1.3)
Exclusive breast-feeding				
Never	3510 (25.1)	1284 (19.7)	816 (18.7)	1797 (21.9)
<4 mo	8003 (57.3)	4377 (67.2)	2994 (68.6)	5453 (66.5)
≥4 mo	1193 (8.5)	723 (11.1)	481 (11.0)	854 (10.4)
Missing	1272 (9.1)	128 (2.0)	73 (1.7)	96 (1.2)
Sex				
Female	6756 (48.3)	3240 (49.8)	2179 (49.9)	3982 (48.6)
Male	7220 (51.7)	3272 (50.2)	2185 (50.1)	4218 (51.4)
Missing	517 (0.01)	0	0	0
Ethnic background				
White	11,474 (82.1)	5915 (90.8)	4013 (92.0)	7533 (91.9)
Nonwhite	609 (4.4)	255 (3.9)	145 (3.3)	299 (3.7)
Missing	1895 (13.6)	342 (5.3)	206 (4.7)	368 (4.5)
Older siblings				
Yes	7212 (51.6)	3474 (53.4)	2289 (52.5)	4288 (52.3)
Missing	1038 (7.4)	212 (3.3)	130 (3.0)	247 (3.0)
Maternal asthma				
Yes	1423 (10.2)	727 (11.2)	464 (10.6)	879 (10.7)
Missing	1519 (10.9)	239 (3.7)	143 (3.3)	231 (2.8)
Maternal allergy				
Yes	2802 (20.1)	1539 (23.6)	991 (22.7)	1856 (22.6)
Missing	1679 (12.0)	311 (4.8)	201 (4.6)	324 (4.0)
Maternal smoking in pregnancy†				
Yes	2791 (20.0)	1118 (17.2)	706 (16.2)	1486 (18.1)
Missing	2143 (15.3)	383 (5.9)	212 (4.9)	365 (4.5)
Environmental tobacco smoke‡				
Not at all	5283 (37.8)	3023 (46.4)	2047 (46.9)	3762 (45.9)
Low	2270 (16.2)	1224 (18.8)	843 (19.3)	1555 (19.0)
Moderate-high	4879 (34.9)	2111 (32.4)	1395 (32.0)	2810 (34.3)
Missing	1546 (11.1)	154 (2.4)	79 (1.8)	73 (0.9)
Mean maternal age (y) at child's birth (SD)	27.7 (5.0)	28.7 (4.6)	28.7 (04.5)	28.6 (04.6)
Wheeze in first 6 mo of life				
Yes	2471 (17.7)	1252 (19.2)	834 (19.1)	1586 (19.3)
Missing	2505 (17.9)	420 (6.4)	235 (5.4)	366 (4.5)

*Values are presented as counts and percentages.

†Smoking in the last 2 months of pregnancy.

‡Exposure to environmental tobacco smoke in the first 4 years of life defined as time in a smoky room each week: not at all (<1 hour per week), moderate (1-2 hours per week), and high (>2 hours per week).