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Original Contribution

Breastfeeding and Childhood Wheeze: Age-Specific Analyses and Longitudinal Wheezing Phenotypes as Complementary Approaches to the Analysis of Cohort Data

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Systematic reviews suggest that breastfeeding is associated with a lower risk of asthma, although marked heterogeneity exists. Using UK Millennium Cohort Study data (n = 10,126 children, born 2000–2002), we examined the association between breastfeeding duration and wheezing in the previous year, first for each age group separately (ages 9 months, 3 years, 5 years, 7 years, and 11 years) and then in terms of a longitudinal wheezing phenotype: "early transient" (wheezing any time up to age 5 years but not thereafter), "late onset" (any time from age 7 years but not beforehand), and "persistent" (any time up to age 5 years and any time from age 7 years). The association between breastfeeding and wheeze varied by age (2-sided P for interaction = 0.0003). For example, breastfeeding for 6–9 months was associated with lower odds of wheezing at ages 9 months, 3 years, and 5 years but less so at ages 7 years and 11 years (adjusted odds ratios = 0.73, 0.78, 0.79, 0.84, 1.06, respectively). There was a strong dose-response relationship for breastfeeding per month and early transient wheeze (adjusted odds ratio for linear trend = 0.961, 95% confidence interval: 0.942, 0.980) but no clear trend for late-onset or persistent wheeze. Our results identified heterogeneity in the association between breastfeeding and wheezing according to age at wheezing and wheezing phenotype.

asthma; breastfeeding; longitudinal; Millennium Cohort Study; phenotype; wheeze

Abbreviation: OR, odds ratio.

Asthma is a common chronic condition in childhood and is associated with significant morbidity. Because there is currently no cure, the priority has been to improve the assessment and management of asthma, as well as to understand the factors associated with it (1). One potential protective factor, which has been studied extensively, is breastfeeding.

Two recent systematic reviews have shown that breastfeeding is associated with a lower risk of asthma (2, 3) and wheeze (3) in childhood, but the effect on both asthma and wheeze seems to be stronger in younger (ages 0–2 years) than in older (ages 7 years or older) children (3). Childhood wheeze represents a heterogeneous condition that does not necessarily develop into asthma. Longitudinal studies of wheezing patterns at different ages have identified a range of heterogeneous phenotypes that include early transient wheezing with onset in early childhood and resolution of symptoms by mid-childhood; late-onset wheezing, which starts later in childhood and continues; and persistent wheezing, with onset in early childhood and which continues (4–8). Some phenotypes also describe the presence of other atopic symptoms such as eczema and hay fever (9, 10). In particular, children with raised immunoglobulin E levels, indicative of atopy, are more likely to exhibit persistent or late-onset wheezing phenotypes (4, 11). Both systematic reviews identified significant heterogeneity of effect across the studies. One possible cause of this may be that the studies measured different wheezing phenotypes, and the association between breastfeeding and wheeze may vary according to wheezing phenotype.

We hypothesized that the association between breastfeeding and wheeze diminishes over time (3) and varies according to wheezing phenotype. We analyzed longitudinal data on wheezing measured at ages 9 months and 3, 5, 7, and 11 years in a

large UK cohort using 2 complementary approaches to examine the association between breastfeeding duration and wheezing symptoms. First each age group was assessed separately and then they were combined according to longitudinal wheezing phenotype, to explore whether the chosen approach explained the inconsistent evidence regarding the association breastfeeding and wheeze.

METHODS

Millennium Cohort Study

The Millennium Cohort Study is a nationally representative longitudinal study of 18,818 infants born in the United Kingdom (12). A random 2-stage sample of all infants born in England and Wales between September 2000 and August 2001, and in Scotland and Northern Ireland between November 2000 and January 2002, who were alive and living in the United Kingdom at age 9 months was drawn from Child Benefit registers. Sampling according to electoral ward, with oversampling of ethnic minority and disadvantaged areas, ensured adequate representation of such areas. Parents were initially interviewed when infants were aged 9 months, and detailed information was collected on socioeconomic and health factors. The interview response rate was 85% at recruitment (12). Children were followed up at ages 3, 5, 7, and 11 years, and response rates ranged between 81% (age 3 years) and 69% (age 11 years) (13).

Study sample

This analysis focused on singleton infants who were present at all 5 interviews (from ages 9 months to 11 years) and had data on breastfeeding, asthma, and wheeze. Hence, 8,692 infants were excluded, sequentially, for the following reasons: multiples ($n = 522$); mother not the birth mother ($n = 27$); and not present at all interviews ($n = 7{,}965$). Interview nonresponse was accounted for using survey weights that were based on data collected at the first few interviews (13). These variables were shown to be independent predictors of response at subsequent surveys and included the child's sex, mother's age and education, family income, housing tenure, and ethnicity. Because missing data on breastfeeding, wheezing, or confounders included in the final model was minimal ($n = 178$), a complete-case analysis was conducted on the remaining 10,126 children.

Breastfeeding

Breastfeeding initiation was assessed by the question "Did you ever try to breastfeed your baby?" Breastfeeding duration was estimated using questions about the age of the infant when last given breast milk and when first given formula, other types of milk, and solids. Infants were grouped into 1-month (0, 1, 2, 3. . .) and approximately 3-month (never, <1 week, 1 week to 2.9 months, 3.0–5.9 months, 6.0–9.0 months) bands according to their duration of breastfeeding and exclusive breastfeeding. Because only approximately 1% of children were exclusively breastfed for 6.0–9.0 months, for some analyses, this group was combined with those breastfed for 3.0–5.9 months.

Wheezing outcomes

At age 9 months, parents were asked about medical consultations for health problems including wheezing. At ages 3–11 years, wheezing in the previous year was assessed by parental response to a validated question from the International Study of Asthma and Allergies in Childhood (14, 15): "Has your child ever had wheezing or whistling in the chest at any time in the past 12 months?"

Children were also classified into recognized wheezing phenotypes based on their wheezing trajectory at age 9 months to 11 years (16):

- "Early transient wheeze," if the child had wheezing in the previous year at least once up to age 5 years and no reported wheezing from age 7 years;
- "Late-onset wheeze," if the child had wheezing in the previous year at least once from age 7 years, but no reported wheezing up to age 5 years;
- "Persistent wheeze," if the child had wheezing in the previous year at least once when they were aged 9 months, 3 years, or 5 years and at least once when they were aged 7 or 11 years; or
- "No wheeze," if the child had no wheezing in the previous year at all ages from 9 months to 11 years.

Statistical methods

All analyses allowed for the clustered, stratified sample using the "survey" commands in Stata, version 13 (StataCorp LLC, College Station, Texas). Hence, all proportions and odds ratios were weighted and all confidence intervals were adjusted for clustering according to electoral ward. All significance tests were 2-sided. The risk of each wheezing outcome was estimated according to the categories of breastfeeding duration. For the age-specific analysis of wheezing, odds ratios for breastfeeding duration were estimated by performing a separate logistic regression analysis for each age group. For the analysis of wheezing phenotypes, odds ratios were estimated using multinomial regression with "no wheeze" as the reference group.

All analyses were automatically adjusted for a priori confounders that were considered essential in a recent meta-analysis (3): birth weight, gestational age, ethnicity, household socioeconomic position, mother's education, mother's history of asthma, father's history of asthma, and smoking during pregnancy. The following variables were also considered, but they were included in the final models only if any category yielded a Wald 2-sided test result of $P < 0.05$ after adjustment for other variables: area deprivation, mother's age at delivery, mode of delivery, whether the child was the firstborn for the mother, and smoking status of parents at the age-9-months interview. The multinomial regression of wheezing phenotypes was used for the model-building process, and the final model for this outcome (adjusting for a priori confounders plus area deprivation, mother's age, and mode of delivery) was used for other outcomes to aid comparability across results.

We hypothesized that the relationship between breastfeeding and wheezing would diminish over time; hence we tested for an interaction with age. Here we expanded the data set to give 5 records per child (1 for each survey) and then fitted a multilevel logistic model with wheeze as the outcome, and included a term

for interaction between breastfeeding (in months, as a linear trend) and age, while allowing for clustering by electoral ward and child. Some studies have observed that the relationship between breastfeeding and wheezing/asthma varies according to maternal asthma and/or child's atopic status (17, 18), although this has not always been replicated (19). Therefore, we tested for interaction between breastfeeding duration (in months, as a linear trend) and both maternal asthma and parent's report of whether the child had ever had eczema or hay fever at the age-11-years survey, as a crude marker of atopy.

RESULTS

Table 1 shows the characteristics of the 10,126 children in the study according to breastfeeding category. All variables were strongly associated with breastfeeding duration ($P \leq 0.005$) except maternal asthma ($P = 0.34$) and paternal asthma ($P = 0.145$). In particular, compared with women who never breastfed, those who breastfed for 3.0–5.9 or 6.0–9.0 months were older, were less likely to smoke in pregnancy, and were more likely to have a university degree, have professional/managerial occupations, and live in relatively advantaged areas.

Age-specific wheezing

At age 9 months, 6.5% of children had a history of wheezing. At age 3 years, 19.5% of children had a history of wheezing in the previous year, and this proportion decreased with age (16.0%, 11.8%, and 11.4% at ages 5, 7, and 11 years respectively).

In univariable analyses, the prevalence of wheeze, as reported at ages 9 months to 5 years, tended to decrease as breastfeeding duration (any or exclusive) increased (Figure 1). In particular,

Table 1. Characteristics at Age 9 Months, According to Breastfeeding Duration, of Children Born During 2000–2002, Millennium Cohort Study, United Kingdom

Characteristic	Duration of Any Breastfeeding									
	Never (n = 2,926)		<1 Week (n = 1,148)		1 Week to 2.9 Months (n = 2,010)		3.0–5.9 Months (n = 1,562)		6.0–9.0 Months (n = 2,480)	
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Child sex, female	51.4		46.9		50.0		47.5		51.7	
Child ethnicity, white	92.0		87.7		87.5		82.9		83.0	
Gestation, weeks		39.1 (1.9)		39.3 (1.9)		39.0 (2.3)		39.3 (1.9)		39.4 (1.8)
Birth weight, kg		3.33 (0.56)		3.41 (0.58)		3.31 (0.62)		3.41 (0.56)		3.44 (0.56)
Mode of delivery, cesarean	20.0		23.2		23.8		19.4		19.6	
Mother smoked during pregnancy	35.6		23.9		21.6		12.8		7.0	
Mother's age at delivery, years		26.7 (5.6)		27.6 (6.1)		28.6 (5.6)		30.2 (5.3)		31.2 (5.2)
Mother's education										
University degree/equivalent	12.8		26.4		30.2		45.0		52.7	
"A levels" or equivalent	12.2		14.3		15.9		15.2		15.3	
Lower than "A levels"	50.6		44.0		41.4		31.3		23.0	
No formal qualifications	24.4		15.3		12.5		8.6		9.0	
Highest occupation of mother and father										
Professional/managerial	24.8		37.7		46.5		59.4		64.4	
Intermediate	19.7		20.8		20.7		18.3		17.5	
Routine and manual	48.3		36.5		29.8		18.7		15.1	
Never worked	7.2		5.1		3.1		3.6		3.0	
IMD quintile[a]										
1 (most deprived)	32.7		26.2		19.2		14.3		14.3	
2	24.1		18.2		19.3		18.6		15.5	
3	20.0		22.9		21.8		21.7		19.2	
4	13.5		16.2		18.9		21.3		24.5	
5 (least deprived)	9.8		16.5		20.8		24.1		26.4	
Maternal history of asthma	17.8		15.9		18.7		16.8		16.3	
Paternal history of asthma[b]	11.9		14.1		14.8		12.5		12.5	

Abbreviations: IMD, Index of Multiple Deprivation; SD, standard deviation.
[a] IMD classifications were based on area of residence at age 9 months.
[b] Percentages calculated after excluding missing data due to mother being single (n = 1,229) or father not completing the interview (n = 765).

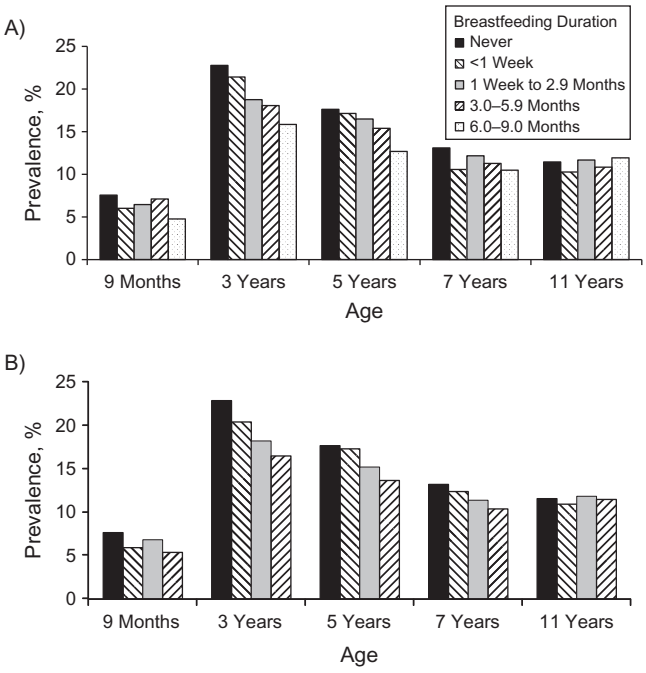

Figure 1. Age-specific prevalence of wheezing according to breastfeeding duration among children born during 2000–2002, Millennium Cohort Study, United Kingdom. A) Any breastfeeding; B) exclusive breastfeeding.

breastfeeding for 6.0–9.0 months was associated with a lower odds of wheezing at age 9 months, 3 years, and 5 years even in fully adjusting models (adjusted odds ratios (ORs) = 0.73, 0.78, and 0.79 respectively; Table 2, Figure 2A). At ages 7 and 11 years, there was no statistically significant association between breastfeeding duration and wheezing. The diminishing relationship between breastfeeding and wheezing over time was confirmed by an interaction between breastfeeding (as a linear trend) and age in the fully adjusting model ($P = 0.0003$).

Exclusive breastfeeding tended to show similar patterns to those for any breastfeeding in univariable analysis (Figure 1B) but the patterns were less clear in models with adjustments (Table 2, Figure 2B). Its strongest relationship was at age 3 years, at which exclusive breastfeeding for 1 week to 2.9 months or 3.0–5.9 months was associated with lower odds of wheezing in the previous year (adjusted ORs = 0.81 and 0.82, respectively).

There was no strong evidence of an interaction with maternal asthma except at age 5 years, when the relationship between breastfeeding and wheezing was stronger in children who had nonasthmatic mothers (linear trend per month of breastfeeding, adjusted OR = 1.018 among asthmatic mothers and 0.961 among nonasthmatic mothers; P for interaction = 0.008; Table 3). There was some evidence that the relationship between breastfeeding and wheezing varied according to whether the child had a history of eczema/hay fever at age 11 years ($P = 0.079$, $P = 0.048$, and $P = 0.059$ at ages 3 years, 5 years, and 7 years, respectively; $P = 0.005$ after allowing for an interaction between breastfeeding and age), with breastfeeding being protective only in children without a history of eczema/hay fever.

Wheezing phenotypes

Overall, 37% of children had wheezing reported at least once from ages 9 months to 11 years, with 18.8% classified as having early transient wheeze, 6.2% with late-onset wheeze, and 11.8% with persistent wheeze. In an adjusting multinomial model, the odds of early transient wheeze dropped as breastfeeding duration increased: Compared with children who were never breastfed, there was a 22% reduction in odds in those breastfed for 3.0–5.9 months and a 31% reduction in odds in those breastfed for 6.0–9.0 months (Table 4, Figure 3A). There was a 4% decrease in the odds of early transient wheeze per month of breastfeeding (for linear trend, adjusted OR = 0.961, 95% confidence interval: 0.942, 0.980; $P < 0.001$). Exclusive breastfeeding was also strongly associated with early transient wheeze, especially if breastfed for 3.0–5.9 months (28% reduction in odds) but even if for 1 week to 2.9 months (20% reduction in odds).

The associations between breastfeeding (any or exclusive) and both late-onset wheeze and persistent wheeze were generally weaker than those for early transient wheeze (Table 4, Figure 3B), except that exclusive breastfeeding for 3.0–5.9 months was associated with a 25% reduction in odds of late-onset wheeze (adjusted OR = 0.75, 95% confidence interval: 0.57, 1.00; $P = 0.048$).

There was less evidence of effect modification for the phenotypes, with breastfeeding tending to be protective for early transient wheeze in both atopic and nonatopic children, breastfeeding having no strong association with late-onset wheeze, and weak evidence for breastfeeding protecting against persistent wheeze in nonatopic children but not in atopic children (for linear trend per month of breastfeeding, adjusted OR = 0.956 among nonatopic children and 1.000 among atopic children; $P = 0.087$ for interaction).

DISCUSSION

Summary of results

Our analysis of a large UK sample identified marked heterogeneity in the association between breastfeeding and wheezing according to age and wheezing phenotype. The strongest associations were between prolonged breastfeeding and reduced risk of wheezing at younger ages, with a statistically significant decline in the strength of association over time. For example, breastfeeding for 6.0–9.0 months was associated with a lower prevalence of wheeze at ages 9 months to 5 years, but this had disappeared by age 11 years. These age-specific associations are mirrored in the analysis of wheezing phenotypes as a relatively strong dose-response relationship for breastfeeding and early transient wheeze but no clear trend for late-onset wheeze. There was also no strong association between breastfeeding and persistent wheeze.

Comparison with other studies

While investigators have assessed the association between breastfeeding and wheeze in many studies (2, 3), few have used longitudinal data to explore how the association between breastfeeding and wheeze changes throughout childhood. In a Dutch study of wheeze during ages 1–4 years, breastfeeding

Table 2. Adjusted Odds Ratios for Breastfeeding Duration and Wheezing in the Previous Year Among Children at Aged 9 Months to 11 Years (Born 2000–2002), Millennium Cohort Study, United Kingdom

Age and Breastfeeding Duration	Any Breastfeeding				Exclusive Breastfeeding			
	Total[a]	%[b]	OR[c]	95% CI	Total[a]	%[b]	OR[c]	95% CI
Age 9 months								
Never	2,926	7.6	1.00	Referent	2,926	7.6	1.00	Referent
<1 week	1,148	6.0	0.82	0.59, 1.12	1,898	5.8	0.80	0.62, 1.04
1 week to 2.9 months	2,010	6.4	0.90	0.70, 1.16	2,520	6.7	0.95	0.74, 1.22
3.0–5.9 months	1,562	7.1	1.06	0.79, 1.42	2,782	5.3	0.83	0.63, 1.10
6.0–9.0 months[d]	2,480	4.8	0.73	0.55, 0.98				
Age 3 years								
Never	2,926	22.8	1.00	Referent	2,926	22.8	1.00	Referent
<1 week	1,148	21.4	1.00	0.81, 1.23	1,898	20.3	0.96	0.80, 1.14
1 week to 2.9 months	2,010	18.8	0.82	0.69, 0.97	2,520	18.1	0.82	0.69, 0.96
3.0–5.9 months	1,562	18.1	0.88	0.71, 1.07	2,782	16.4	0.81	0.68, 0.97
6.0–9.0 months[d]	2,480	15.8	0.78	0.65, 0.94				
Age 5 years								
Never	2,926	17.6	1.00	Referent	2,926	17.6	1.00	Referent
<1 week	1,148	17.1	1.03	0.83, 1.28	1,898	17.2	1.04	0.87, 1.26
1 week to 2.9 months	2,010	16.5	0.95	0.80, 1.14	2,520	15.1	0.89	0.74, 1.06
3.0–5.9 months	1,562	15.4	0.97	0.77, 1.21	2,782	13.5	0.87	0.71, 1.07
6.0–9.0 months[d]	2,480	12.7	0.79	0.65, 0.97				
Age 7 years								
Never	2,926	13.1	1.00	Referent	2,926	13.1	1.00	Referent
<1 week	1,148	10.6	0.82	0.62, 1.07	1,898	12.3	0.96	0.77, 1.20
1 week to 2.9 months	2,010	12.2	0.91	0.74, 1.13	2,520	11.3	0.84	0.69, 1.03
3.0–5.9 months	1,562	11.3	0.89	0.68, 1.16	2,782	10.3	0.82	0.66, 1.03
6.0–9.0 months[d]	2,480	10.5	0.84	0.67, 1.05				
Age 11 years								
Never	2,926	11.4	1.00	Referent	2,926	11.4	1.00	Referent
<1 week	1,148	10.3	0.90	0.66, 1.21	1,898	10.8	0.94	0.72, 1.23
1 week to 2.9 months	2,010	11.7	1.01	0.82, 1.25	2,520	11.8	1.01	0.83, 1.23
3.0–5.9 months	1,562	10.8	0.95	0.73, 1.23	2,782	11.4	1.01	0.80, 1.28
6.0–9.0 months[d]	2,480	11.9	1.06	0.84, 1.35				

Abbreviations: CI, confidence interval; OR, odds ratio (weighted).

[a] Totals are unweighted.

[b] Weighted prevalence of wheezing (%).

[c] Adjusted for child's sex, ethnicity, gestation, birth weight, and mode of delivery; maternal smoking in pregnancy, age at delivery, history of asthma, and education; paternal history of asthma; and family socioeconomic status and Index of Multiple Deprivation (area deprivation).

[d] Approximately 1% of children were exclusively breastfed for 6.0–9.0 months, so this group was combined with those breastfed for 3.0–5.9 months.

was associated with a lower risk of wheeze, especially at ages 1 and 2 years (19). In a US study of wheeze during ages 2–13 years, breastfeeding was associated with a lower risk of wheeze only until age 3 years; and in atopic children with asthmatic mothers, breastfeeding was associated with a higher risk of wheeze from age 6 (17). Similarly, in a Tasmanian study of wheeze during ages 7–44 years, breastfeeding was associated with a lower risk of wheeze at age 7 years but a higher risk from age 14; breastfeeding was not associated with wheeze in children of nonatopic mothers (18). Our results support the limited evidence that breastfeeding is associated with a lower risk of wheeze in early childhood and that the relationship diminishes with age. We found only weak evidence of effect modification by atopy in the mother or child, which has previously been reported in some (19) but not all (17, 18) studies.

Several studies have explored the association between breastfeeding duration and wheezing phenotypes (8, 9, 11, 20–23),

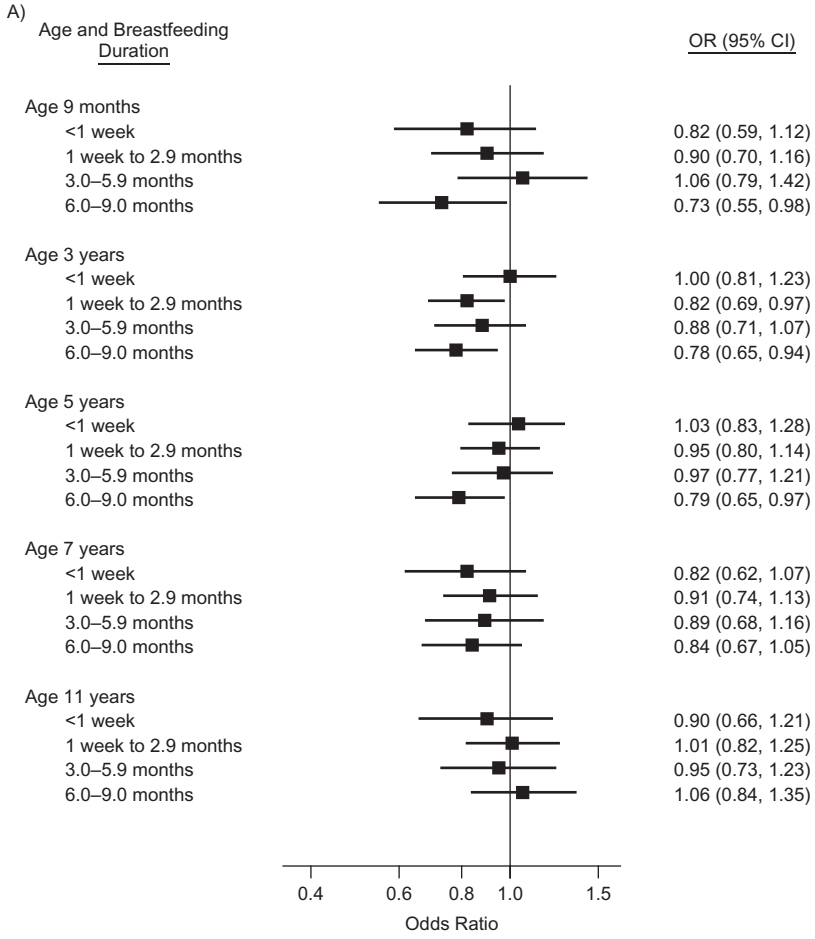

Figure 2 Continues.

although their study designs have varied according to age at wheezing assessment, phenotype definitions, and breastfeeding definitions. In 4 studies with data on breastfeeding duration, a longer duration of breastfeeding was protective against early transient wheeze (8, 11, 21, 23), although the associations with other phenotypes were less clear. A longer breastfeeding duration had a weak protective relationship for persistent (23) or persistent/late wheeze (8) but was also a risk factor for late-onset wheeze (11). Our findings are consistent with these in that we also found a strong protective relationship for early transient wheeze but a less clear association with late-onset and persistent wheeze.

Mechanisms

There are several potential mechanisms that might explain why breastfeeding is associated with lower rates of wheezing or asthma-related symptoms. A likely mechanism is that respiratory infection acts as a mediator between breastfeeding and wheeze. In particular, breast milk contains secretory factors such as immunoglobulin A, cytokines, and long-chain fatty acids, and these promote the development of the infant's immune system (23, 24). These properties of breast milk are believed to play a role in reducing the risk of respiratory infection, as has been observed in this cohort (25, 26) and other studies (27). Respiratory infections in early childhood may result in wheezing, which means that it might be difficult to determine whether breastfeeding is associated with asthma-related wheeze rather than infection-related wheeze. However, respiratory infections in early childhood have also been identified as a risk factor for developing asthma later in childhood, particularly in children with a family history of asthma or allergy (28–30).

On the other hand, there are other plausible mechanisms for the more complex picture that has emerged for studies of breastfeeding and asthma-related symptoms. In infants susceptible to atopy, a lower risk of infections in early childhood—for example, due to breastfeeding—may result in a reduced stimulus of the production of cytokines by type 1 T-helper cells and therefore a dominance of the proinflammatory cytokines involved in asthma-related conditions (11). This may explain why breastfeeding was not associated with a lower risk of persistent wheeze in children with a history of eczema or hay fever at age 11 years.

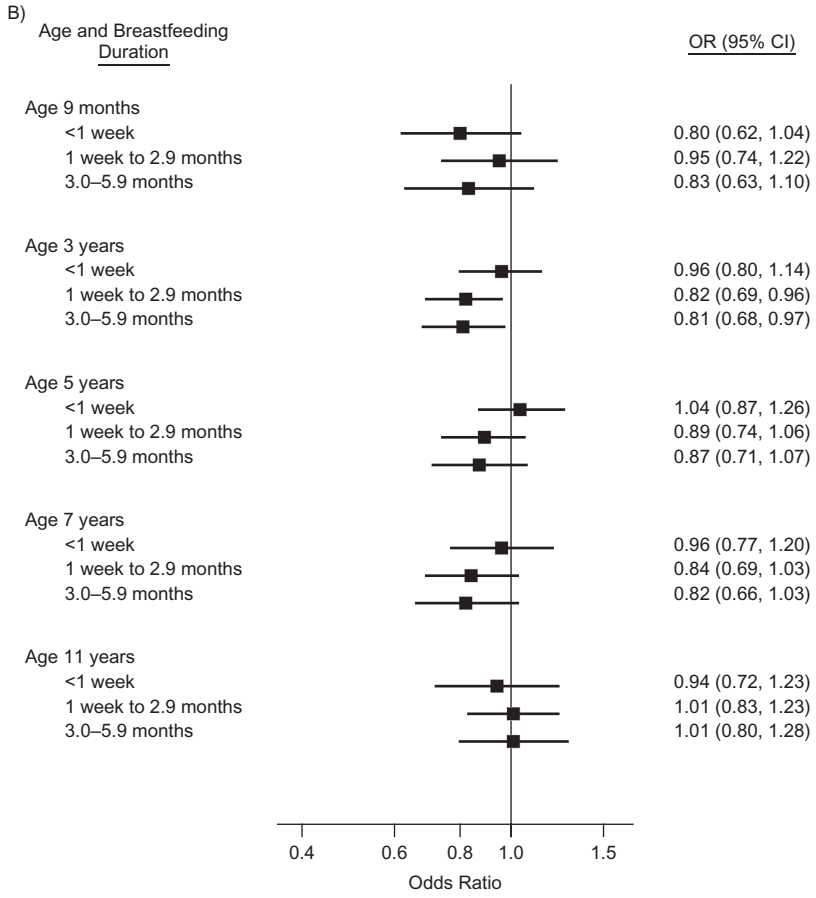

Figure 2. Adjusted odds ratios (ORs) for breastfeeding and wheezing in the previous year, from age 9 months to age 11 years among children born during 2000–2002, Millennium Cohort Study, United Kingdom. A) Any breastfeeding; B) exclusive breastfeeding. Approximately 1% of children were exclusively breastfed for 6.0–9.0 months, so this group was combined with those breastfed for 3.0–5.9 months. CI, confidence interval.

In addition, the breast milk of atopic mothers contains relatively high concentrations of interleukin-4, -5, and -13; these cytokines are involved in the production of immunoglobulin E and the induction of eosinophils, which are part of the immune response to allergic disease (24); this may explain why breastfeeding is not associated with a reduced risk of asthma in children of asthmatic mothers. Finally, wheezing and asthma have multiple causes and triggers, which may vary according to the child's age. Breastfeeding may be important in protecting against wheezing in early childhood, as our results suggest, but at the ages of 7 and 11 years, when the children enter late childhood and approach adolescence, other risk factors and triggers may predominate.

Strengths and limitations

The main strengths of our study are the large, population-based sample and the availability of repeated assessments of wheezing throughout childhood. Our study takes a novel approach to assessing the impact of age on the association between breastfeeding and subsequent wheeze, by exploring both age-specific associations and trajectory-based phenotypes in the same study population. By analyzing the patterns of wheeze across childhood, we can explore the differing relationships with breastfeeding, thus providing new insights into the underlying mechanisms. Our results are also adjusted for the most important known confounders (3) although we cannot rule out residual confounding from other, unmeasured confounders. Our analysis is based on parental report of wheezing in the previous year using a validated measure (14, 15) that has been used to derive wheezing phenotypes. While parental report of wheeze in infancy has a poor correlation with asthma in childhood (31), parental report of wheezing at age 7 years is strongly correlated with physician-diagnosed asthma (6, 7). Unfortunately, owing to the size of the cohort, the Millennium Cohort Study did not collect data on any objective measures of asthma, such as spirometry or peak flow tests, nor did we have data on atopy from skin tests or immunoglobulin E measurements. Such data would have provided objective measures of wheezing severity that parental report (reliant as it is on perception and recall) does not. Poor reporting of wheeze is unlikely to be differential between breastfeeding groups, however, and would likely lead to an underestimate of the true association. Objective

Table 3. Linear-Trend Adjusted Odds Ratios for Any Breastfeeding Duration and Wheeze, Stratified by Maternal Asthma and History of Child Eczema or Hay Fever at Age 11 Years Among Children Born During 2000–2002, Millennium Cohort Study, United Kingdom

Type of Analysis	Maternal Asthma			Child Eczema/Hay Fever		
	Yes	No	*P* Value[a]	Yes	No	*P* Value[a]
Age-specific						
9 months	0.959	0.980	0.56	0.975	0.972	0.90
3 years	0.977	0.977	0.97	0.990	0.961	0.079
5 years	1.018	0.961	0.008	0.988	0.950	0.048
7 years	1.006	0.980	0.25	1.002	0.956	0.059
11 years	1.030	1.005	0.39	1.020	0.992	0.27
All ages	0.987	0.966	0.179	0.985	0.950	0.005
Wheezing phenotype						
Early transient	0.971	0.958	0.58	0.955	0.973	0.68
Late onset	0.994	0.987	0.83	0.989	0.988	0.97
Persistent	0.998	0.985	0.60	1.000	0.956	0.087

[a] *P* value for interaction, 2-sided test.

Table 4. Adjusted Odds Ratios for Breastfeeding Duration and Wheezing Phenotypes Among Children Born During 2000–2002, Millennium Cohort Study, United Kingdom

Wheezing Phenotype and Breastfeeding Duration	Any Breastfeeding				Exclusive Breastfeeding			
	Total[a]	%[b]	OR[c]	95% CI	Total[a]	%[b]	OR[c]	95% CI
Early transient								
Never	2,926	22.7	1.00	Referent	2,926	22.7	1.00	Referent
<1 week	1,148	21.4	0.95	0.75, 1.20	1,898	19.9	0.91	0.76, 1.10
1 week to 2.9 months	2,010	18.9	0.84	0.70, 1.00	2,520	17.9	0.80	0.67, 0.97
3.0–5.9 months	1,562	17.1	0.78	0.63, 0.96	2,782	15.4	0.72	0.60, 0.86
6.0–9.0 months[d]	2,480	14.8	0.69	0.57, 0.83				
Late onset								
Never	2,926	6.2	1.00	Referent	2,926	6.2	1.00	Referent
<1 week	1,148	5.3	0.79	0.54, 1.13	1,898	6.1	0.89	0.66, 1.20
1 week to 2.9 months	2,010	6.3	0.92	0.69, 1.23	2,520	6.2	0.87	0.66, 1.16
3.0–5.9 months	1,562	5.5	0.76	0.55, 1.04	2,782	5.6	0.75	0.57, 1.00
6.0–9.0 months[d]	2,480	6.1	0.82	0.61, 1.11				
Persistent								
Never	2,926	12.3	1.00	Referent	2,926	12.3	1.00	Referent
<1 week	1,148	10.5	0.85	0.64, 1.11	1,898	11.5	0.94	0.74, 1.20
1 week to 2.9 months	2,010	12.2	0.94	0.76, 1.16	2,520	11.5	0.87	0.72, 1.09
3.0–5.9 months	1,562	11.2	0.92	0.69, 1.22	2,782	10.4	0.86	0.68, 1.08
6.0–9.0 months[d]	2,480	10.4	0.85	0.67, 1.06				

Abbreviations: CI, confidence interval; OR, odds ratio (weighted).

[a] Totals are unweighted.

[b] Weighted prevalence of wheezing phenotype (%).

[c] Adjusted for: child's sex, ethnicity, gestation, birth weight, and mode of delivery; maternal smoking in pregnancy, age at delivery, history of asthma, and education; paternal history of asthma; and family socioeconomic status and Index of Multiple Deprivation (area deprivation).

[d] Approximately 1% of children were exclusively breastfed for 6.0–9.0 months, so this group was combined with those breastfed for 3.0–5.9 months.

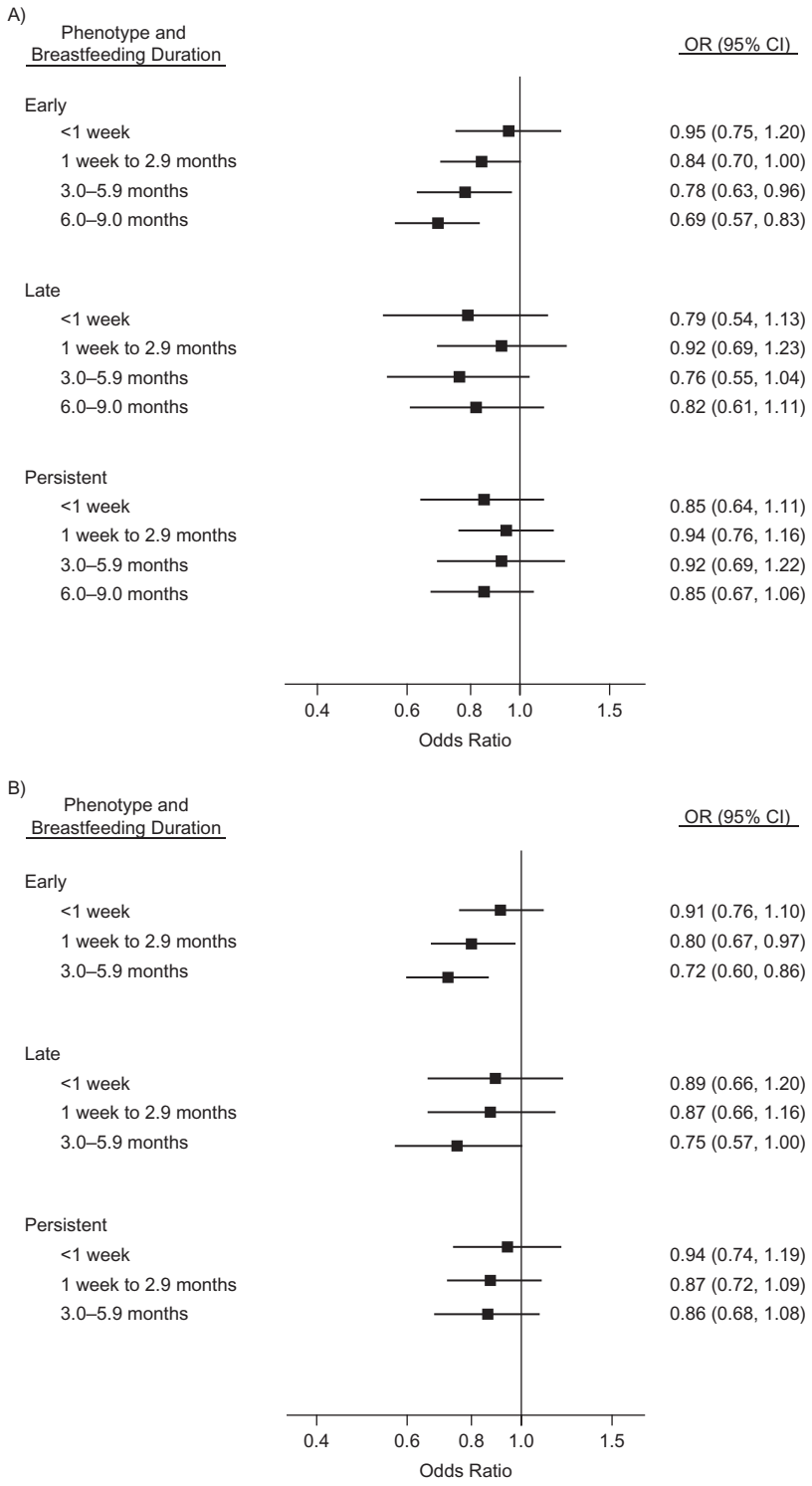

Figure 3. Adjusted odds ratios (ORs) for breastfeeding duration and wheezing phenotypes among children born during 2000–2002, Millennium Cohort Study, United Kingdom. A) Any breastfeeding; B) exclusive breastfeeding. Approximately 1% of children were exclusively breastfed for 6.0–9.0 months, so this group was combined with those breastfed for 3.0–5.9 months. CI, confidence interval.

measures would also have allowed us to incorporate atopic status into the wheezing phenotype or better assess effect modification by atopy. Our results, therefore, should be interpreted as associations with wheeze—which may have a range of underlying causes—rather than asthma or atopy.

In addition, data on infant feeding were obtained through maternal report at the age-9-months interview. These data are not validated, although other studies have shown that mothers accurately report breastfeeding duration within 1 month, up to 3 years after delivery (32, 33). There will be some misclassification in the breastfeeding duration because it is based on the infant's age when last breastfed or first given solids or formula; these estimates will be prone to rounding error, because many responses were given in months rather than days or weeks. Another potential bias in studies of breastfeeding and asthma-related outcomes is that the mother's choice of feeding method may have been influenced by her family history of asthma, although maternal asthma was not strongly associated with breastfeeding duration, at least in a univariable analysis (Table 1).

Conclusions

Our results highlight a complex association between breastfeeding and wheezing in one study population, and this may partly explain the marked heterogeneity observed in meta-analyses. The etiology of wheezing and asthma is complicated by multiple causes and triggers which probably change over time. Hence, it is unlikely that the role of breastfeeding in these conditions can be elucidated using data on wheeze or asthma from a single point in time. Longitudinal studies with repeated measures of asthma-related symptoms across a range of ages are required, ideally with objectively measured clinical markers of allergy and lung function. Systematic reviews and meta-analyses of these studies must take age into account in their analyses in order to provide meaningful evidence to address this unresolved question about breastfeeding and the development of asthma and wheeze during childhood.

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