Breastfeeding and the development of asthma and atopy during childhood: a birth cohort study

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Received: 7 August 2010
Accepted: 14 October 2010

Objective. Within the context of a population based-birth cohort, we investigated the association between breastfeeding and development of asthma and atopy in childhood. **Methods**. Children (n=1072) were followed from birth and reviewed at age one, three, five and eight years. Based on the onset and resolution of symptoms, we assigned children into the wheeze phenotypes (never, transient, intermittent, late-onset and persistent). Atopy was determined by skin testing and specific IgE measurement. According to the duration of breastfeeding, participants were assigned as not breastfed, breastfed ≤ four months and breastfed > four months. **Results**. In a multinomial regression model adjusted for gender, we found that breastfeeding > four months was protective of transient early wheeze (aOR: 0.61, 95% CI 0.41-0.90, p=0.01), with no significant association between breastfeeding and other wheeze phenotypes. In a multivariate model, we found a significant protective effect of breastfeeding >four months on doctor-diagnosed asthma by age eight (aOR 0.59, 95% CI 0.39-0.88, p=0.01). However, we observed a strong trend which failed to reach statistical significance for breastfeeding >four months to increase the risk of atopy at age one year (aOR 2.41, 95% CI 0.94-6.14, p=0.07). There was no significant association between breastfeeding and atopy at any other time point. **Conclusion**. Breastfeeding may prevent viral-infection induced wheezing illnesses in early childhood (transient early wheezing).

Key words: Breastfeeding, Asthma, Atopy, Childhood.

Introduction

Numerous studies have explored the association between breastfeeding in infancy and subsequent development of asthma and allergic disease during childhood. However, there has been considerable inconsistency in the direction of the reported associations, with different studies producing largely contradictory findings (1-4). For example, while some studies reported the protective effect of breastfeeding on the development of asthma and atopy (1), others have found that prolonged breastfeeding in infancy increases

the risk (2). In addition, the effect of breastfeeding may differ in children with different genetic predispositions, and on different phenotypes of childhood asthma. For example, most studies which reported that breastfeeding increases the risk of asthma development observed this association amongst children with a family history of allergic disease. Results from the Tucson Children's Respiratory Study have shown that while exclusive breastfeeding for ≥four months was unrelated to asthma in school age children amongst those with non-asthmatic mothers, it was associated with an increase in risk amongst children who had asthmatic mothers (3). In contrast, when recurrent wheeze during the first three years of life was used as an outcome, breastfeeding was shown to be protective, regardless of the presence or absence of maternal asthma (3). However, in a large population-based birth cohort study from New Zealand, children breastfed for at least four weeks in infancy had increased risk of having asthma and current wheeze at age 9 years, which remained positive after adjustment for parental history of allergic disease (4).

Special consideration needs to be given to the fact that the composition of breast milk varies between individuals, and this may have an impact on asthma and allergic diseases. A small study examining the level of TGF-β_1 and IL-10 in the colostrum and mature milk of allergic and non-allergic mothers found that TGF-β_1 level was significantly lower in the mature milk of allergic mothers (5).

So, why are there such inconsistencies in the reported association between breastfeeding in infancy and the development of asthma and allergies? A part of the answer is that in contrast to most other common complex diseases (e.g. diabetes and hypertension), asthma starts early in life and is an unstable phenotype, with symptoms progressing or remitting over time (6). One of the difficulties when studying this disease arises from the fact that asthma is clearly not a single disease, but a collection of diseases presenting as a syndrome or a collection of symptoms (7-10). This is particularly relevant during childhood, when wheezing may be a common symptom of a number of different diseases, with distinct aetiologies and different environmental risk factors (7, 9, 11). Therefore, the optimum study design to investigate early-life environmental associates of asthma is the population-based birth cohort (6). Using this study design to overcome problems of recall bias and carefully longitudinally phenotyping children, we investigated the association between breastfeeding and development of wheeze, asthma and atopy during childhood.

Methods

Study design, setting and participants

The Manchester Asthma and Allergy Study (MAAS) is an unselected, population-based birth cohort described in detail elsewhere (10, 12-22). Subjects were recruited prenatally and followed prospectively until age eight years. The study is registered as ISRCTN72673620 and approved by the Local Research Ethics Committee. All parents gave written informed consent and children gave their assent if appropriate.

Follow-up: Participants attended follow-up clinics at ages one, three, five and eight years (10, 13, 14, 16, 20-27). Validated questionnaires (28) were interviewer-administered at each time-point to collect information on parentally-reported symptoms, physician-diagnosed illnesses and treatments received.

Definition of exposures and outcomes

Breastfeeding: The information on breastfeeding and its duration was derived from

parental reports at first and third year reviews, based on the answers to questions "Did *you breastfeed your child?*" and "*How long did you breastfeed for (in months, weeks, days)*?". Breastfeeding was described as any breastfeeding during the specified time, including breastfeeding with supplementary formula milk. For the analysis of the association with the outcomes of interest (wheeze, asthma, atopy), we assigned children into three categories according to the duration of breastfeeding: (a) *not breastfed*, (b) *breastfed for ≤ four months* and (c) breastfed for *> four months*.

Wheeze: According to the parentally reported history of wheeze, we defined *current wheeze* at age one, three, five and eight years as a positive response to question "Has your child had wheezing or whistling in the chest in the last twelve months?". In addition, based on prospectively collected data, children were assigned to the following wheeze phenotypes (10, 21); *No wheezing* – no wheeze ever during the first eight years of life; *Transient early wheezing* – wheezing during the first five years, no wheezing after the age of five years; *Late-onset wheezing* – wheeze onset after the child's fifth birthday; *Persistent wheezing* – wheezing at all time points; *Intermittent wheezing* – wheezing at one time point during the first five years, wheezing at age eight years.

Asthma: Parentally-reported asthma was defined as a positive answer to the question *"Does your child have asthma now?"* and Doctor-diagnosed asthma ever as a positive answer to *"Has your doctor ever told you your child has asthma?" at the age of eight years.*

Atopic sensitisation: Atopic sensitisation was ascertained by skin prick testing (Bayer, Elkhart, IND, US) and/or measurement of specific serum IgE (ImmunoCAP; Phadia AB, Uppsala, Sweden) to common inhalant and food allergens (*Dermatophagoides pteronyssinus*, cat, dog, grasses, moulds, milk, egg and peanut); sensitisation was defined as a mean wheal diameter of 3 mm greater than negative control or allergen-specific IgE>0.35 kU_A/l to at least one allergen at age one, three, five and eight years.

Statistical analysis

Statistical analysis was performed using SPSS for Windows 15.0 (SPSS Inc, Chicago Ill, USA). The association between breastfeeding and outcomes of interest (wheeze, asthma and atopy) was initially assessed using the Chi-squared test, with a significant result if p value was below 0.05. Odds ratio (OR) and 95% Confidence Intervals (CI) were determined using univariate logistic regression analysis. A multivariate analysis for wheeze/asthma was performed using a logistic regression model with adjustment for gender, maternal smoking and parental (maternal and paternal) asthma. For wheeze phenotypes, we carried out multinomial logistic regression analysis, before and after adjusting for gender. The association between atopic sensitisation and breastfeeding was tested in a multivariate logistic regression adjusted for gender and maternal atopy. The confounders used in these models were selected on the basis of previously published data, as well as their association with both breastfeeding and clinical outcomes in our study population.

Results

Participant flow and demographics

Of 1185 children whose parents gave consent to take part in the study, 1072 (90.5%) had data on breastfeeding available. Of these 1072 children, 358 (33.4%) were never breastfed, 357 (33.3%) were breastfed for four months or less and 357 (33.3%) were breastfed for longer than four months (Table 1). There was no significant difference in the duration of breastfeeding between boys

and girls. However, children who were born by caesarean section, who had parents who smoked, who were born into low income families and who had non-atopic fathers were less likely to be breastfed at birth (Table 1).

A total of 1028 children were reviewed at age one year, 987 at age three, 943 at age five and 905 at age eight; 343, 780, 758 and 736 participants underwent skin testing at ages one, three, five and eight years respectively. The prevalence of current wheeze was 35.4% (364/1028) in the first year of life, 22.8% (225/987) at age three, 22.0% (207/943) at age five and 17.7% (160/905) at age eight years. Of 905 children who had complete data on the presence of wheeze at each follow-up during the first eight years of life, 410 (45.3%) were classified as never wheezers, 225 (24.9%) had transient early wheeze, 100 (11.0%) intermittent wheeze, 51 (5.6%) late-onset wheeze and 119 (13.1%) persistent wheeze. Within the first eight years of life, 23.4% (204/870) children received doctor diagnosis of asthma; 10.7% (94/881) had parentally-reported current asthma at age eight years. As expected, the prevalence of atopy increased with age both when assessed by skin prick tests (SPT) and sIgE measurement (SPT; age one, 10.9% [50/459]; age three, 23.0% [205/893]; age five, 30.4% [262/861] and age eight 33.6% [281/837]; sIgE: age one, 16.6% [38/229], age three, 27.4% [62/226], age five, 33.5% [182/552] and age eight, 43.0% [230/535]).

Breastfeeding, wheeze and asthma

The association between breastfeeding and wheezing, doctor-diagnosed and parentally-reported asthma is shown in Table 2.

Current wheeze: There was a trend which failed to reach statistical significance for children who were breastfed >four months to wheeze less in the first year of life (OR 0.76, 95% CI: 0.56- 1.04, p=0.08). By the age of three years, children who were breastfed >four months were significantly less likely to have current wheeze (OR 0.66, 95% CI:

Table 1 Demographic characteristics of study population at the time of recruitment

Demographic characteristics	Never breastfed (n=358)	Breastfed ≤4 months (n=357)	Breastfed >4 months (n=357)	P value
Gender (n=1072) Male	192 (53.6%)	208 (58.3%)	182 (51.0%)	0.48
Vaginal delivery (n=852)	212 (72.9%)	237 (83.7%)	223 (80.2%)	**0.03**
Older sibling (n=913)	155 (51.7%)	144 (48.3%)	171 (54.3%)	0.50
Paternal annual income (n=973) < £10,000 £10,000- £20,000 £20,000- £30,000 >£30,000	 76 (23.5%) 139 (42.9%) 68 (21.0%) 41 (12.7%)	 46 (14.3%) 118 (36.8%) 92 (28.7%) 65 (20.2%)	 28 (8.5%) 113 (34.5%) 111 (33.8%) 76 (23.2%)	**<0.0001**
Maternal smoking (n=1066)	86 (24.1%)	47 (13.3%)	18 (5.1%)	**<0.0001**
Paternal smoking (n=1069)	122 (34.2%)	87 (24.4%)	65 (18.3%)	**<0.0001**
Maternal current asthma (n=1069)	55 (15.4%)	48 (13.5%)	48 (13.5%)	0.46
Paternal current asthma (n=1068)	20 (5.6%)	30 (8.5%)	33 (9.2%)	0.07
Maternal (SPT) atopy (n=1032)	199 (57.0%)	195 (57.4%)	210 (61.2%)	0.26
Paternal (SPT) atopy (n=1027)	202 (58.2%)	225(66.6%)	226 (61.1%)	**0.03**

Table 2 The association between breastfeeding and wheeze and asthma during the first 8 years of life (univariate analysis)

Wheeze	Outcome present						
	No		Yes				P value
	N	Percent	N	Percent	OR	95% CI	
Current wheeze at age 1 (N=1028)							
Never breastfed	213	61.2	135	38.8	1.00		
Breastfed ≤ 4 months	220	65.1	118	34.9	0.29	0.62, 1.16	0.29
Breastfed > 4 months	231	67.5	111	32.5	0.76	0.56, 1.04	0.08
Current wheeze at age 3 (N=987)							
Never breastfed	245	73.1	90	26.9	1.00		
Breastfed ≤ 4 months	251	78.0	71	22.0	0.77	0.54, 1.10	0.15
Breastfed > 4 months	266	80.6	64	19.4	0.66	0.46, 0.94	**0.02**
Current wheeze at age 5 (N=943)							
Never breastfed	239	76.8	72	23.2	1.00		
Breastfed ≤ 4 months	236	75.9	75	24.1	1.06	0.73, 1.53	0.78
Breastfed > 4 months	261	81.3	60	18.7	0.76	0.52, 1.12	0.17
Current wheeze at age 8 (N=905)							
Never breastfed	248	83.2	50	16.8	1.00		
Breastfed ≤ 4 months	242	81.8	54	18.2	1.11	0.73, 1.69	0.64
Breastfed > 4 months	255	82.0	56	18.0	1.09	0.72, 1.66	0.69
Parentally reported current asthma at age 8 (N=881)							
Never breastfed	263	90.7	27	9.3	1.00		
Breastfed ≤ 4 months	256	88.3	34	11.7	1.29	0.76, 2.21	0.34
Breastfed > 4 months	268	89.0	33	11.0	1.20	0.70, 2.05	0.51
Doctor diagnosed asthma ever by age 8 (N=870)							
Never breastfed	204	71.1	83	28.9	1.00		
Breastfed ≤ 4 months	221	77.3	65	22.7	0.72	0.49, 1.05	0.09
Breastfed > 4 months	241	81.1	56	18.9	0.57	0.39, 0.84	**0.005**

0.46-0.94, p=0.02). The association between breastfeeding and current wheeze was no longer significant at ages five and eight years (p=0.17 and p=0.69, respectively).

The results of multivariate models at ages one, three, five and eight years are shown in Table 3. In the multivariate logistic regression model adjusted for gender, maternal smoking and maternal and paternal current asthma, the association between breastfeeding and wheeze in the first year of life was not significant (aOR 0.88, 95 % CI 0.63-1.22, p=0.43, Table 3). In this model, significant associates of wheeze in the first year of life were male gender (aOR 1.50, 95% CI 1.15-1.96, p=0.003), maternal current asthma (aOR 1.98, 95% CI 1.38-2.83, p<0.0001) and maternal smoking (aOR 2.03, 95% CI 1.40-2.94, p<0.0001). However, the association between current wheeze at age three years and breastfeeding for longer than four months remained significant in a multivariate model (aOR 0.68, 95% CI 0.47-1.00, p=0.05). Another significant and independent associate of current wheeze at age three was maternal current asthma, with children of asthmatic mothers having 1.87 times higher odds of wheeze at the age three years (95% CI 1.26-2.77, p=0.002).

Wheeze phenotypes: In a multinomial regression model in which we explored the association between breastfeeding and phenotypes of wheezing during the first eight years of life (reference group: *no wheezing)*,

we found that breastfeeding >four months was protective of *transient early wheeze* (OR 0.60, 95% CI 0.40-0.89, p=0.01). There was no significant association between breastfeeding and other wheeze phenotypes. In a multivariate model adjusted for gender, the association between breastfeeding >four months and transient early wheeze remained significant (aOR: 0.61, 95% CI 0.41-0.90, p=0.01), with male gender being another significant independent risk factor (aOR 1.84, 95% CI 1.32-2.57, p<0.0001).

Asthma: Children who were breastfed >four months were less likely to have doctor-diagnosed asthma by age eight years (p=0.005, Table 2). However, there was no

Table 3 Multivariate analysis: breastfeeding and wheeze/asthma in the first 8 years of life

Wheeze	aOR	95% CI	p value
Current wheeze at age 1 (N=1023)			
Breastfed ≤ 4 months	0.91	0.66, 1.26	0.57
Breastfed > 4 months	0.88	0.63, 1.22	0.43
Male gender	1.50	1.15, 1.96	**0.003**
Maternal smoking	2.03	1.40, 2.94	**<0.0001**
Maternal asthma	1.98	1.38, 2.83	**<0.0001**
Paternal asthma	1.11	0.68, 1.80	0.69
Current wheeze at age 3 (N=983)			
Breastfed ≤ 4 months	0.77	0.54, 1.11	0.17
Breastfed > 4 months	0.68	0.47, 1.00	**0.05**
Male gender	1.20	0.89, 1.63	0.24
Maternal smoking	1.27	0.84, 1.94	0.26
Maternal asthma	1.87	1.26, 2.77	**0.002**
Paternal asthma	1.28	0.75, 2.22	0.37
Current wheeze at age 5 (N=938)			
Breastfed ≤ 4 months	1.09	0.75, 1.60	0.64
Breastfed > 4 months	0.87	0.58, 1.30	0.49
Male gender	1.49	1.08, 2.05	**0.02**
Maternal smoking	1.84	1.20, 2.83	**0.006**
Maternal asthma	1.83	1.22, 2.76	**0.004**
Paternal asthma	1.02	0.57, 1.81	0.95
Current wheeze at age 8 (N=901)			
Breastfed ≤ 4 months	1.09	0.71, 1.68	0.69
Breastfed > 4 months	1.09	0.70, 1.69	0.71
Male gender	1.27	0.89, 1.80	0.19
Maternal smoking	1.18	0.70, 1.98	0.53
Maternal asthma	1.47	0.93, 2.33	0.10
Paternal asthma	1.44	0.81, 2.57	0.22
Parentally reported asthma at age 8 (N=878)			
Breastfed ≤ 4 months	1.16	0.67, 1.99	0.60
Breastfed > 4 months	1.11	0.64, 1.92	0.72
Male gender	1.42	0.91, 2.22	0.12
Maternal smoking	0.63	0.29, 1.37	0.24
Maternal asthma	1.09	0.60, 1.97	0.79
Paternal asthma	2.01	1.05, 3.85	**0.04**
Ever doctor diagnosed asthma by age 8 (N=867)			
Breastfed ≤ 4 months	0.68	0.46, 1.00	**0.05**
Breastfed > 4 months	0.59	0.39, 0.88	**0.01**
Male gender	1.64	1.18, 2.29	**0.003**
Maternal smoking	1.21	0.76, 1.93	0.43
Maternal asthma	2.18	1.44, 3.31	**<0.0001**
Paternal asthma	1.87	1.10, 3.17	**0.02**

significant difference in the duration of breastfeeding between children who had parentally-reported current asthma at age eight and those who did not. In a multivariate model, we confirmed the significant protective effect of breastfeeding >four months on doctor-diagnosed asthma by age eight (aOR 0.59, 95% CI 0.39-0.88, p=0.01), with a strong trend for a similar association with breastfeeding ≤four months (aOR 0.68, 95% CI 0.46-1.00, p=0.05, reference group: never breastfed, Table 3). Male gender (OR 1.64, 95% CI 1.18-2.29, p=0.003), maternal current asthma (aOR 2.18, 95% CI 1.44-3.31, p<0.0001) and paternal current asthma (aOR 1.87, 95% CI 1.10-3.17, p=0.02) were other significant independent risk factors for doctor-diagnosed asthma by age eight years.

Breastfeeding and atopic sensitisation

The association between duration of breastfeeding and atopic sensitisation at ages one, three, five and eight years is shown in Table 4.

Table 4 The association between breastfeeding and atopy during the first 8 years of life (univariate analysis)

Atopy	Outcome present						
	No		Yes				
	N	Percent	N	Percent	OR	95% CI	p value
Atopy (SPT) at age 1 (n=343)							
Never breastfed	114	94.2	7	5.8	1.00		
Breastfed ≤ 4 months	92	88.5	12	11.5	2.12	0.80, 5.61	0.13
Breastfed > 4 months	102	86.4	16	13.6	2.56	1.01, 6.46	**0.05**
Atopy (sIgE) at age 1 (n=172)							
Never breastfed	47	88.7	6	11.3	1.00		
Breastfed ≤ 4 months	44	88.0	6	12.0	1.07	0.32, 3.56	0.91
Breastfed > 4 months	55	79.7	14	20.3	1.99	0.71, 5.60	0.19
Atopy (SPT) at age 3 (n=780)							
Never breastfed	203	79.6	52	20.4	1.00		
Breastfed ≤ 4 months	209	79.8	53	20.2	0.99	0.65, 1.52	1.00
Breastfed > 4 months	202	76.8	61	23.2	1.18	0.78, 1.79	0.44
Atopy (sIgE) at age 3 (n=164)							
Never breastfed	43	78.2	12	21.8	1.00		
Breastfed ≤ 4 months	40	76.9	12	23.1	1.08	0.43, 2.67	0.88
Breastfed > 4 months	42	73.7	15	26.3	1.28	0.54, 3.06	0.58
Atopy (SPT) at age 5 (n=758)							
Never breastfed	182	72.2	70	27.8	1.00		
Breastfed ≤ 4 months	179	72.2	69	27.8	1.00	0.68, 1.48	1.00
Breastfed > 4 months	182	70.5	76	29.5	1.09	0.74, 1.59	0.68
Atopy (sIgE) at age 5 (n=486)							
Never breastfed	118	72.8	44	27.2	1.00		
Breastfed ≤ 4 months	102	64.2	57	35.8	1.50	0.93, 2.41	0.10
Breastfed > 4 months	115	69.7	50	30.3	1.17	0.72, 1.88	0.53
Atopy (SPT) at age 8 (n=736)							
Never breastfed	175	73.2	64	26.8	1.00		
Breastfed ≤ 4 months	159	66.0	82	34.0	1.41	0.95, 2.09	0.09
Breastfed > 4 months	173	67.6	83	32.4	1.31	0.89, 1.93	0.17
Atopy (sIgE) at age 8 (n=471)							
Never breastfed	82	61.7	51	38.3	1.00		
Beastfed ≤ 4 months	92	56.8	70	43.2	1.22	0.77, 1.95	0.40
Breastfed > 4 months	105	59.7	71	40.3	1.09	0.69, 1.73	0.72

Table 5 Multivariate analysis: breastfeeding and atopy in the first 8 years of life

Atopy	aOR	95% CI	p value
Atopy (SPT) at age 1 (N=343)			
Breastfed ≤ 4 months	1.95	0.73, 5.19	0.18
Breastfed > 4 months	2.41	0.94, 6.14	0.07
Male gender	1.38	0.67, 2.85	0.38
Maternal atopy	2.36	0.94, 5.90	0.07
Atopy (SPT) at age 3 (N=770)			
Breastfed ≤ 4 months	0.94	0.60, 1.46	0.78
Breastfed > 4 months	1.20	0.78, 1.85	0.41
Male gender	2.05	1.41, 2.97	**<0.0001**
Maternal atopy	2.13	1.48, 3.08	**<0.0001**
Atopy (SPT) at age 5 (N=738)			
Breastfed ≤ 4 months	1.00	0.66, 1.50	1.00
Breastfed > 4 months	1.08	0.73, 1.62	0.69
Male gender	1.84	1.32, 2.58	**<0.0001**
Maternal atopy	1.45	1.04, 2.02	**0.03**
Current wheeze at age 8 (N=719)			
Breastfed ≤ 4 months	1.38	0.92, 2.07	0.12
Breastfed > 4 months	1.31	0.88, 1.95	0.19
Male gender	1.69	1.21, 2.35	**0.002**
Maternal atopy	1.47	1.06, 2.04	**0.02**
Atopy (sIgE) at age 1 (N=172)			
Breastfed ≤ 4 months	1.01	0.30, 3.41	1.00
Breastfed > 4 months	2.46	0.84, 7.15	0.10
Male gender	3.82	1.41, 10.40	**0.009**
Maternal atopy	1.17	0.45, 3.07	0.75
Atopy (sIgE) at age 3 (N=162)			
Breastfed ≤ 4 months	0.98	0.39, 2.50	0.97
Breastfed > 4 months	1.17	0.48, 2.87	0.73
Male gender	1.53	0.70, 3.35	0.29
Maternal atopy	2.44	0.98, 6.06	0.054
Atopy (sIgE) at age 5 (N=478)			
Breastfed ≤ 4 months	1.23	0.76, 1.97	0.40
Breastfed > 4 months	1.13	0.70, 1.80	0.62
Male gender	1.25	0.86, 1.83	0.24
Maternal atopy	1.30	0.89, 1.89	0.17
Atopy (sIgE) at age 8 (N=466)			
Breastfed ≤ 4 months	1.23	0.76, 1.97	0.40
Breastfed > 4 months	1.13	0.70, 1.80	0.62
Male gender	1.25	0.86, 1.83	0.24
Maternal atopy	1.30	0.89, 1.89	0.17

At age one year, we found that breastfeeding >four months increased the risk of atopy assessed by SPT (p=0.05, Table 4). Although the association between breastfeeding and atopy assessed by sIgE at the same time point was in the same direction, it did not reach statistical significance (most likely due to fewer children providing blood samples for measurement of specific IgE). We found no significant association between breastfeeding and atopic sensitisation at ages three, five and eight years, assessed by either SPT or sIgE measurement.

The results of multivariate models at ages one, three, five and eight years are shown in Table 5. In a multivariate logistic regres-

sion adjusted for gender and maternal atopy, we observed a strong trend which failed to reach statistical significance for breastfeeding >four months to increase the risk of atopy (SPT) at age one year (aOR 2.41, 95% CI 0.94-6.14, p=0.07). There was no significant association between breastfeeding and atopy at any other time (Table 5).

Discussion

Principal findings

Our findings indicate that children who were breastfed longer than four months were less likely to wheeze at age three years and were less likely to receive the doctor diagnosis of asthma during the first eight years of life. However, we found no association between breastfeeding and current wheezing at ages five and eight years. We confirmed the finding of the protective effect of prolonged breastfeeding on wheezing in early life in the analysis in which we used prospectively collected data to assign children to different wheeze phenotypes; children who were breastfed longer than four months were protected from transient early wheezing, with no association between breastfeeding and other wheeze phenotypes (intermittent, late-onset and persistent). We observed a strong trend for prolonged breastfeeding (more than four months) to increase the risk of atopy at age one year, but found no association between breast feeding and atopic sensitisation at ages three, five and eight years.

The strengths and limitations of the study

One of the strengths of this study is that data on breastfeeding was collected early in life, which reduced the chance of recall bias amongst parents of children who developed wheeze and asthma later in childhood. Also, data on wheezing and asthma were collected prospectively, increasing the accuracy of outcome measures and the validity of our findings. Moreover, due to the prospective nature of the study we had detailed information on multiple other factors known to increase the risk of wheeze and asthma during childhood (such as maternal smoking and parental asthma), which we used for adjustment in the multivariate analysis. However, one of the limitations is that at the time of clinical follow up at age one and three years, rather than assessing exclusive breastfeeding, we recorded it as any breastfeeding at a specified time. A further limitation is that some of the outcomes are based on parental report, which is unreliable as many parents have little understanding of what physicians mean by the term "wheeze"(24).

The meaning of the study

In this study we observed a significant protective effect of prolonged breastfeeding against wheezing during the first three years of life. However, this association was not confirmed in later childhood, and we found no relationship between breastfeeding and current wheeze at ages five and eight years. The finding that breastfeeding was protective against wheeze only among children who were classified as transient early wheezers may be interpreted as the non-specific effect of breastfeeding on anti-microbial immunity, with the consequent prevention of viral infections [given that a high proportion of early-life wheeze is caused by respiratory viruses (29)].

In addition to the effect of breastfeeding, we found that maternal smoking was a significant risk factor for wheezing during the first year of life. This is in agreement with a finding from another prospective study which found that children who were exposed to smoking in their household had 1.58 higher odds of wheeze in the first year of life (30), and with our previous findings,

which demonstrated that maternal smoking was an associate of early-life wheezing independently of lung function measured at age four weeks (31). Another significant predictor of childhood wheeze in our study, at both age one and three years was maternal asthma. Both passive smoking and maternal asthma are well described risk factors for early life wheezing and childhood asthma, respectively.

Our findings are in agreement with the Tucson Children's Respiratory Study, which reported that children who were exclusively breastfed for ≥four months were 2.2-times less likely to have recurrent wheeze in the first two years of life, independent of the presence of maternal asthma (3). However, similar to our findings, there was no association between exclusive breastfeeding and recurrent wheeze at age six years (3). Similar results were reported from the ALSPAC study (an unselected birth cohort of several thousand children), in which breastfeeding for longer than six months was protective against wheeze in the first three years of life, but not wheeze at age seven and eight years (32). These data indirectly support the concept that childhood wheezing illness is a conglomerate of diseases, with different environmental associates and probably different genetic backgrounds (6).

Although we found that breastfeeding for longer than four months tended to increase the risk of atopy at age one, this was not confirmed at later ages. The higher prevalence of atopic sensitisation at age one year among children who have been breastfed for longer than four months may be due to reverse causality (e.g. we demonstrated that these children were more often born to atopic fathers, who, in line with previous infant feeding recommendations may be more supportive and encouraging of their partners for prolonged breastfeeding). Similar observation of longer duration of breastfeeding among children of allergic parents compared to children of non-allergic parents was described in the Dutch PIAMA birth-cohort study (33).

In our study, the lack of association between breastfeeding and atopy at later ages is contrary to the findings from the PIAMA study, which reported a lower rate of atopic sensitisation to inhalant allergens (assessed by specific IgE measurement) at age eight years among children breastfed longer than four months (33). This difference may be explained by the fact that in our study we measured specific IgE to 10 common inhalant and food allergens, while the PIAMA study only looked at sensitisation to six inhalant allergens. Inevitably, we found a higher proportion of sensitised children within our study population at age eight years (40.8%) compared to children in the PIAMA study (27.5%).

Conclusions

Prolonged breastfeeding practice should be advocated as it prevents early life gastrointestinal and respiratory infections due the unique content of breast milk. Within the context of respiratory diseases during childhood, breastfeeding may prevent transient early wheezing which is predominantly induced by viral infection. However, we did not find any evidence that breastfeeding prevents asthma and atopic sensitisation at a later age, amongst school-age children.

Acknowledgements

The authors would like to thank the children and their parents for their continued support and enthusiasm. We greatly appreciate the commitment they have given to the project. We would also like to acknowledge the hard work and dedication of the study team (research fellows, nurses, physiologists, technicians and clerical staff).

Conflict of interest: The authors declare that they have no conflict of interest. This study was supported by Asthma UK Grant No 04/014 and Moulton Charitable Trust, and is currently supported by MRC Grant G0601361.

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