Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study

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Summary

Background Breastfeeding is widely advocated to reduce risk of atopy and asthma, but the evidence for such an effect is conflicting. We aimed to assess long-term outcomes of asthma and atopy related to breastfeeding in a New Zealand birth cohort.

Methods Our cohort consisted of 1037 of 1139 children born in Dunedin, New Zealand, between April, 1972, and March, 1973, and residing in Otago province at age 3 years. Children were assessed every 2–5 years from ages 9 to 26 years with respiratory questionnaires, pulmonary function, bronchial challenge, and allergy skin tests. History of breastfeeding had been independently recorded in early childhood.

Findings 504 (49%) of 1037 eligible children were breastfed (4 weeks or longer) and 533 (51%) were not. More children who were breastfed were atopic at all ages from 13 to 21 years to cats (p=0·0001), house dust mites (p=0·0010), and grass pollen (p<0·0001) than those who were not. More children who were breastfed reported current asthma at each assessment between age 9 (p=0·0008) and 26 years (p=0·0008) than those who were not. Breastfeeding effects were not affected by parental history of hayfever or asthma. Multifactor analysis controlling for socioeconomic status, parental smoking, birth order, and use of sheepskin bedding in infancy, showed odds ratios of 1·94 (95% CI 1·42–2·65, p<0·0001) for any allergen positive at age 13 years, 2·40 (1·36–4·26, p=0·0003) for current asthma at 9 years, and 1·83 (1·35–2·47, p<0·0001) for current asthma at 9–26 years by repeated-measures analysis.

Interpretation Breastfeeding does not protect children against atopy and asthma and may even increase the risk.

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Introduction

Most reviews of risk factors for asthma recommend extended breastfeeding to reduce the probability of development of atopy and asthma in childhood. Although such a view is widely accepted and promoted, few investigators have adequately addressed the issue, and their results are conflicting.

In 1988, Kramer[1] proposed 12 criteria for studies in which the relation between breastfeeding and development of atopy and asthma are assessed (panel). He suggested that previous studies contained flaws in design or implementation, including selection of the study population, retrospective recall bias about feeding history, short duration of follow-up, inadequate definition of outcomes, and failure to consider confounding variables. Despite further studies, controversy persists. Some investigators have reported protection,[2–7] whereas others suggest an increased risk of allergy and asthma associated with breastfeeding.[8–12]

We have examined outcomes of asthma and atopy related to breastfeeding in a population-based birth-cohort study of New Zealand children which fulfills the criteria shown in the panel. Our hypothesis was that breastfeeding would protect against development of atopy and asthma in childhood.

Methods

Participants

All 1661 live-born children delivered at Queen Mary Hospital, Dunedin, New Zealand, between April, 1972, and March, 1973, were included in a neonatal study.[13] Children from this cohort who were resident in the province of Otago at age 3 years were invited to participate in the longitudinal Dunedin Multidisciplinary Health and Development Research Study. We enrolled

Criteria proposed by Kramer[1] for assessing adequacy of studies of the effect of breastfeeding on development of allergy and asthma

Exposure
Non-reliance on late maternal recall of breastfeeding
Blind ascertainment of infant feeding history
Sufficient duration of breastfeeding
Sufficient exclusivity of breastfeeding

Outcome
Strict diagnostic criteria
Blind ascertainment of outcomes
Consideration of severity of outcome
Consideration of age of onset of outcome

Statistics
Control for confounding
Assessment of dose-response effects
Assessment of effects in children at high risk of outcome
Adequate statistical power

1037 (91%) of 1139 eligible children. Cohort families represented the full range of socioeconomic status in the general population of New Zealand's South Island and were mainly white. Socioeconomic status was classified by the Elley-Irving scale (high 1–3, low 4–6).[14]

The research ethics committee of the Otago hospital board granted ethical approval for assessments. Participants gave written informed consent before participating in each assessment from age 18 years, as did a parent or guardian in assessments before age 18 years.

Procedures

Participants were assessed within a month of their birthday at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, and 26 years, unaccompanied after age 11 years. Children who completed respiratory questionnaires at ages 9, 11, 13, 15, 18, 21, and 26 years were respectively 79%, 77%, 71%, 93%, 84%, 92%, and 96% of the living cohort. Skin testing was done in 714 (69% of the living cohort) children at age 13 years and in 885 (87%) at age 21 years.

Initiation and duration of breastfeeding were documented independently by interviewers who assessed the cohort at age 3 years. These interviewers were unaware of the atopy and asthma outcomes, since these were recorded in later life.[15] Duration of breastfeeding and age at introduction of cow's milk and other foods to the infant's diet were verified at age 3 years from records maintained through the New Zealand Plunket Nurse programme, in which newborns and infants were assessed through regular home and clinic visits, weekly at first then less frequently, until children were aged 2–3 years. Although many newborns who were breastfed received a nightly formula feed while in hospital to allow the mother to sleep, most had hospital stays of only 3–4 days. Thus, the extent of other feeding, if only in that period, was minor. Those infants not breastfed generally received formula feeding prepared from dried cow's milk powder.

At the assessment at age 7 years, trained interviewers asked whether the child had ever had asthma, wheezing, hayfever, bronchitis, or allergies.[16] From age 9 years, a more comprehensive questionnaire was used by an interviewer, who recorded occurrence and frequency of symptoms of wheezing, diagnoses of asthma and hayfever, drugs, clinical characteristics, admissions, and environmental exposures.[17,18] At ages 18, 21, and 26 years, participants also completed questions derived from questionnaires from the American Thoracic Society[19] and the International Union Against Tuberculosis and Lung Diseases.[20] Current asthma was defined as a positive response to the question "Do you (does your child) have asthma?" together with symptoms reported within the previous 12 months, and was not dependent on whether treatment was prescribed or used.

At 7 years, the adult attending with the child (usually mother) was asked whether the natural mother or father had asthma, hayfever, or allergies.[16] The family history was again obtained at 18 years. Preference was given to the information recorded at age 7 years (if available).

Participants using bronchodilators were asked to withhold these on the day of study, but inhaled steroids and other treatments were not withheld. Spirometry was done at every assessment from ages 9 to 26 years, and we recorded the best of at least three satisfactory measurements of forced exhaled volume in 1 s (FEV_1) and vital capacity. Except at ages 18 and 26 years, an abbreviated four-dose validated methacholine challenge test was done by all consenting participants.[18] Airway hyper-responsiveness was defined as a fall of FEV_1 of 20% or more after inhalation of methacholine in a concentration of 8 g/L or less. Children with baseline airflow obstruction (FEV_1/vital capacity ratio <70%) were not given methacholine, but response to salbutamol (5 g/L nebulised for 2 min) was measured instead. We judged airway hyper-responsiveness to be present if the FEV_1 increased by 10% or more from baseline after use of a bronchodilator. At ages 18 and 26 years, all participants had a bronchodilator response test only.

Skin prick tests were done at ages 13 and 21 years on the forearm without specific skin preparation.[21] Results were excluded if antihistamines had been used within 2 days. A positive skin test was defined as a weal at least 2 mm greater than the size of the weal to the negative control at 15 min. Allergens included house dust mite (*Dermatophagoides pteronyssinus*) (Bencard Brentford, Middlesex, UK), rye grass pollen (*Lolium perenne*), cat dander, dog dander, horse hair, kapok, cladosporium, *Aspergillus fumigatus*, *Penicillium* spp, *Alternaria* spp, and wool (all Hollistier-Stier, Spokane, Washington, USA), together with positive (histamine 0·1%) and negative (diluent) controls. Ingested allergens relevant to early

	Whole population (n=1037)	Not breastfed (n=504)	Breastfed >4 weeks (n=533)	Odds ratio (95% CI)	p	Population attributable risk
Atopy at age 13 years	n=714	n=359	n=355			
Cat	94 (13%)	30 (8%)	64 (18%)	2·41 (1·52–3·83)	0·0001	36%
House dust mite	213 (30%)	87 (24%)	126 (36%)	1·72 (1·24–2·38)	0·0010	19%
Grass	232 (32%)	87 (24%)	145 (41%)	2·16 (1·57–2·98)	<0·0001	26%
Alternaria	43 (6%)	15 (4%)	28 (8%)	1·96 (1·03–3·74)	0·0373	30%
Any allergen positive	319 (45%)	132 (37%)	187 (53%)	1·91 (1·42–2·58)	<0·0001	18%
Atopy at age 21	n=885	n=442	n=443			
Cat	240 (27%)	100 (23%)	140 (32%)	1·58 (1·17–2·13)	0·0027	17%
House dust mite	491 (55%)	224 (51%)	267 (60%)	1·48 (1·13–1·93)	0·0041	10%
Grass	388 (44%)	159 (36%)	229 (52%)	1·91 (1·46–2·49)	<0·0001	18%
Alternaria	114 (13%)	41 (9%)	73 (16%)	1·93 (1·28–2·90)	0·0014	28%
Any allergen positive	573 (65%)	266 (60%)	307 (69%)	1·49 (1·13–1·97)	0·0045	7%
Asthma						
Ever by age 9 years	74/815 (9%)	27/417 (6%)	47/398 (12%)	1·93 (1·18–3·17)	0·0081	29%
Current at age 9 years	62/815 (8%)	19/417 (5%)	43/398 (11%)	2·54 (1·45–4·44)	0·0008	40%
Current at age 11 years	93/802 (12%)	31/405 (8%)	62/397 (16%)	2·23 (1·42–3·52)	0·0004	34%
Current at age 13 years	95/735 (13%)	27/371 (7%)	68/364 (19%)	2·93 (1·83–4·69)	<0·0001	43%
Current at age 15 years	138/968 (14%)	55/494 (11%)	83/474 (18%)	1·69 (1·17–2·45)	0·0046	22%
Current at age 18 years	128/868 (15%)	51/441 (12%)	77/427 (18%)	1·68 (1·15–2·47)	0·0072	22%
Current at age 21 years	154/957 (16%)	64/479 (13%)	90/478 (19%)	1·50 (1·06–2·13)	0·0214	17%
Current at age 26 years	187/980 (19%)	74/496 (15%)	113/484 (23%)	1·74 (1·26–2·40)	0·0008	22%

Values are number (%).

Table 1: **Frequency of atopy (skin test weal ⩾2 mm) at ages 13 and 21 years, and asthma at ages 9–26, by breastfeeding history**

childhood were not included since skin testing was first undertaken at age 13 years. Investigators unaware of the data for infant feeding determined all respiratory outcomes (questionnaires, pulmonary function testing, and skin allergy testing).

Statistical analysis

We analysed data using SAS (Statistical Analysis Systems, Cary, NC, USA) version 8. We used χ^2 tests to compare characteristics between children who were breastfed and those who were not and likelihood ratio tests to assess the relation between breastfeeding and risk of atopy and asthma. A step-forward (multivariate) approach was used, starting with a univariate model for each individual variable. The level of significance to enter the model was 0·1. The outcome of asthma which was determined at several time points from 9 to 26 years was also analysed with the generalised estimating equations approach,[22] incorporating the repeated nature of these data.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report.

Results

Of 1037 children in the longitudinal study, 463 (45%) were not breastfed. In 70 (7%) children, breastfeeding was attempted but was discontinued before the child was 4 weeks old. Preliminary analyses showed that these 70 children had outcomes much the same as those who were not breastfed, and quite different to those breastfed for 4 weeks or longer. These 70 children were therefore included in the non-breastfed group, making a total of 533 children (51%). Mean duration of breastfeeding in the comparison group of 504 children (49%) was 21·1 weeks (SD 16·6). Unless otherwise specified, the term breastfeeding in this report does not necessarily mean exclusive breastfeeding. Early childhood characteristics of those 1037 children who participated in the study did not differ significantly from those of the 102 children who did not participate.

Children were more often breastfed than formula fed if they were first-born (216 of 384 [56%] *vs* 288 of 653 [44%], p=0·0001), born to parents of higher socioeconomic status (220 of 368 [60%] *vs* 249 of 527 [44%], p=0·0001 for SES levels 1–3 *vs* 4–6), or born to non-smoking mothers (273 of 497 [55%] *vs* 154 of 371 [42%], p=0·0001). Children who were breastfed were more likely to have a sheepskin on their bed in infancy than those who were not (122 of 396 [31%] *vs* 97 of 414 [23%], p=0·018). Family history of hayfever or asthma (mother or father) and sex of the child did not affect the probability of being breastfed.

At age 13 years, positive skin tests to cat, house dust mite, grass, alternaria, or any allergen, were significantly more frequent in children who were breastfed than in those who were not (table 1). At age 21 years, positive skin tests to all allergens tested except aspergillus were significantly more frequent in those who were breastfed than in those who were not (table 1). Population attributable risks for atopy at age 13 varied between 19% and 36% for different allergens, and at age 21 between 10% and 28% (table 1).

At age 9 years, more children who were breastfed had been diagnosed with asthma, had current asthma, and had current wheeze (symptoms within the last 12 months) than those who were not breastfed (tables 1 and 2). The effect identified with current asthma persisted at all ages to 26 years (table 1), with population attributable risks varying between 17% and 43% at different ages, Among those with daily wheezing at age 9 years, seven of eight (88%) had been breastfed, as had 16 of 21 (76%) of those reporting wheeze at least weekly, and 62 of 92 (67%) of those with any wheezing.

The relation with breastfeeding remained strong even when airway hyper-responsiveness was needed to confirm the diagnosis of asthma, or that wheezing was due to asthma.[23] Children who were breastfed were more likely than those who were not to have current asthma with airway hyper-responsiveness or current wheeze with airway hyper-responsiveness at all ages up to 21 years with one exception (table 2). With generalised estimating equations, allowing for repeated measures analysis, children who were breastfed were more than twice as likely as those who were not breastfed to have wheeze with airway hyper-responsiveness or current asthma with airway hyper-responsiveness (table 2).

Any duration of breastfeeding for longer than 3 weeks raised risk of atopy and asthma (table 3). To compare our data with results from other studies, we determined the effect that selection of cutpoints other than 4 weeks to define breastfeeding would have had on the odds ratios for effects on atopy and asthma. Breastfeeding was associated with increased risk of asthma or atopy irrespective of whether we had selected a cutpoint of 0 weeks (any breastfeeding *vs* no breastfeeding), 4 weeks, 8 weeks, or 12 weeks (table 3). For example, the odds ratios for the outcome of any allergen positive at age 13 were 1·72 (95% CI 1·27–2·33; p=0·0004) for 0 weeks, 1·91 (1·42–2·58;

	Whole population (n=1037)	Not breastfed (n=504)	Breastfed >4 weeks (n=533)	Odds ratio (95%CI)	p	Population attributable risk
Current wheeze with AHR						
9 years	76/794 (10%)	22/409 (5%)	54/385 (14%)	2·87 (1·71–4·81)	<0·0001	44%
11 years	57/754 (8%)	18/381 (5%)	39/373 (10%)	2·36 (1·32–4·20)	0·0029	38%
13 years	45/700 (6%)	9/350 (3%)	36/350 (10%)	4·34 (2·06–9·16)	<0·0001	60%
15 years	59/822 (7%)	25/418 (6%)	34/404 (8%)	1·44 (0·85–2·47)	0·1763	17%
21 years	57/856 (7%)	21/430 (5%)	36/426 (8%)	1·80 (1·03–3·13)	0·0364	27%
9–21 years*	..	..	..	2·09 (1·42–3·08)	0·0002	..
Current asthma with AHR						
9 years	39/794 (5%)	11/409 (3%)	28/385 (7%)	2·83 (1·39–5·78)	0·0028	45%
11 years	51/754 (7%)	15/381 (4%)	36/373 (10%)	2·61 (1·40–4·85)	0·0018	43%
13 years	37/700 (5%)	6/350 (2%)	31/350 (9%)	5·57 (2·29–13·5)	<0·0001	68%
15 years	50/822 (6%)	18/418 (4%)	32/404 (8%)	1·91 (1·05–3·46)	0·0302	30%
21 years	43/856 (5%)	14/430 (3%)	29/426 (7%)	2·17 (1·13–4·17)	0·0174	34%
9–21 years*	..	..	..	2·33 (1·46–3·72)	0·0004	..

Values are number (%). *Repeated measures analysis.

Table 2: **Prevalence of current significant wheeze with airway hyper-responsiveness (AHR) to methacholine (or salbutamol in those with baseline obstruction), and of current asthma with AHR, by breastfeeding history**

	Duration of breastfeeding (weeks)						
	Never	1–3	4–7	8–11	12–15	16–25	>26
Atopy at 13 years (n)	312	47	71	47	56	79	102
Cat	24 (8%)	6 (13%)	14 (20%)	8 (17%)	10 (18%)	12 (15%)	20 (20%)
Mite	78 (25%)	9 (19%)	28 (39%)	17 (36%)	25 (45%)	26 (33%)	30 (29%)
Any allergen	116 (37%)	16 (34%)	41 (58%)	23 (49%)	38 (68%)	38 (48%)	47 (46%)
Atopy at 21 years (n)	377	65	88	54	65	106	130
Cat	87 (23%)	13 (20%)	31 (35%)	19 (35%)	27 (42%)	29 (27%)	34 (26%)
Mite	191 (51%)	33 (51%)	57 (65%)	31 (57%)	45 (69%)	60 (57%)	74 (57%)
Any allergen	227 (60%)	39 (60%)	60 (68%)	37 (69%)	50 (77%)	72 (68%)	88 (68%)
Asthma at 9 years (n)	365	52	79	48	61	91	119
Asthma current	18 (5%)	1 (2%)	10 (13%)	5 (10%)	6 (10%)	12 (13%)	10 (8%)
Asthma ever	25 (7%)	2 (4%)	10 (13%)	5 (10%)	6 (10%)	13 (14%)	13 (11%)

Values are number (%) of those assessed for these outcomes at each age.

Table 3: **Effect of duration of breastfeeding on development of atopy and asthma**

p<0·0001) for 4 weeks, 1·53 (1·16–2·13; p=0·0033) for 8 weeks, and 1·55 (1·13–2·12; p=0·0063) for 12 weeks. For the outcome of current asthma at age 9 years, odds ratios were 2·09 (1·19–3·68; p=0·0095), 2·54 (1·45–4·44; p=0·0008), 1·86 (1·10–3·13; p=0·0182), and 1·73 (1·02–2·92; p=0·0385), respectively, for these cutpoints.

As expected, more children who had a parental history of hayfever or asthma developed atopy or asthma than those who did not have such a history. However, the effects of breastfeeding were not affected by family history (table 4).

No duration of exclusive breastfeeding had a protective effect against development of atopy and asthma in later childhood. Rather, most analyses showed such disorders in more children who were breastfed than in those who were not. For example, asthma ever at age 9 years was reported by 20 (13%) of 160 who were exclusively breastfed for longer than 4 weeks compared with 51 (8%) of all others (n=635, p=0·077). Because of the smaller numbers in whom exclusive feeding could be firmly documented, these comparisons were not significant, but were of similar direction and magnitude to all other analyses.

In multifactor analysis, controlling for socioeconomic status, birth order, sheepskin use in infancy, and maternal smoking, asthma and atopy outcomes all remained highly significantly associated with breastfeeding (table 5). Male sex was a risk factor for atopy, as was the mother's history of asthma or hayfever for the outcome of any positive skin test at age 13 years. Other factors were considered in the final model, but were not significant. Table 5 shows the adjusted odds ratios for development of any positive skin test at age 13 years, for current asthma at age 9 years, and for positive skin test to house dust mite at age 13 years. With generalised estimating equations to analyse asthma outcomes, allowing for the repeated nature of this assessment, the odds ratio for current asthma was 1·83 (1·35–2·47; p<0·0001).

Discussion

Our results provide substantial evidence against our initial hypothesis that breastfeeding is protective against atopy and asthma. By contrast, breastfeeding for 4 weeks or longer increased the likelihood of skin test responses to common allergens at age 13 years, and more than doubled the risk of diagnosed asthma in mid-childhood, with effects persisting into adulthood.

We investigated a large unselected population-based birth cohort, in which roughly equal numbers were breastfed and not breastfed. Data for breastfeeding were gathered in early childhood, and varied widely by duration of exclusive and total breastfeeding. Ascertainment of feeding history was undertaken by investigators who were unaware of asthma and allergy outcomes, and vice versa. Our results were strengthened by the long (26 year) period of follow-up with reviews every few years, together with clearly defined allergy and asthma outcomes, and objective confirmation of allergy by skin-testing and of asthma by measurement of airway responsiveness. We also considered the effects of duration of breastfeeding (an approximation for a dose-response effect), effects in high-risk versus low-risk children, and effects of exclusive breastfeeding. Relevant confounding variables were taken into account. Hence this study meets all of the requirements of Kramer[1] outlined in the panel.

The reasons why some studies of breastfeeding show protection against atopy and asthma,[2–7] whereas others

	Family history negative			Family history positive			p*
	Not breastfed	Breastfed >4 weeks	Odds ratio (95% CI)	Not breastfed	Breastfed >4 weeks	Odds ratio (95% CI)	
Atopy at 13 years (n)	196	193		155	158		
Cat	9 (5%)	30 (16%)	3·82 (1·76–8·29)	21(14%)	34 (22%)	1·75 (0·96–3·18)	0·117
Mite	47 (24%)	60 (31%)	1·43 (0·91–2·24)	39 (25%)	66 (42%)	2·13 (1·32–3·45)	0·233
Any allergen	66 (34%)	87 (45%)	1·62 (1·07–2·44)	64 (41%)	98 (62%)	2·32 (1·48–3·65)	0·245
Atopy at 21 years (n)	235	227		179	196		
Cat	41 (17%)	61 (27%)	1·74 (1·11–2·72)	49 (27%)	77 (39%)	1·72 (1·11–2·65)	0·968
Mite	103 (44%)	124 (55%)	1·54 (1·07–2·23)	103 (58%)	136 (69%)	1·67 (1·09–2·56)	0·778
Any allergen	127 (54%)	146 (64%)	1·53 (1·06–2·23)	120 (67%)	150 (77%)	1·60 (1·02–2·52)	0·881
Asthma at 9 years (n)	229	216		174	174		
Asthma ever	10 (4%)	23 (11%)	2·61 (1·21–5·62)	16 (9%)	23 (13%)	1·50 (0·77–2·96)	0·291
Asthma current	8 (3%)	19 (9%)	2·66 (1·14–6·22)	11 (6%)	23 (13%)	2·26 (1·06–4·79)	0·774

Values are number (%) of skin tested at each age, or the number providing questionnaire data at age 9 years. *p value for difference between odds ratios for effect of breastfeeding in those with and without a family history.

Table 4: **Effect of family history of allergy (either parent reporting asthma or hayfever) on effect of breastfeeding on development of atopy and asthma in the New Zealand birth cohort**

	Current asthma at 9 years		House dust mite at 13 years		Any allergen at 13 years		Current asthma*	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Univariate analysis								
Breastfed >4 weeks	2·54 (1·45–4·44)	0·0011	1·72 (1·24–2·38)	0·0011	1·91 (1·42–2·58)	<0·0001	1·79 (1·34–2·40)	<0·0001
Family history positive	1·68 (0·99–2·84)	0·0542	1·33 (0·96–1·84)	0·0836	1·65 (1·22–2·36)	0·0010	2·23 (1·65–3·02)	<0·0001
Father's history positive	1·36 (0·76–2·45)	0·3035	1·31 (0·90–1·90)	0·1629	1·56 (1·09–2·22)	0·0140	1·74 (1·24–2·44)	0·0014
Mother's history positive	1·57 (0·92–2·70)	0·0982	1·45 (1·02–2·04)	0·0359	1·82 (1·31–2·52)	0·0003	1·96 (1·44–2·66)	<0·0001
Male sex	1·47 (0·87–2·51)	0·1520	1·77 (1·27–2·45)	<0·0001	1·82 (1·35–2·45)	<0·0001	1·07 (0·80–1·42)	0·6610
Cat ownership to 9 years	0·54 (0·31–0·95)	0·0336	0·66 (0·45–0·98)	0·0369	0·80 (0·55–1·14)	0·2047	0·76 (0·52–1·11)	0·1572
Socioeconomic status	0·95 (0·78–1·15)	0·5844	0·91 (0·80–1·03)	0·1194	0·91 (0·81–1·02)	0·1173	0·98 (0·88–1·09)	0·7207
Father smoked	1·34 (0·79–2·28)	0·2821	0·82 (0·59–1·15)	0·2503	0·81 (0·60–1·10)	0·1852	1·13 (0·83–1·53)	0·4364
Mother smoked	1·04 (0·61–1·77)	0·8817	1·01 (0·72–1·41)	0·9497	0·86 (0·63–1·18)	0·3565	1·08 (0·80–1·47)	0·6099
Firstborn	1·17 (0·69–1·98)	0·5653	1·05 (0·75–1·46)	0·7805	1·22 (0·90–1·65)	0·2043	1·17 (0·87–1·57)	0·3081
Use of sheepskin in infancy	1·42 (0·82–2·47)	0·2090	0·98 (0·68–1·42)	0·9088	1·10 (0·78–1·54)	0·5977	1·07 (0·74–1·53)	0·7322
Multivariate analysis								
Breastfed >4 weeks	2·40 (1·36–4·26)	0·0027	1·70 (1·21–2·38)	0·0020	1·94 (1·42–2·65)	<0·0001	1·83 (1·35–2·47)	<0·0001
Family history positive	1·60 (0·93–2·74)	0·0881	..	..	..	..	2·20 (1·62–2·98)	<0·0001
Mother's history positive	..	..	..	..	1·90 (1·36–2·66)	0·0002	..	..
Male sex	..	..	1·78 (1·27–2·49)	0·0008	1·91 (1·40–2·61)	<0·0001	..	..
Cat ownership to 9 years	0·56 (0·32–1·01)	0·0532	0·68 (0·46–1·01)	0·0564	..	..	..	..
Father smoked	1·60 (0·93–2·77)	0·0903	..	..	..	..	..	..

Table 5: **Univariate and multivariate analyses of risk factors for current asthma at age 9 years, positive skin test responses to mite or to any allergen at age 13 years, and for current asthma age 9–26 years by repeated measures analysis**

show increased risk[8–12] mainly relate to duration of follow-up and ages at which outcomes are assessed. Results of studies in which early childhood outcomes (eczema or wheezing illness before age 2 years) were assessed show protection from prolonged or exclusive breastfeeding, whereas those in which outcomes in later childhood were assessed show increased atopy and asthma. Use of different cutpoints for established breastfeeding, different maternal IgE concentrations, different confounding factors, and different time periods may also be relevant.

In studies[2] showing decreased risk of asthma or atopy, breastfeeding in Swedish children delayed onset of allergic disease but only in those whose mother and father both had a history of allergy. Those very high-risk children who were not breastfed developed early allergic disease.[2] In infants of allergic mothers in California, none of 24 breastfed infants with only one parent who had a history of allergy and negative skin tests had asthma compared with five of 34 (15%) of those not breastfed.[3] However, no protective effect was recorded in infants with positive skin tests. Chandra and colleagues[4] followed up 72 breastfed and 216 non-breastfed high-risk infants for 5 years, and reported reduced atopic disease in breastfed children, with less eczema and asthma.

In 2187 Australian children recruited through an antenatal clinic and assessed at age 6 years, exclusive breastfeeding for longer than 4 months reduced risk of atopy and asthma.[5] Introduction of other milk before 4 months was a risk factor for asthma, as was wheeze three or more times a year since age 1 year, wheeze in the past year, sleep disturbance, and at least one positive allergy skin test.[5]

Exclusive breastfeeding was associated with reduced severity of asthma in Kenyan children, but did not affect the age of onset.[6] In 5182 Brazilian children, those not breastfed were more likely to have doctor-diagnosed asthma and exercise-induced wheeze than those breastfed for longer than 6 months.[7] However the effect was only noted in children without a family history of asthma.

By contrast, investigators of several large longitudinal studies report increased risk of atopy and asthma. In a review of the 1958 UK national birth cohort at age 7 years, Kaplan and coworkers[8] showed that 2% of non-breastfed children developed asthma, compared with 4% of those breastfed for 1 month or longer (p<0·0002). In the 1970 UK national birth-cohort, eczema was reported more frequently at age 5 years in those breastfed for longer than 3 months than in those breastfed for shorter periods (p<0·01).[9]

In Tucson children, breastfeeding protected against recurrent wheeze before age 2 years.[10,24] However, the opposite effect was recorded with follow-up beyond 6 years, especially in those genetically at risk.[10] Breastfeeding greatly increased risk of wheezing, and diagnosed asthma in children born to mothers who had asthma. Risk of transient wheeze in early childhood, which is often related to infection[25] seems reduced by breastfeeding, whereas older children whose asthma is more often atopic have increased risk when breastfeeding. Furthermore, in 16 333 Italian children aged 6–7 years, breastfeeding for longer than 6 months was slightly protective against early wheezing, but was a risk factor of borderline significance for late-onset wheezing.[11]

The effect of breastfeeding might depend on the concentration of IgE in the mother. In children of Tucson mothers with IgE concentrations in the lower two tertiles, breastfeeding was associated with reduced IgE in the child, whereas in children of mothers with serum IgE in the highest tertile, breastfeeding was associated with increased IgE in the child.[12] The mechanisms by which breastfeeding increase atopy and asthma in children could include not only maternal transmission of immunological responses, but also the effects of feeding patterns on gut flora,[26–28] and factors related to the hygiene hypthesis.[29]

Sepp and colleagues[26] examined infants in Estonia and Sweden, countries with a low and high prevalence of atopy, respectively, and reported different gut flora in these infants. Lactobacilli and eubacteria were the most frequent bacteria in 1-year-old Estonian children, with clostridia most frequent in Swedish children. Children who developed allergies had less lactobacilli and more coliform and *Staphylococcus aureus* at age 2 years than did those who did not develop allergies. The investigators suggested that a change in gut flora because of westernisation could have contributed to the increase in allergy. Kalliomaki and colleagues[27] investigated infants at high risk of atopic disease, and at 3 weeks recorded fewer bifidobacteria than clostridia at 3 weeks in infants who subsequently showed atopy with at least one positive skin test reaction at age 12 months. Rubaltelli and colleagues[28] showed that bifidobacterium was more frequent in infants who were breastfed than in those who were not

(48% *vs* 15%; p=0·0474), whereas enterococci prevailed in infants who were fed with formula. These findings suggest that breastfeeding might affect the balance of intestinal bacteria, and thereby enhance development of atopy.

The hygiene hypothesis is now widely accepted as an explanation for increase in allergy, and therefore asthma, in westernised countries.[29] Development of mature immune responses after birth with a shift from Th-2 dominance in infants to Th-1 in later childhood might be enhanced by exposures to immune stimulants such as bacteria and endotoxins which might therefore protect against allergies. Results of epidemiological studies[30] showing low prevalences of allergy in children growing up in close contact with animals lend support to this notion. Breastfeeding might reduce the effect of bacteria and endotoxins on the immune system, perhaps by direct reduction of exposure, or by passive transfer of immune responses from the mother, so that the infant does not fully develop mature immune response mechanisms. Rook and Stanford[31] suggested that inadequate microbial stimulation in early life could result in inadequate priming of T-helper cells, leading to a cytokine imbalance (input deprivation syndrome) and a failure to fine tune the T-cell repertoire in relation to epitopes that are cross-reactive between self and micro-organisms (uneducated T-cell regulation syndrome).

Occasionally, infants being breastfed develop colitis or other forms of gut inflammation when formula feeding is introduced,[32] although colitiis can also arise in children who are exclusively breastfed, possibly because of reactions to cow's milk in the mother's diet.[33] Whether addition of cow's milk formula as a supplement to breastfeeding has a greater or lesser effect on the infants' allergic and immunological development than breast-feeding by a mother who herself consumes cow's milk products is not known.

The duration of breastfeeding needed to show an effect seems to be short (as little as 4 weeks in our study and the Tucson study[10]). Results of studies in which the cutpoint used to determine effects of breastfeeding was 3 months or longer might therefore fail to show significant differences between comparison groups.

Studies focusing on outcomes in the first 1–2 years of life sometimes show protective effects not evident with longer follow-up. In the Australian study,[5] the outcome included all wheezing up to age 6, including early transient wheeze, perhaps accounting for the beneficial effect seen. Results of longer-term studies[10,24] consistently show increased atopy and asthma associated with breastfeeding, even after showing protection in the short term.

In our study, most infants were exposed to cow's milk formula in the maternity hospital. However such exposure should not bias our findings, since we recorded more atopy and asthma in those breastfed than in those not. Had the outcome been in the other direction, such an effect would have confounded interpretation. Our analyses comparing outcomes in those known to have had exclusive breastfeeding after discharge versus all others continue to show higher prevalence rates in those exclusively breastfed than those not, even though the comparison group now includes some breastfed children with those not breastfed. These analyses argue against any confounding effect of less than complete exclusivity of breastfeeding. Reported exclusive breastfeeding can be quite inaccurate, as shown in a Swedish study.[34]

Our cohort was born when rates of breastfeeding were low in New Zealand. Rates fell below 50% between 1967 and 1971, but by 1980 had exceeded 80%.[35] It is possible, in view of the calculated population attributable risks for developing atopy and asthma, that some of the increase in atopy and asthma in the past three decades in developed populations could be associated with the increased emphasis on, and prevalence of, breastfeeding.

Breastfeeding could be promoted for many reasons, including optimum nutrition and reduction of risk of infant infections.[36,37] However, the role of breastfeeding in protection of children against atopy and asthma cannot be supported on the basis of the present balance of evidence.

Contributors

M Sears was the director of the asthma study and wrote the report. J Greene managed and analysed the data, supervised by A Willan. E Flannery and J Cowan did the interviews and pulmonary function testing, supervised by D Taylor. R Poulton gave overall direction to the multidisciplinary study. G Herbison did the statistical analysis in the multidisciplinary study.

Conflict of interest statement

None declared.

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Clinical picture

Pseudo vocal paralysis caused by a fish bone

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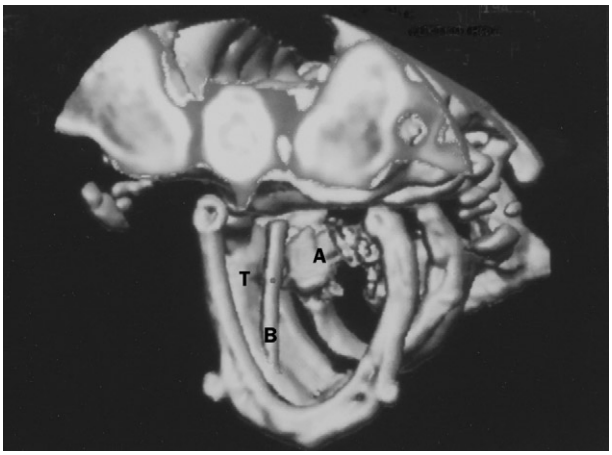
A 62-year-old woman was referred by her otolaryngologist to search for the cause of her right arytenoid oedema. 4 days previously, the patient had felt a bone stick in her throat after eating baked fish. She had not experienced pain or dysphagia. Laryngoscopy showed right vocal cord immobility and a right pyriform sinus narrowed by right arytenoid oedema. Barium fluoroscopy during swallowing showed right vocal cord immobility. 3-dimensional computed tomography (figure) showed a 2·6 cm long fish bone (B) lodged between the right arytenoid cartilage (A) and the thyroid cartilage (T), making it impossible for the arytenoid cartilage to rotate, in turn preventing vocal cord movement and producing pseudo vocal cord paralysis. We removed the bone through a rigid laryngoscope under general anaesthesia. The arytenoid oedema completely resolved and vocal cord movement became symmetrical.



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