

Review article

Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966–2001) on the mode of early feeding in infancy and its impact on later atopic manifestations

Background: Strategies to prevent children from developing allergy have been elaborated on the basis of state-of-the-art reviews of the scientific literature regarding pets and allergies, building dampness and health, and building ventilation and health. A similar multidisciplinary review of infant feeding mode in relation to allergy has not been published previously. Here, the objective is to review the scientific literature regarding the impact of early feeding (breast milk and/or cow's milk and/or formula) on development of atopic disease. The work was performed by a multidisciplinary group of Scandinavian researchers.

Methods: The search in the literature identified 4323 articles that contained at least one of the exposure and health effect terms. A total of 4191 articles were excluded mainly because they did not contain information on both exposure and health effects. Consequently, 132 studies have been scrutinized by this review group.

Results: Of the 132 studies selected, 56 were regarded as conclusive. Several factors contributed to the exclusions. The studies considered conclusive by the review group were categorized according to population and study design.

Conclusions: The review group concluded that breastfeeding seems to protect from the development of atopic disease. The effect appears even stronger in children with atopic heredity. If breast milk is unavailable or insufficient, extensively hydrolysed formulas are preferable to unhydrolysed or partially hydrolysed formulas in terms of the risk of some atopic manifestations.

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The development of atopic disease depends on many variables and reflects the interaction between genetic factors and environmental exposure. Although allergic diseases of the respiratory tract are increasing among children and adolescents (1) the incidence of food allergy appears to be stable (2). Although early exposure to different food proteins are most likely to be involved in

the pathogenesis of allergy, breastfeeding has been claimed to afford protection against allergy. However, uncertainties remain as to whether breast milk in fact does prevent or reduce the incidence of allergic disease. Another issue of relevance to infant feeding is whether hydrolysis of the proteins in formulas reduces the risk of development of allergy.

Heredity plays an important role in the development of allergic disease. It is well documented that a child with a family history of atopy runs a significantly increased risk of becoming allergic (3). However, most children with asthma do not belong to such high-risk groups (4). Therefore, it is important to evaluate the impact of feeding mode both in high-risk and unselected populations. Both intervention and nonintervention studies should be considered.

Strategies to prevent children from developing allergy have been elaborated on the basis of state-of-the-art reviews of the scientific literature regarding e.g. pets and allergies, building dampness and health, and building ventilation and health (5–8). A similar multidisciplinary review of infant feeding mode in relation to allergy has not been published previously.

Here, the objective is to review the scientific literature regarding the impact of early feeding (breast milk and/or cow's milk and/or formula) on development of atopic disease. The work was performed by a multidisciplinary group of Scandinavian researchers.

The issues selected for evaluation were:

- Does breastfeeding protect against development of atopic disease and other allergic manifestations?
- If so, how long should breastfeeding be continued?
- Are there differences between feeding with hypoallergenic formulas/hydrolysate and cow's milk formulas regarding the development of atopic disease?
- Are conclusions different for high-risk and unselected populations?
- Is early introduction of cow's milk a risk factor in the development of cow's milk allergy?

Method

The National Institute of Public Health in Sweden initiated this multidisciplinary review. The design was influenced by earlier works (5–8). A planning seminar was held to reach an agreement on the composition of the group of researchers and on guidelines for the work. Scandinavian scientists with experience in evaluating scientific literature and with expert knowledge in the different areas involved were invited. These scientists had documented expertise in at least one of the following disciplines: nutrition, paediatrics, immunology, allergology, epidemiology, microbiology, or occupational and environmental medicine.

A literature search in MEDLINE (articles published prior to October 2001) was carried out. The search profile was:

Exposures: Breast feeding, breast-feeding, breast milk, breast-milk, human milk, cows milk, cow's milk, formula, infant feeding, formula feeding and hydrolysate.

Health effects: Allergy, atopy, atopic disease, sensitisation, sensitization, asthma, astma, bronchial asthma, eczema, atopic dermatitis, rhinoconjunctivitis, food allergy, allergic rhinitis, wheezing, wheeze, hay fever, hayfever, neurodermatitis and eczematous.

The literature search identified 4323 articles that contained at least one of the exposure and health effect terms. Of these, 4191 articles were excluded for one or more of the following reasons:

(i) lacked data on exposures or health effects, (ii) were reviews, (iii) were studies performed on single cases, (iv) conducted in developing countries, (v) were experimental animal studies, and (vi) were written in a language other than English or Scandinavian. Consequently, 132 studies have been scrutinized by this review group. The selected articles were sent in advance at random among the reviewers. During the review seminars, all articles were distributed to all participants. The reviewer presented each article with comments from an assessor, after which the articles were discussed and evaluated by the entire panel on the basis of the following criteria:

- Are exposure and health effects recorded and described in a relevant manner, for instance with regard to time of exposure (e.g. infancy, childhood years, actual exposure)?
- Is the selection of the investigated individuals satisfactory?
- Is the statistical analysis satisfactory, including control for possible confounding and effect-modifying factors?

Of the 132 evaluated studies, 12 articles were excluded because they did not fulfil the relevant criteria. Furthermore, 64 articles were classified as 'noninformative' and/or 'inconclusive'. The term 'noninformative' indicates that the article lacks essential information concerning exposure or health effects or that the analysis did not consider confounding factors. The term 'inconclusive' indicates that data processing or reporting made it impossible to draw conclusions concerning the relationship between exposure to 'breast-milk or formula' and health effects. It should be noted that many of the studies that were excluded had been designed for other purposes than to investigate the association between breastfeeding and allergic disease. Ten articles of the inconclusive category were classified as background articles because they were considered to be of interest to this review as complementary reading. Fifty-six studies were considered conclusive for this review work.

During the review seminars, the author or co-author of an article under evaluation had to leave the room during the discussion. The group agreed on the position taken regarding each article, concerning both its relevance to the issues at hand, and the conclusions that could be drawn. A proposal was then made for a joint consensus statement concerning all scrutinized studies. At final seminars a smaller number of important articles were again discussed, and the consensus statement was then adopted.

Results

Dietary factors

A number of different definitions of breastfeeding had been used in the articles; 'exclusive breastfeeding', 'partial breastfeeding' or 'any breastfeeding'. The criterion for exclusive breastfeeding given by WHO is that no other food or drink is given except for breast milk, not even water. Ten of the studies had used 'any breastfeeding' for weeks or months as an exposure index and could not be judged on the same basis as the other studies because information about complementary feeding was lacking.

The formulas used in intervention studies were mainly cow's milk or soy formulas and/or extensively or partially hydrolysed cow milk-based formulas. The formulas were based on whey or casein or a mixture of both. In some earlier studies, human bank milk had been used to feed the infants.

Health effects

To minimize the risk of bias, the ideal study should include blinded independent observations of the health effects and the exposure to relevant dietary variables. Objective tests of health effects, such as results of serum tests, skin-prick tests, inflammatory markers and lung function tests are not influenced by recall bias. In this review, the results of 34 studies were based on clinical examinations. Symptoms were mostly recorded in a subjective manner, and the only measure of health effects was sometimes derived from self-report questionnaires.

Atopic heredity

The terms 'atopic heredity' and 'high-risk children' for development of allergic disease are used differently by various authors. Many studies had selected children with a family history of atopy, which was mainly defined as one or both parents or one parent and/or one sibling having asthma, allergic rhinitis, hay fever or atopic dermatitis. Information about atopic heredity had been collected by interviews at the clinic (9–12), through questionnaires (13), from medical records (14) and in one study been confirmed by serum tests (15).

Categories of studies

The studies were divided into one or more of four categories depending on the type of data for exposure and population group (Tables 1–4).

Studies of breastfeeding and atopic manifestations in cross-sectional populations. This group included 26 studies (10, 16–40) (Table 1). In the prospective studies, the follow-up time ranged from 3 months to 17 years. About half of the studies ($n = 14$) reported that breastfeeding reduced the risk of asthma, wheezing, atopic dermatitis, and cow's milk allergy. Three of four studies that had examined 'any breastfeeding' indicated a decreased risk of recurrent wheezing, asthma and atopic dermatitis in an cross-sectional population. The protective effect was reported to persist for 5 years or more (18, 30, 36, 39), even up to 17 years (23), and increased with the duration of breastfeeding up to at least 4 months. In two studies, breastfeeding was reported as a risk factor, in one for eczema up to the age of 5 years (18), and in one retrospective study, for 'hay fever' at the age of 11–16 years (37).

In six studies, there was no effect of breastfeeding on the evaluated health outcome. Two investigations dealt with asthma (17, 19), two with cow's milk allergy (22, 33) and two with atopic dermatitis (26, 31).

Six studies are listed separately in Table 1 because they have a long recall time, but are otherwise of adequate design (35–40). Five of them had studied asthma and wheezing and all reported protective effect of breastfeeding.

Other studies in this category were considered to be inconclusive or noninformative because of a long recall time with considerable risk of bias, weak measures of health effects, or undefined feeding exposure. Also studies including other interventions besides dietary restrictions were deemed to be noninformative or inconclusive (Table 5).

Studies of breastfeeding and atopic manifestations in children with atopic heredity. In this group, 19 studies were identified as conclusive (9–16, 18, 41–50) (Table 2). Breast milk seemed to provide a protective effect up to at least 1–3 years, except in one study (43) where the follow-up time was only 6 months. Moore et al. (45) reported a protective effect against eczema at the age 3 months (first examination), but not later on (examined up to 12 months). Gruskay et al. (10) published a 15-year follow-up study in which a positive effect of breastfeeding (not described as exclusive) appeared in the offspring of allergic families. Saarinen et al. (16) noted a protective effect of exclusive breastfeeding for 6 months in children examined up to 3 years of age regarding wheezing and atopic dermatitis. However, this material contained data on self-selected groups, which might have introduced a bias that was not taken into account.

There seemed to be an overall protective effect of breastfeeding in infants with atopic heredity. Only one study (13), in which the data analysis was not described in sufficient detail, reported a negative effect.

Studies of formula feeding and atopic manifestations in children with atopic heredity. The 14 studies in this category were of a prospective design (10, 12, 15, 33, 43, 47–55) (Table 3). All studies replacing cow's milk formula with extensively hydrolysed whey or casein formula reported a protective effect of hydrolysate. There was no apparent trend in the reviewed studies that one hydrolysate formula is better than the other (e.g. whey vs casein). Almost all studies in this category were regarded to be convincing because of their prospective design and well-defined health effects based on clinical examinations.

Studies of cow's milk exposure and development of atopic manifestations. Four of seven studies that were identified in this category had studied the effect of cow's milk given on the first day (or first few days) of neonatal care (56–59) (Table 4). The three of four studies with a good confounding control all showed a protective effect. The studies of Lindfors et al. (60, 61) reported a significantly lower frequency of allergic symptoms after 5 years in a subgroup with a family history of allergy that had been fed cow's milk formula early. Saarinen et al. (33) reported that feeding with cow's milk during the first days of life increased the risk of cow's milk allergy, but exclusive breastfeeding did not abolish the risk.

Table 1. Association between breastfeeding and atopic manifestations in unselected populations

Study, country	Study design	n	Exposure time	Exclusive BF described	Follow-up (years)	Confounder control (yes/no)	Health effects measured	Conclusion, Effect of diet
Prospective studies								
Saarinen et al. Fin (16)	Cohort	256	≥6 months	Yes	3	No	AD; wheezing, FA	+, wheeze, AD
Fergusson et al. NZ (17)	Cohort	1110	4 months	Yes	4	Yes	Asthma	0
Pratt UK (18)	Cohort	198	3 months	Yes	5	No	Eczema	–
Horwood et al. NZ (19)	Cohort	1056	4 months	Yes	6	No	Asthma	0
Vandenplas and Sacre Bel (20)	Cohort	943	3 months	No	0.25	No	CMA	+, CMA
Savilahti et al. Fin (21)	Cohort	183	<3, >9 months	No	2	Yes	Eczema, wheeze	+
Lucas et al. UK (22)	Cohort, randomised	777 preterm	Initial diet bank milk	No	1.5	No	AD, asthma, wheeze, allergic reactions to food	0, CMA 0, Atopic disease +, AD
Saarinen and Kajosaari Fin (23)	Cohort	150	≥6 months	Yes	17	No	AD, resp. allergy, FA	+, Resp. allergy
Wright et al. USA (24)	Cohort	988	Any BF	No	6	Yes	Recurrent wheeze	+, Nonatopics 0, In atopics
Elder et al. NZ (25)	Cohort	525 preterm	>1 months	No	1	Yes	Recurrent wheeze	+
Berth-Jones et al. UK (26)	Cohort	499	4 months	Yes	1		AD	0
Baker et al. UK (27)	Cohort	8501	0–3 months, >3 months	No	0.5	Yes	Wheeze	+, increases with >3 m BF
Tariq et al. UK (28)	Cohort	1218	3 months	Yes	4	Yes	Eczema, asthma, FA, rhinitis	++, Asthma
Wilson et al. UK (29)	Cohort	545	>3 months	Yes	7	Yes	Asthma, wheeze	+, No protection from partial BF
Oddy et al. Aust (30)	Cohort	2187	≥4 months	Yes	6	Yes	Asthma, wheeze	++, Asthma, wheeze
Harris et al. UK (31)	Cohort	624	Any BF	No	2	Yes	Eczema	0
Wright et al. USA (32)	Cohort	1043	<4 months, >4 months	Yes	13	Yes	Asthma, recurrent wheeze	+, recurrent wheeze at age 2 years, but no effect at age 6 years –, for atopic children with maternal asthma at age 6 years
Intervention studies								
Gruskay et al. USA (10)	Prospective, intervention	908	4 months	No	15	Yes	AD, asthma, AR	+, AD and asthma
Saarinen et al. Fin (33)	Prospective, cohort intervention	6209	2 months	No	1.5–3	Yes	CMA	0
Kramer et al. Can (34)	Prospective Intervention, cohort	16491	Any BF	No	1	Yes	AD, resp tract disease	+, AD
Retrospective studies								
Wright et al. UK (35)	Both retrospective and prospective cohort	1006	Any BF	No	1	Yes	Wheeze	+, up to 4 months but not later
Lewis et al. UK (36)	Retrospective, cohort	15712	0, <1, 1–3, >3 months	No	5 (16)	Yes	Wheeze ever	+, up to 5 years
Strachan et al. UK (37)	Retrospective, cohort	11765	1 month	No	11–16	Some	Hay fever	–
Raisler et al. USA (38)	Retrospective, cohort	7092	6 months	Yes	0.5	Yes	Wheeze	(+)
Ronmark et al. Swe (39)	Cohort retrospective	3431	3 months	No	8	Yes	Asthma	+, Nonatopic asthma
Haby et al. Aust (40)	Retrospective cross-sectional	974 (650)	Any BF	No	3–5	Yes	Asthma	+

+, Protective effect of breastfeeding; ++, strong protection; (+) suggestive of protective effect; 0, no effect; –, breastfeeding is nonprotective or increases risk of atopy; (–) suggestive of no protective effect.

AD, atopic dermatitis; FA food allergy; CMA, cow's milk allergy; AR, atopic rhinitis; BF, breastfeeding.

Table 2. Association between breastfeeding and atopic manifestations in children with atopic heredity

Study, country	Study design	n	Exposure time	Exclusive BF described	Follow-up (years)	Confounder control (Y/N)	Health effects measured	Conclusion, Effect of diet
Prospective studies								
Chandra Can (41)	Cohort	74	≥6 weeks	Yes	2	No	Atopic eczema, recurrent wheeze	(+)
Pratt UK (18)	Cohort	198	3 months	Yes	5	No	Eczema	+
Geller-Bernstein et al. Isr (42)	Cohort	80	3 months	Yes	4	No	Persistent wheeze	+
Burr et al. UK (9)	Randomized	483	Any BF 6 months	No	1	Yes	Eczema, wheeze	(+), any BF, wheeze
Chandra et al. Can (43)	Prospective	216	≥4 months	Yes	0.5	Yes	Atopic eczema, rhinitis, wheeze	(+)
Bruno et al. It (15)	Prospective	174	6 months	Yes	4	No	AD, asthma, AR, FA	0
Gustafsson et al. Swe (44)	Prospective and retrospective	94	Any BF	No	7	Yes	Allergic symptoms	(0)
Wetzig et al. Ger (13)	Cohort	475	5 months	Yes	2	No	Eczema, egg sensitisation	+, at age 1 year; 0, at age 2 years
Intervention studies								
Saarinén et al. Fin (16)	Cohort	256	≥6 months	Yes	3	No	AD; wheeze, FA	+, Wheeze and AD
Gruskay USA (10)	Intervention	328	4 months	No	15	Yes	AD, asthma, AR	+
Moore et al. UK (45)	Intervention	475	3 months	Yes	1	No	AD	+, at 3 months but not at 6,12 months
Merrett et al. UK (11)	Intervention	487	Any BF	No	1	No	AD, wheeze ever	+, Wheeze
Miskelly et al. UK (46)	Intervention	487	Any BF	No	1	No	Wheeze	(+)
Chandra and Hamed Can (47)	Prospective, cohort, intervention	263	≥4 months	Yes	1.5	No	Atopic eczema, recurrent wheeze, rhinitis	+, Atopic eczema
Burr et al. UK (48)	Randomized, intervention	453	Any BF	No	7	Yes	AD; asthma, wheeze, AR	(+), Any BF, wheeze
Halken et al. Den (49)	Intervention	154 + 75	6 months	Yes	1.5	Yes	CMA	+
Halken et al. Den (53)	Intervention	162	6 months	Yes	1.5	No	AD, recurrent wheeze, FA	+, Wheeze, AD, FA
Chandra Can (50)	Intervention	288	≥4 months	Yes	5	No	Atopic eczema, asthma, FA	++
Oldaeus et al. Swe (12)	Cohort, intervention	155	≥4 months	Yes	1.5	Yes	AD, asthma, AR, GI allergy	++
Retrospective studies								
McConnochie et al. USA (14)	Retrospective	223	6 months	Yes	6–10	No	Wheeze	+

+, Protective effect of breastfeeding; ++, strong protection; (+) suggestive of protective effect; 0, no effect; –, breastfeeding is nonprotective or increases risk of atopy; (–) suggestive of no protective effect.

AD, atopic dermatitis; FA, food allergy; CMA, cow's milk allergy; AR, atopic rhinitis; BF, breastfeeding; GI, gastrointestinal.

Discussion

According to the majority of the studies examined in this multidisciplinary review, breastfeeding seems to protect against development of allergic disease, especially among children with an atopic heredity. Some studies were more convincing than the others, mainly because of sufficient duration and stringent definition of exclusive of breastfeeding. Most published studies investigating the association between breastfeeding and atopic disease suffered from methodological insufficiencies. Thus, of 132 eligible studies < 50 % were considered conclusive. Many of the excluded studies had a retrospective design, which increased the risk of recall bias. Recall of feeding mode during infancy is a major methodological problem according to Huttly and co-workers (62); as many as 25% of 1000 studied mothers misclassified the duration of breastfeeding after 1 year.

Collecting data on infant feeding demands well-characterized and validated questionnaires. A potential source of misclassification of self-reported data regarding exclusivity of breastfeeding is the possibility that milk supplements had been given to the newborn in the maternity ward without the mother's knowledge.

Study design

The randomized controlled trial provides, mainly the best scientific design on which to base the evaluation of cause-effect relationships but random allocation to either breastfeeding or nonbreastfeeding is clearly unethical. However, one study employed cluster randomization to a programme aiming at increasing breastfeeding at community level (34). Randomization of the subjects included is important for a good study design. Breastfeeding and bottle-feeding are not merely two

Table 3. Association between formula feeding and atopic manifestations in children with atopic heredity

Study, country	Study design	n	Exposure time	Follow-up (years)	Confounder control Y/N	Health effects measured	Conclusion, Effect of diet
Prospective studies							
Gruskay USA (10)	Intervention	328	4 months	15	Yes	AD, asthma, AR	0, CMF or soy F
Chandra et al. Can (43)	Intervention	216	≥4 months	0.5	Yes	Atopic eczema, wheezing, rhinitis, GI symptoms	++, eHF vs soy F and CMF
Chandra and Hamed Can (47)	Cohort	263	≥4 months	1.5	No	Atopic eczema, recurrent wheezing, rhinitis, GI	+, eHF (whey) vs soy F and CMF on atopic eczema
Mallet and Henocq Fr (51)	Prospective	177	4 months	4	No	Eczema, asthma	(+), eHF (casein) for eczema; 0, for asthma
Vandenplas et al. Bel (52)	Intervention, randomized	67	6 months	1	No	Eczema, wheeze, urticaria, cronic rhinitis	+, pHF (whey) to CMF
Bruno et al. It (15)	Prospective	174	6 months	4	No	AD, asthma, AR, FA	(+), soy F vs CMF
Burr et al. UK (48)	Intervention, randomized	453	4 months	7	Yes	AD, asthma, wheeze, all rhinitis	0, CM or soy F
Halken et al. Den (49)	Intervention	154 + 75	6 months	1.5	Yes	CMPA	+, eHF (whey and casein) but no differences between them; ++, BM and eHF and no solids
Halken et al. Den (53)	Intervention, cohort	172	6 months	1.5	No	AD, wheeze, CMA,	+, eHF (whey and casein) but no differences between them (CMA)
Vandenplas et al. Bel (54)	Intervention, randomized	58	6 months	5	No	Eczema, wheeze, urticaria, cronic rhinitis	+, pHF vs CMF up to 1 year
Chandra Can (50)	Intervention	216	≥4 months	5	No	Atopic eczema, asthma,	++, pHF (whey) vs CMF
Oldaeus et al. Swe (12)	Cohort, intervention	155	≥4 months	1.5	Yes	AD, asthma, AR,, GI allergy	++, eHF (casein) vs pHF and CMF
Saarinén et al. Fin (33)	Cohort	6209	4 days	3	Yes	CMPA	+, eHF
Halken et al. Den (55)	Intervention, randomized	478 compl.	4 months	1.5	Yes	CMA	+, eHF (casein or whey) –, pHF

+, Protective effect of diet; ++, strong protection; (+) suggestive effect of diet; 0, no effect; –, nonprotective effect of diet; (–) suggestive no effect of diet.

bm, breast milk; eHF, extensively hydrolysed formula; pHF, partially hydrolysed formula; CMPA, cow's milk protein allergy; CMA, cow's milk allergy; CM, cow's milk; soy F, soy milk formula; AD, atopic dermatitis; AR, atopic rhinitis; GI, gastrointestinal; FA, food allergy.

Table 4. Association between early exposure to cow's and atopic manifestations in children

Study, country	Study design	n	Exposure time	Follow-up (years)	Confounder control (Y/N)	Health effects measured	Conclusion, Effect of diet
Prospective studies							
Höst et al. Den (57)	Cohort	1749	CMF first 5 days	1	Yes	CMA	++, CMF
de Jong et al. (59)	Intervention	1533	CM first 3 days	1	No	Atopy	0
Lindfors and Enochsson Swe (60)	Intervention	216	CMF first days	1.5	No	CMPA	(–)
Höst A Den (58)	Cohort	1749	CMF first 5 days	1	Yes	CMA	++, CMF
Lindfors et al. Swe (61)	Prospective/retrospective intervention	183	CMF first days	4–6	No	Obvious and probable allergy	+, up to age 5 years
Saarinén et al. Fin (33)	Cohort	6209	CMF	3	Yes	CMPA	+, CMF
Retrospective studies							
Stintzing and Zetterstrom Swe (56)	Retrospective	25 + 52	CM first week	1	No	CMPA	+, CM

+, Risk from exposure; ++, strong risk; 0, no effect; –, no risk from exposure; (–), suggestive.

CM, cow's milk; CMF, cow's milk formula; CMA, cow's milk allergy; CMPA, cow's milk protein allergy.

different kinds of alimentation. The reasons for selecting one over the other depend on demographic, socio-economic, educational, ethnic, genetic, cultural and psychological factors (63). A particular problem is that mothers who intend to breastfeed might be the ones whose children run the largest risk of developing allergic disease (18). Such a selection bias could mask the

protective effect of breastfeeding because genetic factors would particularly predispose these children to allergic disease anyway.

Another well-known problem is the association between a short period of breastfeeding, low socio-economic status and a relatively poor education (64). Such variables might confound the result and should be

Table 5. Studies considered inconclusive or noninformative for the review

Author	Comments
Aberg N, et al. Allergic diseases in Swedish school children. <i>Acta Paediatr Scand</i> 1989;78(2):246–52.	Inconclusive
Arshad SH, et al. Effect of allergen avoidance on development of allergic disorders in infancy. <i>Lancet</i> 1992;339(8808):1493–7.	Inconclusive
Astarita C, et al. An epidemiological study of atopy in children. <i>Clin Allergy</i> 1988;18(4):341–50.	Inconclusive
Backer V, et al. Allergy and bronchial reactivity in children and adolescents from Copenhagen. <i>Ugeskr Laeger</i> 1993; 155(49):3982–6.	Noninformative, Inconclusive
Baker D, et al. Differences between infants and adults in the social aetiology of wheeze. The ALSPAC Study Team. <i>Avon Longitudinal Study of Pregnancy and Childhood. J Epidemiol Community Health</i> 1999;53(10):636–42.	Inconclusive
Bottcher et al. Cytokines in breast milk from allergic and nonallergic mothers. <i>Pediatr Res</i> 2000;47(1):157–62.	Background article
Buisseret PD. Common manifestations of cow's milk allergy in children. <i>Lancet</i> 1978;1(8059):304–5.	Inconclusive
Burr ML, et al. The development of allergy in high-risk children. <i>Clin Exp Allergy</i> 1997;27(11):1247–53.	Noninformative
Businco L, et al. Prevention of atopic disease in 'at-risk newborns' by prolonged breast-feeding. <i>Ann Allergy</i> 1983;51(2 Pt 2):296–9.	Noninformative
Businco L, et al. Predictive value of cord blood IgE levels in 'at-risk' newborn babies and influence of type of feeding. <i>Clin Allergy</i> 1983;13(6):503–8.	Noninformative
Butland BK, et al. Investigation into the increase in hay fever and eczema at age 16 observed between the 1958 and 1970 British birth cohorts. <i>Bmj</i> 1997;315(7110):717–21.	Inconclusive
Cogswell JJ, et al. Parental smoking, breast feeding, and respiratory infection in development of allergic diseases. <i>Arch Dis Child</i> 1987;62(4):338–44.	Inconclusive
de Martino M, et al. Food allergy in preterm infants fed human milk. <i>Biol Neonate</i> 1989;56(6):301–5.	Noninformative, Inconclusive
Duchen K, et al. Human milk polyunsaturated long-chain fatty acids and secretory immunoglobulin A antibodies and early childhood allergy. <i>Pediatr Allergy Immunol</i> 2000;11(1):29–39.	Background article
Exl BM, et al. Improved general health status in an unselected infant population following an allergen-reduced dietary intervention programme: the Zuff- study-programme. Part II: infant growth and health status to age 6 months. <i>ZUg-FrauenFeld. Eur J Nutr</i> 2000;39(4):145–56.	Noninformative
Fergusson DM, et al. Eczema and infant diet. <i>Clin Allergy</i> 1981;11(4):325–31.	Inconclusive
Fergusson DM, et al. Risk factors in childhood eczema. <i>J Epidemiol Community Health</i> 1982;36(2):118–22.	Noninformative, Inconclusive
Fukushima Y, et al. Preventive effect of whey hydrolysate formulas for mothers and infants against allergy development in infants for the first 2 years. <i>J Nutr Sci Vitaminol (Tokyo)</i> 1997;43(3):397–411.	Inconclusive
Gordon RR, et al. Immunoglobulin E and the eczema-asthma syndrome in early childhood. <i>Lancet</i> 1982;1(8263):72–4.	Noninformative
Gustafsson D, et al. Risk of developing atopic disease after early feeding with cows' milk based formula. <i>Arch Dis Child</i> 1992;67(8):1008–10.	Inconclusive
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Halpern SR, et al. Development of childhood allergy in infants fed breast, soy, or cow milk. <i>J Allergy Clin Immunol</i> 1973;51(3):139–51.	Noninformative, Inconclusive
Hide DW, et al. Effect of allergen avoidance in infancy on allergic manifestations at age two years. <i>J Allergy Clin Immunol</i> 1994;93(5):842–6.	Noninformative
Hide DW, et al. Allergen avoidance in infancy and allergy at 4 years of age. <i>Allergy</i> 1996;51(2):89–93.	Noninformative
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Johnstone DE, et al. Dietary prophylaxis of allergic disease in children. <i>N Engl J Med</i> 1966;274(13):715–9.	Inconclusive
Juvonen P, et al. Development of immunoglobulin G and immunoglobulin E antibodies to cow's milk proteins and ovalbumin after a temporary neonatal exposure to hydrolyzed and whole cow's milk proteins. <i>Pediatr Allergy Immunol</i> 1999;10(3):191–8.	Background article
Kalliomaki M, et al. Transforming growth factor-beta in breast milk: a potential regulator of atopic disease at an early age. <i>J Allergy Clin Immunol</i> 1999;104(6):1251–7.	Background article
Kaplan MS, et al. Immunoglobulin E to cow's-milk protein in breast-fed atopic children. <i>J Allergy Clin Immunol</i> 1979;64(2):122–6.	Noninformative
Kaufman HS, et al. The development of allergy in infants of allergic parents: a prospective study concerning the role of heredity. <i>Ann Allergy</i> 1976;37(6):410–5.	Inconclusive
Kay J, et al. The prevalence of childhood atopic eczema in a general population. <i>J Am Acad Dermatol</i> 1994;30(1):35–9.	Inconclusive
Kjellman NI, et al. Soy versus cow's milk in infants with a biparental history of atopic disease: development of atopic disease and immunoglobulins from birth to 4 years of age. <i>Clin Allergy</i> 1979;9(4):347–58.	Noninformative
Kramer MS, et al. Do breast-feeding and delayed introduction of solid foods protect against subsequent atopic eczema? <i>J Pediatr</i> 1981;98(4):546–50.	Inconclusive
Lopez N, et al. Genetic and environmental influences on atopic immune response in early life. <i>J Investig Allergol Clin Immunol</i> 1999;9(6):392–8.	Inconclusive
Luoma R. Environmental allergens and morbidity in atopic and non-atopic families. <i>Acta Paediatr Scand</i> 1984;73(4):448–53.	Noninformative
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Table 5. Continued

Author	Comments
Machtinger S, et al. Cow's milk allergy in breast-fed infants: the role of allergen and maternal secretory IgA antibody. <i>J Allergy Clin Immunol</i> 1986;77(2):341–7.	Background article
Midwinter RE, et al. Infant feeding and atopy. <i>Arch Dis Child</i> 1987;62(9):965–7.	Inconclusive
Mok JY, et al. Outcome of acute lower respiratory tract infection in infants: preliminary report of seven-year follow-up study. <i>Br Med J (Clin Res Ed)</i> 1982;285(6338):333–7.	Noninformative
Nafstad P, et al. Breastfeeding, maternal smoking and lower respiratory tract infections. <i>Eur Respir J</i> 1996;9(12):2623–9.	Background article
Nakamura Y, et al. Relationship between breast milk feeding and atopic dermatitis in children. <i>J Epidemiol</i> 2000;10(2):74–8.	Inconclusive
Neuspiel DR, et al. Parental smoking and post-infancy wheezing in children: a prospective cohort study. <i>Am J Public Health</i> 1989;79(2):168–71.	Noninformative, inconclusive
Odelram H, et al. Whey hydrolysate compared with cow's milk-based formula for weaning at about 6 months of age in high allergy-risk infants: effects on atopic disease and sensitization. <i>Allergy</i> 1996;51(3):192–5.	Inconclusive
Ponsonby AL, et al. Cross sectional study of the relation between sibling number and asthma, hay fever, and eczema. <i>Arch Dis Child</i> 1998;79(4):328–33.	Inconclusive
Porro E, et al. Early wheezing and breast feeding. <i>J Asthma</i> 1993;30(1):23–8.	Noninformative, Inconclusive
Poysa L, et al. Atopy in children with and without a family history of atopy. I. Clinical manifestations, with special reference to diet in infancy. <i>Acta Paediatr Scand</i> 1989;78(6):896–901.	Inconclusive
Poysa L, et al. Atopy in childhood and diet in infancy. A nine-year follow-up study. I. Clinical manifestations. <i>Allergy Proc</i> 1991;12(2):107–11.	Inconclusive
Rusconi F, et al. Risk factors for early, persistent, and late-onset wheezing in young children. SIDRIA Collaborative Group. <i>Am J Respir Crit Care Med</i> 1999;160(5 Pt 1):1617–22.	Inconclusive
Saarienen UM, et al. Serum IgE in healthy infants fed breast milk or cow's milk-based formulas. <i>Clin Allergy</i> 1979;9(4):339–5.	Background article
Saarienen UM, et al. Birch pollen allergy in children. Role of milk feeding during the first birch season of life. <i>Allergy</i> 1982;37(5):345–50.	Noninformative, Inconclusive
Saarienen KM, et al. Infant feeding patterns affect the subsequent immunological features in cow's milk allergy. <i>Clin Exp Allergy</i> 2000;30(3):400–6.	Background article
Savilahti E, et al. Early feeding of preterm infants and allergic symptoms during childhood. <i>Acta Paediatr</i> 1993;82(4):340–4.	Inconclusive
Schwartz J, et al. Predictors of asthma and persistent wheeze in a national sample of children in the United States. Association with social class, perinatal events, and race. <i>Am Rev Respir Dis</i> 1990;142(3):555–62.	Noninformative
Selcuk ZT, et al. The prevalence of allergic diseases in primary school children in Edirne, Turkey. <i>Clin Exp Allergy</i> 1997;27(3):262–9.	Inconclusive
Shohet L, et al. Breast feeding as prophylaxis for atopic eczema: a controlled study of 368 cases. <i>Acta Paediatr Hung</i> 1985;26(1):35–9.	Inconclusive
Stahlberg MR. Breast feeding, cow milk feeding, and allergy. <i>Allergy</i> 1985;40(8):612–5.	Inconclusive
Strachan DP, et al. Childhood antecedents of allergic sensitization in young British adults. <i>J Allergy Clin Immunol</i> 1997;99(1 Pt 1):6–12.	Inconclusive
Takemura Y, et al. Relation between breastfeeding and the prevalence of asthma: the Tokorozawa Childhood Asthma and Pollinosis Study. <i>Am J Epidemiol</i> 2001;154(2):115–9.	Inconclusive
Taylor B, et al. Breast feeding, eczema, asthma, and hayfever. <i>J Epidemiol Community Health</i> 1983;37(2):95–9.	Inconclusive
Van Asperen PP, et al. Relationship of diet in the development of atopy in infancy. <i>Clin Allergy</i> 1984;14(6):525–32.	Inconclusive
Wittig HJ, et al. Risk factors for the development of allergic disease: analysis of 2,190 patient records. <i>Ann Allergy</i> 1978;41(2):84–8.	Inconclusive
Zeiger RS, et al. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. <i>J Allergy Clin Immunol</i> 1989;84(1):72–89.	Noninformative, Inconclusive

considered in all studies of early infant feeding. Smoking and breastfeeding have been dealt with in two inconclusive studies, which were classified as background articles. Rylander et al. (65) reported that urinary cotinine excretion was negatively associated with breastfeeding in children of smoking mothers but there was no such association in children of nonsmoking mothers. The risk of wheezing bronchitis was reported to increase both in relation to parental smoking and urinary cotinine concentration. Nafstad et al. (66) found a protective effect of long-term breastfeeding on the risk of lower respiratory tract infection during the first year of life. The results suggested that the protective effect was strongest in children exposed to environmental tobacco smoke.

Assessment of dietary intake by experienced health personnel unaware of health effects, provides a method to reduce information bias. It should be stressed that

the reliability of epidemiological data will be enhanced by the use of validated questionnaires instead of data from many different physicians because the latter information might decrease the consistency of the study (67).

Studies acknowledging financial support from the food industry should be particularly scrutinized for a possible reporting bias favouring any commercial formula product used for infant feeding. This was also taken into consideration during our review.

The protective effect of breastfeeding may be attributed to several possible mechanisms such as decreased exposure to exogenous antigens, protection against infections, beneficial development of the gastrointestinal flora or immunomodulatory factors (68). In conclusion, the review panel agreed on the following consensus statements based on all relevant articles evaluated.

For all children

- 1 Exclusive breastfeeding reduces the risk of asthma. (Note: The definition of asthma is referred to the author's definition.)
- 2 Any breastfeeding decreases the risk of recurrent wheezing. (Note: Recurrent wheezing is mainly caused by viral infection.)
- 3 These protective effects increase with the duration of breastfeeding, up to at least 4 months.
- 4 The protective effects seem to persist at least during the first decade of life.
- 5 Breastfeeding protects against the development of atopic dermatitis.
- 6 Exposure to small doses of cow's milk during the first days of life appears to increase the risk of cow's milk allergy but does not affect the incidence of atopic diseases later on.

In children with atopic heredity

- 1 The beneficial effects of breastfeeding seen in all children are particularly strong in infants with atopic heredity.
- 2 In addition, breastfeeding protects against cow's milk allergy.
- 3 When breastfeeding is insufficient, extensively hydrolysed cow's milk-based formula, as opposed to cow's milk formula, reduces the risk of cow's milk allergy.
- 4 Extensively hydrolysed cow's milk formulas also somewhat reduces the risk to develop atopic dermatitis and asthma or other wheezing.

- 5 Partially hydrolysed cow's formula also reduces this risk, but to a lesser degree.

Addendum after completion of the study

Recent reports have suggested that long term breastfeeding by an asthmatic mother may, in a limited group of children, rather increase the risk of getting asthma (32, 69). Furthermore Bergmann et al. (70) showed in a large study from Germany that for each additional week of breastfeeding of children with atopic parents the risk of atopic excema increased. On the other hand, a large study by Oddy et al. (71) from Australia could confirm a protective effect by breastfeeding not considerably altered by adjusting for atopy, infections or maternal asthma. An explanation for these regional differences may relate to the fact that maternal diets and milk contain lower ratios of n6/n3 fatty acids in Australia than in USA or Germany (72).

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