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PEDIATRIC ALLERGY AND IMMUNOLOGY

Dietary prevention of allergic diseases in infants and small children

Part III: Critical review of published peer-reviewed observational and interventional studies and final recommendations*

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The role of primary prevention of allergic diseases has been a matter of debate for the last 40 years. In order to shed some light on this issue, a group of experts of the Section of Pediatrics EAACI reviewed critically the existing literature on the subject. An analysis of published peer-reviewed observational and interventional studies was performed following the statements of evidence as defined by WHO. The results of the analysis indicate that breastfeeding is highly recommended for all infants irrespective of atopic heredity. A dietary regimen is unequivocally effective in the prevention of allergic diseases in high-risk children. In these patients breastfeeding combined with avoidance of solid food and cow's milk for at least 4–6 months is the most effective preventive regimen. In the absence of breast milk, formulas with documented reduced allergenicity for at least 4–6 months should be used.

*An extensive review by an expert group set up by the Section on Pediatrics, European Academy of Allergology and Clinical Immunology

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Observational and interventional studies

Only studies published in peer-reviewed scientific journals are included in the following review. In observational and interventional studies reported here, most authors have not used the nomenclature as proposed by the task force on Nomenclature within EAACI (1) and recently revised by WAO (2). Therefore, in case the terms have not been used in agreement with this position paper we use single citation marks as indicated in the list of definitions (see Appendix 1).

Tables including important issues of the method used in different interventional studies are enclosed as Appendices 2–7. In these tables it is also concluded whether the study provides data that are conclusive as regards prevention of allergic diseases. Earlier non-randomized studies reporting effect of dietary measures in self-selected groups have not been included in this review.

Observational studies

Breastfeeding

More than 60 yr ago Grulee and Sanford reported that undiluted cow's milk gave a sevenfold increase in the risk of 'eczema' at 9 months of age in a huge cohort of children compared with babies breastfed and fed mixed food (3). One cohort study has demonstrated an association between early cow's milk formula feeding and development of cow's milk protein allergy (4). In a Finnish study of non-selected, non-high-risk newborns followed until 17 yr of age, 6 months exclusively breastfeeding was associated with less 'eczema' and food allergy (FA) at 1 and 3 yr as well as a lower 'score of respiratory allergy' (not well defined) up to 17 yr of age compared with exclusively breastfeeding for < 3 months (5). Another prospective study (6) found that non-atopic children (negative skin prick test) at age 6 yr who had not been breastfed had increased risk of wheezing recurrently in comparison with breastfed children (odds ratio 3.03, 95% CI 1.06–8.69), but the same association was not found for atopic children. In a recent Australian study (7–11) introduction of milk other than breast milk before 4 months of age was a significant risk factor for all asthma and 'atopy' outcomes in children up to 5 yr (odds ratio 1.25, 95% CI 1.02–1.52), and for current asthma (odds ratio 1.31, 95% CI 1.05–1.64). Breastfeeding has also been shown to reduce the risk of wheezy bronchitis during infancy (12, 13). Meanwhile, contradictory results exists, e.g., in a recent large prospective study from 3 to 21 yr of age, the authors concluded that breastfeeding for at least 4 wk does not protect children against atopy and asthma and may even increase the risk (14). However, the methods and data presented in that study do not seem to confirm the conclusion. Thus, e.g., data on breastfeeding were documented retrospectively at the age of 3 yr and the information on 'atopic' heredity is uncertain without clear definitions and without inclusion of atopic eczema and atopic siblings. No significant effect of exclusively breastfeeding for at least 4 wk was found and no data or conclusion on exclusively breastfeeding for a longer duration is presented.

Prospective birth cohort studies including data on preventive effects of breastfeeding on FA, atopic eczema (E), sensitization and respiratory symptoms are shown in Table 1 (4–8, 10, 11, 13, 15–23).

Common factors apparent in studies reporting benefit of breastfeeding were: (i) prolonged

breastfeeding (> 4–6 months) and (ii) late solid food introduction (after 4–6 months).

A possible protective effect of breastfeeding on the development of allergic diseases may be due to either: (i) a protective effect of human milk (the constituents) or (ii) avoidance of 'high-dose' of cow's milk proteins.

In a few studies (13, 22, 23) an association between breastfeeding and asthma or E may be explained as 'reverse causation', meaning that those with the highest degree of atopic heredity will tend to be breastfed for the longest period.

The issue whether breastfeeding has an allergy-preventive effect remains controversial due to the lack of evidence in some studies and due to the fact that infants cannot ethically be randomly assigned to breastfeeding or formula feeding to enable a definitive study (24, 25).

Recently, three meta-analyses (26–28), using predetermined standardized inclusion criteria for trial appraisal, demonstrated an overall protective effect of exclusive breastfeeding during the first 3 months of life on atopic eczema (27) and asthma (28), whereas no significant effect on allergic rhinitis in childhood was found (26) (Table 3). In the latter an insufficient number of studies and short follow-up periods represented a problem considering the late onset of allergic rhinitis in children.

Recent studies on the possible allergy-preventing effect of breastfeeding indicate that variations in the composition of human milk, e.g., low levels of α-linolenic acid and relationship between the n-3 and the n-6 fatty acids (29) or varying concentrations of cytokines (30) may in part explain some of the controversies regarding the protective effect of breastfeeding against allergy. No association between nucleotide and polyamine levels in human milk and atopic development during the first year of life has been found (31). However, prospective long-term follow-up studies with a proper sample size are desirable for confirmation of these possible relationships.

Solid foods

As for introduction of cow's milk proteins before 4 months of age, the introduction of complementary foods (solid foods) before 4 months of age has been associated with a higher risk of atopic eczema (13, 32) up to the age of 10 yr (33) (Table 2).

Conclusion

According to present knowledge from prospective observational studies, atopic predisposition is associated with a significantly increased risk for

Table 1. Dietary allergy prevention – breastfeeding. Non-interventional studies in unselected infants

Study	n	Follow-up (yr)	Diet	Diet period (months)	Health effect	Statement of evidence
Saarinen et al. (15)	236 43% +FH	3	Excl. BF	6	↓ 'FA' and E at 1 and 3 yr in −FH ↓ 'FA' and E at 1 and 3 yr in +FH	IIb
Gruskay (16)	328 +FH 580 −FH	15	BF vs. soy/CMP	≥4	↓ 'E' and 'asthma'	IIb
Pratt (17)	122 +FH 76 −FH	5	Excl. BF	≥3	↓ 'eczema' in children +FH → 'eczema' in children −FH	IIb*
Moore et al. (18)	475 +FH	1	Excl. BF	≥1	↓ 'eczema' at 3 and 6 months	IIb*
Høst et al. (4)	1749	1	Excl. BF vs. CMF	≥3 0–3	Incidence of CMA: 0.5%† ↑ CMA at 1 yr	IIa
Saarinen and Kajosaari (5)	150	17	Excl. BF	6	↓ resp. allergy score* at 17 yr	IIb*
Wright et al. (19)	1006	4 months	BF	4	↓ wheezing	IIa
Wright et al. (6)	988	6	BF	any	↓ wheezing at 6 yr in non-atopics	IIa
Elder et al. (20)	560 preterm	1	BF	any	↓ wheezing	IIa
Wilson et al. (13)	674	1	Excl. BF	≤ 15 wk	↑ respiratory illness	IIa
Tariq et al. (21)	1218	4	Excl. BF	≤ 3	↑ Asthma	IIa
Oddy et al.‡ (7, 8)	2187	6	BF	≤ 4	↑ Asthma	IIa
Wright et al. (19)	1246	11	BF	4	↓ wheeze up to 6 yr	IIa
Oddy et al. (10, 11)	2602	6	Excl. BF	≤ 4	↑ Asthma	IIa
Bergman et al. (23)	1314	7	Excl. BF	≥1	↑ 'Atopic eczema'§	IIb*

Effect of infants diet indicated by arrows: ↑ increase, ↓ decrease or → no change in the incidence of disease/symptoms in infants having the diet as mentioned. Excl., exclusively; FA, food allergy; FH, family history; BF, breast fed; CMA, cow's milk allergy; CMP, cow's milk protein; E, atopic eczema.

*Diagnostic criteria loose (diagnostic uncertainties).

†A total of 39/1749 developed CMA. Nine of 39 with CMA were exclusively BF, but had received supplement of CMF during 0–3 days in newborn nursery. None of 210 exclusively breastfed without supplement of CMF developed CMA.

‡Logistic regression analyses adjusted for important confounders: sex, gestational age (GA), environmental tobacco smoke (ETS), early childcare.

§Reverse causation cannot be excluded. BF compared with formula feeding.

Table 2. Non-interventional studies – role of solid food introduction

Study	n	Follow-up (yr)	Diet	Diet period (months)	Health effect	Statement of evidence
Kajosaari and Saarinen (32)	135 +FH	1	Solid foods	≤6	↑ 'FA' and 'atopic eczema' at 1 yr	IIb
Fergusson et al. (33)	1210	10	Solid foods	≤4	↑ childhood 'eczema'	IIb*
Wilson et al. (13)	674	1	Solid foods	≤15 wk	↑ wheeze	IIa

Effect of infants diet indicated by arrows: ↑ increase, ↓ decrease or → no change in the incidence of disease/symptoms in infants having the diet as mentioned. FA, food allergy; FH, family history.
*Diagnostic criteria loose (diagnostic uncertainties).

Table 3. Results from three meta-analyses on the relation between exclusive breastfeeding during the first 3 months of life and development of atopic disease

				Population	
	Effect measure	Studies (n) included and period	Summary*, OR (95% CI)	Atopic heredity†, OR (95% CI)	Combined‡, OR (95% CI)
Gdalevich et al. (27)	Atopic dermatitis	18, 1966–2000	0.68 (0.52–0.88)	0.58 (0.41–0.92)	−1.43 (0.72–2.86)
Gdalevich et al. (28)	Asthma by 2–5 yr	12, 1966–1999	0.70 (0.60–0.81)	0.52 (0.35–0.79)	0.99 (0.48–2.03)
Bloch et al. (26)	Allergic rhinitis	6, 1966–2000	0.74 (0.54–1.01)	0.87 (0.48–1.58)	0.68 (0.47–0.99)

OR, odds ratio; CI, confidence interval.
*Analysis of pooled data.
†Analysis of high-risk populations.
‡Analysis of combined high-risk and non-high-risk populations.

development of atopic disease in childhood. However, the majority of children who develop atopic disease, particularly recurrent wheezing and asthma, during early childhood do not belong to high-risk groups for development of atopic disease. In this age group male sex and exposure to tobacco smoking has been shown to be independent risk factors for recurrent wheezing and asthma.

In prospective observational studies breastfeeding for at least 3–6 months and late introduction of solid foods (after 4–6 months) is associated with a decreased risk of cow's milk protein allergy/FA and atopic eczema up to 3 yr and recurrent wheeze/asthma up to 6 (−17) yr. As such exclusively breastfeeding for the first 6 months of life as recommended by World Health Organization should be attempted in all infants and also recommended as an allergy-preventive measure (Table 3).

Interventional studies

Unselected/non-high-risk infants

Only a few prospective intervention studies have been performed in infants without a hereditary atopic predisposition (Table 4). In premature unselected infants Lucas et al. (34) found no difference in the development of atopic symptoms or cow's milk allergy (CMA) whether the infants were fed *human bank milk* or *cow's milk*-based formula. In other studies (35–37) it was concluded that cow's milk-based formula given during the first few days of life did not increase the risk of 'atopic' disease when determined at the age of 1 (37), 2 (35) and 5 (38). These studies implemented an intervention diet only during the first few days of life, included low birth weight infants in one (37), and the outcome was based on data from medical files and questionnaires obtained at 7, 11 and 14 yr. In one study (35, 38) the diagnostic criteria were unspecific and outcome measures were mainly based on questionnaires. A recent randomized study including a large number (n = 6209) of full term, unselected newborns (39) indicated that feeding of cow's milk-based formula at maternity hospital increases the risk of CMA when compared with feeding an extensively hydrolyzed whey formula, but exclusively breastfeeding for 8 wk did not eliminate the risk of CMA. Meanwhile, the dietary intervention only included the first 4 days of life and no data on the diet after that period is given.

Another large prospective study investigated the overall health benefits of an allergen reduced dietary regimen in a large unselected study population (40, 41) allocated (not randomized) to an intervention and a non-intervention cohort according to place of birth. The authors concluded that an allergen-reduced dietary recommendation that includes a partially hydrolyzed whey

Table 4. Dietary allergy prevention. Interventional studies in unselected infants

Study	n	Follow-up (yr)	Diet	Health effect	Statement of evidence
Lucas et al.* (34)	777	$1\frac{1}{2}$	Human bank milk vs. CMF	→ 'Atopic' disease → CMA	Ib
Lindfors et al.† (37)	183	4–6	BM ± CMF‡	→ 'Atopic' symptoms	Ib?§
Schmitz et al. (36)	189	1	pHF vs. CMF‡	→ Total and asp-CM-IgE	Ib?§
de Jong et al. (35, 38)	1533	2	CMF‡ vs. no CMF	→ 'Atopic' symptoms → RAST	Ib?§
Saarinen et al. (39)	5385	18–34 months	CMF‡ vs. eHF/HM	↑ CMA	Ib

Effect of infants diet indicated by arrows: ↑ increase, ↓ decrease or → no change in the incidence of disease/symptoms in infants having the diet as mentioned. CMF, cow's milk formula; CMA, cow's milk allergy; BM, breast milk; pHF, partly hydrolyzed formula; eHF, extensively hydrolyzed formula; HM, human milk; RAST, radio-allergo-sorbent test.
*Premature infants.
†Low birth weight.
‡Included diet only for the first few days.
§Diagnostic criteria not well described.

hydrolyzate infant formula led to improved general health status, mainly due to improvements in skin findings when compared with a control cohort (40). However, the two study cohorts were significantly different as regards duration of breastfeeding, introduction of solid foods, parent education, household pets, number of older siblings, exposure to tobacco smoke and urban residence. This study did not aim at identifying or assessing specific allergic symptoms and does not allow any conclusions as regards allergy prevention.

High-risk infants

As reviewed in a position paper of European Society of Pediatric Allergy and Clinical Immunology (ESPACI) (42) and a recent joint statement of ESPACI and European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) prospective studies on high-risk infants have shown a preventive effect of different dietary allergy prevention programs on the cumulative incidence of FA especially CMA and E. An effect of dietary allergy prevention has only been demonstrated in high-risk infants, i.e., infants with at least one first-degree relative (parent or sibling) with documented atopic disease (physician diagnosed), possibly combined with elevated cord blood immunoglobulin E (IgE) in case of single atopic predisposition. Due to great variations in study design and diagnostic criteria it is difficult to compare the effect of these programs (Table 5).

Breastfeeding. From previous studies (34, 43–49) it is presumed that breastfeeding has an allergy-preventive effect compared with cow's milk formula feeding, but the extent of the preventive effect remains to be determined. Meta-analyses showed that exclusive breastfeeding for at least 3 months, in infants with atopic heredity resulted in a reduced odds ratio of 0.58 (95% CI 0.4–0.92) for atopic eczema and an odds ratio of 0.52 (95% CI 0.35–0.79) for 'recurrent wheezing' in the first 5 yr of life (27, 28), whereas no significant effect on allergic rhinitis was found (26). The only prospective, randomized study used banked human milk vs. cow's milk formula in a preterm infant cohort, and it was found that cow's milk formula feedings increased the risk of developing 'eczema' and CMA by 18 months in the subgroup of neonates with an atopic heredity (34).

In high-risk infants, exclusively breastfeeding during ≥4 months in combination with avoidance of solid foods has resulted in a significant reduction of the cumulative incidence of CMA and E during the first 4 yr of life. However, infants cannot ethically be randomly assigned to breast or formula feeding to enable a definitive study. Thus confounding factors may highly influence the results of comparisons. There is no conclusive evidence for a protective effect of a maternal exclusion diet during pregnancy (50–52). A few studies indicate that the preventive effect of breastfeeding on development of eczema may be enhanced by maternal avoidance of potential food allergens (milk, egg, and fish) while breastfeeding (44, 53, 54), whereas other studies do not confirm this finding (52, 55–57) (Table 6).

Formulas. Some prospective studies have shown that *soy formulas* are as allergenic as conventional cow's milk-based formulas, and on this basis they should not be recommended for the prevention of FA (42, 44), but controversy still exist (58–62). One study (58) found no preventive effect of soy formula, whereas another (60) indicated a possible preventive effect of soy

Table 5. Dietary intervention in 'high-risk' infants. Prospective studies including control group. Infant diet – breastfeeding ≥4 months

Study	n	Follow-up (months)	Diet	Health effect	Statement of evidence
Chandra et al. (43)	121	24	BF	↓ E and 'wheeze'	Ib*
Miskelly et al. (46)	487	12	BF CM = soy	↓ 'Atopy' → 'Atopy'	Ib*
Burr et al. (48)	440	7 yr	BF CM = soy	↓ 'Wheeze' in non-'atopics' → 'Wheeze'	Ib*
Vandenplas et al. (47)	45	4	BF	↓ 'Atopy' ↓ CMA	Ib*
Chandra et al. (44)	221	18	BF CM = soy	↓ E → E	Ib*
Lucas et al. (34)	160 777 preterms	18	BF	↓ 'Atopy' ↓ 'CMA'	Ib
Chandra and Hamed (72)	263	18	BF CM = soy	↓ E and 'Atopy' → E and 'Atopy'	Ib*
Halken et al. (45)	141	18	BF	↓ CMA	Ib*
Schoetzau et al. (49)	1121	12	Excl BF (16 wk)	↓ E E in family: ↑↑ risk E E: × 4 ↑ risk of asp-CM-IgE E: × 8 ↑ risk asp-egg-IgE	Ib*

Effect of infants diet indicated by arrows: ↑ indicate increase, ↓ decrease or → no change in the incidence of disease/symptoms in infants having the diet as mentioned. BF, breast fed; E, atopic eczema; CMA, cow's milk allergy.
*Not randomized to breastfeeding.

Table 6. Dietary intervention in 'high-risk' infants. Prospective studies including control group. Effect of maternal exclusion diet during pregnancy and/or lactation

Study	n	Follow-up (yr)	Maternal diet	Health effect	Statement of evidence
Fälth Magnusson et al. (50)	180	0	Pregnancy	→ Total IgE → Spec. IgE	Ib
Fälth Magnusson et al. (51)	180	5	Pregnancy	→ 'Atopy'	Ib
Lilja et al. (52)	63	$1\frac{1}{2}$	Pregnancy	→ 'Atopy'	Ib
Chandra et al. (54)	109	1	Pregnancy and lactation	↓ E in BF children → E in CMF children	Ib
Zeiger et al. (68)	225	4	Pregnancy and lactation	↓ FA (CMA)	Ib
Lilja et al. (52)	107	$1\frac{1}{2}$	Pregnancy and lactation	→ 'Atopy'	Ib
Businco et al. (53)	101	2	Lactation	↓ 'Atopy'	Ib
Chandra et al. (44)	225	$1\frac{1}{2}$	Lactation	↓ E	Ib
Lilja et al. (52)	107	$1\frac{1}{2}$	Lactation	→ 'Atopy'	Ib
Sigurs et al.* (55)	115	4	Lactation	→ 'Atopy' ↓ E at 3 months, 1/2 and 4 yr	Ib†
Hattevig et al.* (56)	105	10	Lactation	→ 'Atopy', E at 10 yr → SPT, RAST at 10 yr	Ib†

Effect of maternal diet indicated by arrows: ↑ indicate increase, ↓ decrease or → no change in the incidence of disease/symptoms in infants having the diet as mentioned. BF, breast fed; E, atopic eczema; CMF, cow's milk formula; CMA, cow's milk allergy; SPT, skin prick test; RAST, radio-allergic-sorbent test.
*Follow-up at different time-points of the same study population.
†Groups assigned by hospital rather than true randomization.

formula but only to allergen-non-specific atopic symptoms. Further studies may be useful to clarify the allergenicity of soy formula in infants who are at risk for development of allergy. Prospective intervention studies (44, 58, 60) have compared the preventive effect of soy formula with cow's milk-based formula in high-risk infants, but none included controlled elimination/challenge procedures in order to diagnose FA.

Extensively hydrolyzed formulas (eHF) have been investigated in studies on prevention of FA in high-risk infants. Several prospective studies (44, 45, 63–70) show a preventive effect of eHF in combination with avoidance of cow's milk proteins and solid foods during ≥4 months in high-risk infants on the cumulative incidence of atopic eczema and FA, especially CMA until the age of 4 yr. In two prospective studies (65, 69) the cumulative incidence of FA and CMA was significantly reduced until the age of 5 and 7 yr. Thus, a real prevention, and not only a postponement of the onset of the disease, was documented (Table 7).

Partially hydrolyzed formulas (pHF) (with moderately reduced allergenicity) have been

Table 7. Dietary intervention in 'high-risk' infants. Prospective studies including control group. Infant diet – hypoallergenic formula ≥4 months

Study	n	Follow-up (yr)	Diet	Health effect	Statement of evidence
Vandenplas et al. (47)	45	4	PHF	↓ CMA, 'Atopy'	Ib*
Vandenplas et al. (74)	67	$1\frac{1}{2}$	pHF vs. CMF	CMA 15.6%, 'Atopy' 21.8% vs. CMA 42.8%, 'Atopy' 48.6%	Ib*
Vandenplas et al. (75)	58	5	pHF vs. CMF	CMA 29% vs. 60% (cum)	Ib*
Chandra and Hamed (72)	263	$1\frac{1}{2}$	PHF	↓ 'Eczema', 'Atopy'	Ib*
Chandra (73)	216	5	PHF BF	↓ 'Eczema', 'Atopy', 'FA', 'asthma'	Ib*†
Chan et al. (76)	110	30 months	pHF	↓ Eczema	Ib‡
Chandra and Hamed (72)	221	$1\frac{1}{2}$	eHF	↓ 'Eczema'	Ib‡
Mallet and Henocq (70)	177	4	eHF	↓ 'Eczema'	Ib‡
Zeiger et al. (67–69)	225	$1\frac{1}{2}$, 4	eHF	↓ FA/CMA (cumulated) at $1\frac{1}{2}$ and 4 yr	Ib
	165	7			
Halken et al. (45)	141	$1\frac{1}{2}$ (5)	eHF	↓ CMA (3.6%)	Ib
Oldæus et al. (77)	50	$1\frac{1}{2}$	eHF	↓ 'Atopic' symptoms 51%	Ib
	45		pHF	↓ 'Atopic' symptoms 64%	
	46		CMF	↓ 'Atopic' symptoms 84%	
Halken et al. (78)	478	$1\frac{1}{2}$	PHF vs. EHF	CMA 4.7% vs. 0.6% ($p = 0.05$)	Ib
Von Berg et al. (79)	945	1	eHF-caseine	↓(>50%) AE	Ib
			eHF-whey	→ AE	
			pHF-	↓(>50%) AE	

CMA, cow's milk allergy; CMF, cow's milk formula; FA, food allergy; eHF, extensively hydrolyzed formula; pHF, partly hydrolyzed formula.
*Diagnostic criteria inclusive food challenge procedure and time for investigation unclear.
†Not conclusive as regards food allergy.
‡Controlled challenges not performed.

Table 8. Combined dietary and environmental intervention in 'high-risk' infants. Prospective studies including control group

			Intervention		
Study	n (I/C)	Follow-up years	Dietary	Environmental	Effect of intervention (I vs. C)
Hide et al. (63, 66, 81)	120 (58/62)	1, 2 and 4	9 months exclusive BF/eHF SF after 4 months	Mattress encasing + acaracide	↓ HDM SPT 5.2 vs. 24%* ↓Allergy†
Chan-Yeung et al. (82)	493 (251/242)	1	12 months BF/pHF SF after 6 months	Mattress encasing + benzoate	↓ 'A'/'AR' RR 0.66 (0.44–0.98)

I, intervention group; C, control group; SF, solid food; HDM, house dust mite; SPT, skin prick test; BF, breast fed; eHF, extensively hydrolyzed formula; pHF, partly hydrolyzed formula; A, asthma; AR, allergic rhinitis.
*$p < 0.02$.
†Allergy = asthma, allergic rhinitis, eczema, food allergy + pos SPT.

investigated in randomized prospective studies (47, 71–76) in high-risk infants, and an allergy-preventive effect has been reported. Because of great variations in study design and diagnostic criteria, the relative efficacy of the different interventions tested in the various studies cannot be compared directly (47, 72–75). One of these studies (74, 75) reported a very high prevalence of CMA; the reason for this is unclear, but it may be due to less strict diagnostic criteria or selection bias. Recent data from studies comparing the allergy-preventive effect of pHF and eHF indicate a greater effect with eHF in three (77–79) of four studies (77–80) with well-defined diagnostic criteria (Table 7). In a recent study (79) the preventive effect, a reduction in the prevalence of atopic eczema, was particularly seen in infants with family history of atopic eczema (Table 7).

Combined dietary and environmental intervention. In two properly conducted studies combined dietary and environmental preventive measures have been applied not allowing evaluation of the causative measure of effect (63, 66, 81, 82) (Table 8).

Solid foods. The introduction of complementary foods during the first 4–6 months of life has been associated with a higher risk of eczema (24). A preventive effect of breastfeeding or hydrolyzed formulae has only been shown in studies including avoidance of complementary foods during at least the first 4 months of life.

Duration of the diet. The duration and the dietary restrictions vary in different studies. All studies showing a preventive effect have included solely breastfeeding or eHF and avoidance of cow's milk and solid foods ≥4–6 months. Studies including restrictive diets for a long period > 12–24 months and studies with dietary restrictions for only 4–6 months have shown comparable results. In one recent study (83) no significant effect of supplement with hydrolyzate formula (eHF) compared with cow's milk-based formula after the age of 6 months in breastfed high-risk infants was found. Controlled studies concerning the possible preventive effect of avoidance of other potential food allergens, e.g., egg, fish, etc., after the age of 4–6 months of life have not been published. Thus, there is no evidence of allergy preventing effect of restrictive diets after 6 months of age.

Intestinal microbial flora. It has been hypothesized that the intestinal microbial flora may influence the development of sensitization (84). One recent prospective study showed a preventive effect of supplementing the diet of high-risk infants by probiotics 2–4 wk prenatally and the first 6 months of life as regards mild E at the age of 2 yr, but no effect was shown as regards sensitization/proven allergic disease (85). This theory needs confirmatory evidence.

Conclusion

At present prospective interventional studies in high-risk infants show evidence of the effect of dietary allergy-preventive measures as regards FA, especially cow's milk protein allergy, and eczema:

- Feeding exclusively human milk for at least 4 months is associated with a lower cumulative incidence of CMA until 18 months.
- No convincing evidence for a preventive effect of maternal diet during pregnancy or lactation.
- A documented hypoallergenic formula (eHF) combined with avoidance of solid foods for 4–6 months reduces the cumulative incidence of CMA and eczema.
- pHF may have an effect, although it seems to be less than that of eHF at present.
- No evidence for a preventive effect of a diet after the age of 4–6 months, although this needs additional investigation.
- This preventive effect have *only* been demonstrated in *high-risk infants*.

Preventive effect of dietary measures

Intervention	Effect
Exclusively breastfeeding, at least 4 months. For nutritional reasons WHO recommend breastfeeding for the first 6 months for all children	↓ cumulative incidence of CMA until 18 months ↓ cumulative incidence of E until 3 yr ↓ recurrent wheeze/asthma until 6 (–16) yr
eHF* combined with avoidance of solid foods ≥4–6 months	↓ cumulative incidence of CMA until 5–7 yr and E until 4 yr
pHF* combined with avoidance of solid foods ≥4–6 months	Some effect, although less than eHF

*Exclusively or as a supplement to breastfeeding.
No convincing evidence for a preventive effect of maternal diet during pregnancy or lactation; no convincing evidence for a preventive effect of a diet after the age of 4–6 months; an allergy-preventive effect has been documented only in high-risk-infants.

Dietary recommendations based on present knowledge

All infants
- No special diet during pregnancy or to the lactating mother
- Exclusively breastfeeding preferable for 6 months but at least 4 months. If supplement is needed conventional cow's milk-based formula is recommended
- Avoidance of solid foods until preferable for 6 months but at least 4 months of age

*Further recommendations for infants with a high risk for allergic disease**
- If supplement is needed extensively hydrolyzed formula is recommended until 4 months of age. After the age of 4 months high-risk children can be nourished like non-high-risk children

*High-risk infants: infants with a well-defined increased risk of developing allergic disease; that is, infants with at least one first-degree relative (parent or sibling) with documented allergic disease.
Based on allergy prevention studies exclusively breastfeeding and avoidance of solid foods for at least 4 months seems to be sufficient for allergy prevention; but according to dietary recommendations from WHO, exclusively breastfeeding for 6 months is recommended. Regarding non-dietary recommendations avoidance of exposure to tobacco smoke – also during pregnancy – is most important in all children.

Conclusions

From a detailed analysis of these reports it appears that often the collection of the data is incomplete, the methodology used inappropriate or the end-points inadequately defined.

In order to evaluate the efficacy of a well-defined dietary regimen on the prevention of allergic diseases in childhood, this paper reviews critically the existing literature on the subject applying to the analysis the statements of evidence established by the WHO. Only those studies meeting the criteria for the WHO statements of evidence I and II were considered adequate for final recommendations.

Based on this review the following major topics were defined:

- Target groups for dietary prevention
- Criteria of hypoallergenicity of formulas
- Methods and diagnostic criteria for prevention studies
- Effective dietary regimen for allergy prevention.

Breastfeeding is highly recommended for all infants irrespective of atopic heredity. Although the number of high quality observational and interventional studies is limited, the following evidence-based recommendations should be followed:

- A dietary regimen is effective in the prevention of allergic diseases in high-risk patients
- The most effective dietary regiment is exclusively breastfeeding for at least 4–6 months or, in case of lack of breast milk, formulas with documented reduced hypoallergenicity for at least 4 months combined with avoidance of solid food and cow's milk for the same period.

Based on this analysis no conclusive evidence for protective effect of maternal exclusion diet during pregnancy or lactation could be shown. In addition, no controlled studies have yet determined the role of peanut avoidance in the prevention of atopic diseases. Prospective prevention studies currently available indicate that soy formulas are as allergenic as conventional cow's milk formulas.

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Appendix 1. Definitions

Full name	Definition
Atopy	A personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis or eczema/dermatitis
Allergic diseases	The clinical manifestation of allergy
Allergy	A hypersensitivity reaction initiated by immunologic mechanisms
Allergenicity	The ability to stimulate an IgE response and induce IgE-mediated reactions
Antigenicity	Ability to stimulate an immune response
Cow's milk allergy	An immunologically mediated hypersensitivity reaction to cow's milk, including IgE-mediated and/or non-IgE-mediated allergic reactions
E	Eczema, replaces the provisional term Atopic eczema dermatitis syndrome, AEDS and in most countries the old term Atopic dermatitis, AD
Food allergy	An immunologically mediated hypersensitivity reaction to any food, including IgE-mediated and/or non-IgE-mediated allergic reactions
Partly hydrolyzed formula	A formula with moderately reduced allergenicity*
Extensively hydrolyzed formula	A formula with extensively reduced allergenicity*
Hypersensitivity	Objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus that is tolerated by normal subjects
Hypoallergenic	With reduced allergenicity† both IgE and non-IgE-mediated allergenicity
Hypoallergenic formula for treatment	A formula with low allergenicity tolerated with 95% confidence by 90% of CMA patients
IgE-mediated allergy	An allergy with proven IgE-mediated reaction
Non-IgE-mediated allergy	An allergy (immunologically mediated hypersensitivity reaction) without involvement of IgE. In food allergy probably T-cell-mediated
Sensitization, immunologic	Any immune response to a foreign antigen
Sensitization, IgE-mediated	An IgE response to foreign antigen (allergen), as measured by *in vitro* IgE determination or SPT
Sensitization, non-IgE-mediated allergy	A reactivity toward allergen as measured by cell stimulation or APT

*Commission of the European Communities. Commission directive 96/4 EC of 16 February 1996 amending directive 91/321/EEC on infant formulae and follow-on formulae. Official Journal of the European Commission 1996: 39: 12–16.
†Reduced allergenicity is defined as: content of immunoreactive protein of <1% of nitrogen containing substances.

Appendix 2. Prospective interventional studies in unselected infants

Study	Number at follow-up/ total number	Population-based cohort/ inclusion period (months)	Inclusion criteria defined	Exclusion criteria defined	Definition of HR infants	Randomization at birth	Intervention period	Blinded	Control group defined	Outcome measures predefined	Sensitization markers defined	Exact def. and diagn. criteria	Controlled challenges	Follow-up period (yr)	Follow-up only based on questionnaires	Investigation at fixed intervals	Investigation at symptoms	Drop-outs described	Confoundings described	Adjusted for confoundings	Adequate sample size and statistics	Authors conclusions adequate	Published in peer reviewed journal	Conclusive
Lucas et al.* (34)	777	+*/24	+	+	+	+ ?	5 wk	?	+	+	–	+	(+)	$1\frac{1}{2}$	No	+	?	No	No	No	+	+	+	Yes
Schmitz et al.† (36)	189/256	?/$4\frac{1}{2}$	+	No	No	+‡	5 days	+	+	+	RAST SPT§	No	No	1	No	+	+	+	No	No	+	No	+	No
Lindfors et al.¶ 1986 (86)	183/216	+¶/18	+	No	+**	+‡	Few days	No	+	+	SPT	No	No	4–6	No	+	No	+	+	No	?	+	+	?
de Jong et al. (35)	1220/1693	+/24	+	+	No	+	3 days	+	+	+	RAST**	+‡‡	No	2	No	+	No	No	+	No	+	No	+	?
de Jong et al. (38)	1108/1693	+/24	+	+	+§§	+	3 days	+	+	+	RAST**	+‡‡	No	5	No	+	No	No	+	+	+	No	+	?
Saarinen et al. (39)	6209/6267	+/15	+	No	+§§	+	+	+	+	+	–	+‡‡	+	$1\frac{1}{2}$–3	No	No	+‡‡	No	No	+	+	+	+	+
Exl et al. (40, 41)	1001/1130§§	+¶¶/18	+	No	No	No***	4 months	No	+***	+†††	–	No	No	1/2 (2)	+‡‡‡	+‡‡‡	?‡‡‡	+	(+)	(+)	+	No	+	No

*Preterm.
†pHF.
‡Allocated according to month of birth.
§Method and cut-off value for a positive SPT not described.
¶Term infants with a birth weight between −1 s.d. and −2 s.d.
**RAST performed, but method and cut-off value for a positive test not mentioned.
††Very broad definition and loose criteria of atopic symptoms.
‡‡Outcome measure = CMA was defined, but different atopic symptoms were nor defined.
§§Only symptomatics were investigated by one of the authors.
¶¶Out of a potential study population of 7350 infants, reasons for not to participate is not given.
***Allocated according to place (city) of birth.
†††Outcome measures included nutritional behaviour, growth parameters and health status but not allergic diseases.
‡‡‡Based on questionnaires and information from local health care providers, personal mothers consultants and the family's medical physician.

Appendix 3. Prospective interventional studies in high-risk infants – breastfeeding or eHF

Study	Number at follow-up/ total number	Population-based cohort/ inclusion period (months)	Inclusion criteria defined	Exclusion criteria defined	Definition of HR infants	Randomization at birth	Intervention period (months)	Blinded	Control group defined	Outcome measures predefined	Sensitization markers defined
Lucas et al.* (34)	160	+*/24	+	+	+	+ ?	5 wk	?	+	+	–
Chandra et al. (44)	221/?	?/?	+†	No	+†	+	6	+ ?	+	+	–
Zeiger et al. (67)	265/288	+/56	+	+	+	+	12–36	No	+	+	SPTRAST
Zeiger et al. (68)	225/288	+/56	+	+	+	+	12–36	No	+	+	SPTs-IgE
Zeiger and Heller (69)	165/288	+/56	+	+	+	+	12–36	No	+	+	SPTs-IgE
Mallet and Henocq (70)	139/177	+/13	+	No	+†	+‡	4	No	+	+	s-IgECM-IgE§
Halken et al. (64)	229/233	+/12	+	+	+	+¶	6	No	+	+	–
Burr et al. (4)	440/497	?/?	No	No	+†	+	4	No	+	No	SPT
Odelram et al. (83)	91	+/12?	+	+	+	+**	12	SB	+	+	SPTSp-IgE

*Preterm.
†Very loose criteria: atopic symptoms/disease not defined.
‡No information on time or method for randomization.
§CM-IgE only measured if total IgE > 2 s.d. above the mean.
¶Stratified by year of birth: a 'historical' control group.
**Randomized after breastfeeding for 0–9 months when supplement was needed.

Appendix 4. Prospective interventional studies in high-risk infants – pHF

Study	Number at follow-up/ total number	Population-based cohort/ inclusion period (months)	Inclusion criteria defined	Exclusion criteria defined	Definition of HR infants	Randomization at birth	Intervention period (months)	Blinded	Control group defined	Outcome measures predefined	Sensitization markers defined
Vandenplas et al. (47)	68/75	?/?	(+)	No	+*	No	4	No	+	(+)	SPT† RAST†
Vandenplas et al. (74)	67/75	?/?	(+)	No	+*	+‡	6	+	+	(+)	SPT† RAST†
Vandenplas et al. (75)	58/75	No/14	(+)	No	+*	+‡	6	(+)	+	No	SPT† RAST†
Chandra et al. (44)	246/288	?/?	(+)	No	+*	**	4	+	+	No	CM-IgE††
Chandra and Hamed (72)	263/288	?/?	(+)	No	+*	**	4	+	+	No	SPT† RAST†
Chandra (73)	276/288	?/?	(+)	No	+*	**	4	+	+	No	SPT
Willems et al. (87)	122/135	+/10	+	No	No	+§§	3	No	No	No	–
Matejek et al. (88)	84	?/?	+	+	No	No	1 wk	No	No	No	–
Chan et al. (76)	110/153	?/?	No	Yes	+	?	4	SB	+	(+)	s-IgE CM-IgE**

*No definition of atopic disease.
†Cut-off value for a positive test not defined.
‡Time and method not described.
§Apart from atopic dermatitis and colic the diagnostic criteria are very loose and unspecific (vomiting, diarrhea, urticaria, wheezing of possible allergic origin ar
¶Method not described (e.g., blinding method, placebo).
**Not described.
††Not defined.
‡‡Double-blind placebo-controlled food challenge (DBPCFC) described in this paper for the first time, not described in the previous papers from the same study. Only performed in children with positive SPT. The method, the time for challenges and the number of challenges performed is unclear and difficult to evaluate.
§§Stratified by month of birth, but results based on retrospectively created groups according to adherence to the diet.
¶¶Only 13 in the intervention group.
***Not conclusive as regards food allergy.

Exact def. and diagn. criteria	Controlled challenges	Follow-up period (yr)	Follow-up only based on questionnaires	Investigation at fixed intervals	Investigation at symptoms	Drop-outs described	Confoundings described	Adjusted for confoundings	Adequate sample size and statistics	Authors conclusions adequate	Published in peer reviewed journal	Conclusive
+	(+)	$1\frac{1}{2}$	No	+	?	No	No	No	+	+	+	Yes
+	No	$1\frac{1}{2}$	No	+	(+)	(+)	+	+	+	+	+	Yes
+	+	2	No	+	+	(+)	No	No	+	+	+	Yes
+	+	4	No	+	+	+	+	+	+	+	+	Yes
+	+	7	No	+	+	+	+	+	+	+	+	?
No	No	4	No	+	No	+	No	No	+	+	+	No
+	+	$1\frac{1}{2}$	No	+	+	+	+	(no)	+	+	+	Yes
No	No	7	No	+	No	No	+	No	+	+	+	No
+	+	$1\frac{1}{2}$	No	+	?	No	+	No	No	+	+	?

Exact def. and diagn. criteria	Controlled challenges	Follow-up period (yr)	Follow-up only based on questionnaires	Investigation at fixed intervals	Investigation at symptoms	Drop-outs described	Confoundings described	Adjusted for confoundings	Adequate sample size and statistics	Authors conclusions adequate	Published in peer reviewed journal	Conclusive
No	No	4 mo	No	+	?	+	No	No	?	+	+	Yes
No§	?¶	1	No	+	No	No	+	No	?	No	+	Yes
No	?	5	No	+	+	+	+	No	?	+	+	Yes
No§	No	6	No	+	+	+	+	?	+	(+)	+	Yes
No§	No	$1\frac{1}{2}$	No	+	?	No	No	No	+	No	+	Yes
+	+‡‡	5	No	?	?	+	No	No	+	(+)	+	Yes***
No	No	1	+	+	No	No	No	No	No¶¶	No	+	No
No	No	1	No	+	No	No	No	No	No	No	?	No
No	No	30 mo	No	+	No	(+)	No	No	?	No	+	No

Appendix 5. Prospective interventional studies in high-risk infants – breastfeeding or soy

Study	Number at follow-up/ total number	Population-based cohort/ inclusion period (months)	Inclusion criteria defined	Exclusion criteria defined	Definition of HR infants	Randomization at birth	Intervention period (months)	Blinded	Control group defined	Outcome measures predefined	Sensitization markers defined
Johnstone et al. (89)	240/283	?/?	+	+	+*	+†	5–9	No	+	+	–
Kjellman et al. (90)	48/51	+/18	+*	No	+	+†	9	No	+	+	SPT RAST
Miskelly et al. (46)	487/519	?/?	+	+	+*	+	4	No	+	No	SPT
Burr et al. (58)	440/497	?/?	No	No	+*	+	4	No	+	No	SPT AlaTOP‡
Chandra et al. (44)	221/?	?/?	+*	No	+*	+	6	+ ?	+	+	–
Bardare et al. (60)	462/900	?/?	+*	No	+*	No§	6–12	No	+*	+	–

*Very loose criteria: atopic symptoms/disease not defined.
†Method and time for randomization not described.
‡A multiscreen test for inhalant IgE antibodies; cut-off value for a positive test not described.
§Stratified by place of birth.

Appendix 6. Prospective interventional studies in high-risk infants – pHF vs. eHF

Study	Number at follow-up/ total number	Population-based cohort/ inclusion period (months)	Inclusion criteria defined	Exclusion criteria defined	Definition of HR infants	Randomi-zation at birth	Intervention period (months)	Blinded	Control group defined	Outcome measures predefined	Sensitization markers defined
Oldæus et al. (77)	155	?/?	+	+	+	No*	4–12	+	+	+	SPT RAST
Porch et al. (91)	130/181	?/?	+	No	+†	+	12	+	–	(+)	–
Halken et al. (78)	514/550	+/12	+	+	+	+	4	+	–	+	–
Nentwich et al. (80)	72	No/36?	+	+	+§	+¶	6	+	No	+	CM-PBMC proliferation CM-IgE
Von Berg et al. (79)	1083/2252	+/33	+	+	+§	+	6	+	+	+	SPT Specific IgE

*Randomized when weaning started.
†Parental history of allergy were poorly defined.
‡Open challenges mentioned, but not described.
§Family history of atopy obtained by means of a questionnaire only.
¶Method and time not described.
°Controlled elimination/challenge procedures only performed in case of suspected food allergy with manifestations from gastrointestinal tract.

Appendix 7. Prospective interventional studies with combined dietary and environmental measures

Study	Number at follow-up/ total number	Population-based cohort/ inclusion period (months)	Inclusion criteria defined	Exclusion criteria defined	Definition of HR infants	Randomization at birth	Intervention period (months)	Blinded	Control group defined	Outcome measures predefined	Sensitization markers defined
Arshad et al. (63)	120/136	+/12	+	+	+	+	9	No	+	+	SPT
Hide et al. (66)	120/136	+/12	+	+	+	+	9	No	+	+	SPT
Hide et al. (81)	120/136	+/12	+	+	+	+	9	No	+	+	SPT
Marini et al. (92)	285/398	?/?	(+)	No	+†	(+)‡	5–12	+	+	+	RAST SPT
Chan-Yeung et al. (82)	493/545/1069	?/?	+	No	+†	+	12	SB	+	+	SPT§

*Open challenge, not described further.
†Loose criteria, not defined strictly.
‡No information on time or method for randomization. Non-intervention group formed by self-selection.
§Cut-off value for a positive test not defined.
¶Only asthma and rhinitis considered.

Exact def. and diagn. Criteria	Controlled challenges	Follow-up period	Follow-up only based on questionnaires	Investigation at fixed intervals	Investigation at symptoms	Drop-outs described	Confoundings described	Adjusted for confoundings	Adequate sample size and statistics	Authors conclusions adequate	Published in peer reviewed journal	Conclusive
+	No	10	No	+	?	+	No	No	+	+	+	Yes
No	No	4	No	+	No	+	+	No	?	+	+	?
No	No	1	No	+	No	+	+	No	?	+	+	?
No	No	7	No	+	No	No	+	No	+	+	+	?
+	No	$1\frac{1}{2}$	No	+	(+)	(+)	+	+	+	+	+	Yes
+	No	2	No	+	No	No	No	No	?	No	+	No

Exact def. and diagn. criteria	Controlled challenges	Follow-up period	Follow-up only based on questionnaires	Investigation at fixed intervals	Investigation at symptoms	Drop-outs described	Confoundings described	Adjusted for confoundings	Adequate sample size and statistics	Authors conclusions adequate	Published in peer reviewed journal	Conclusive
+	+	$1\frac{1}{2}$	No	+	No	No	(+)	(+)	+	+	+	Yes
No	No‡	2	No	+	No	+	No	No	?	No	+?	No
+	+	$1\frac{1}{2}$	No	+	+	+	+	No	+	+	+	Yes
+	No	1	No	+	No	No	+	No	No	+	+	Yes
+	+°	1	No	+	+	+	+	+	+	+	+	Yes

Exact def. and diagn. criteria	Controlled challenges	Follow-up period	Follow-up only based on questionnaires	Investigation at fixed intervals	Investigation at symptoms	Drop-outs described	Confoundings described	Adjusted for confoundings	Adequate sample size and statistics	Authors conclusions adequate	Published in peer reviewed journal	Conclusive
+	+*	$1\frac{1}{2}$	No	+	+	+	+	+	+	+	+	Yes
+	No	2	No	+	+	+	+	+	+	+	+	Yes
+	No	4	No	+	+	+	+	+	?	+	+	Yes
(+)	No	3	No	?	?	+	+	+	?	No	No	No
+¶	No	1	No	+	No	+	+	No	?	+	+	Yes