Evidence Tables 6 – 24 Months

Evidence is presented to answer the following questions:

1. What interventions effectively promote the timely introduction of appropriate supplementary feeds/solids, and/or family foods?
2. What interventions effectively promote uptake of recommended vitamin and micronutrient supplements?
3. What dietary strategies effectively reduce the risk of food allergies and intolerance?
4. What dietary interventions help to prevent diet-related dental caries, tooth loss and dental erosion in infants and young children?
5. What interventions effectively help mothers continue breastfeeding after 6 months, both at home and out of home? (e.g. to return to paid employment)

   (A number of studies have been identified that examine interventions that aim to increase the duration of breastfeeding (these are included in the 0-6 month review). Only one study specifically aimed to support breastfeeding in women who planned to return to paid employment.)

1 What interventions effectively promote the timely introduction of appropriate supplementary feeds/solids, and/or family foods?

Studies to be included	Evidence type	UK studies (other than RCTs)
Systematic reviews Randomised controlled trials	<u>Systematic reviews</u> Elkan 2000 Tedstone 1998 <u>Randomised controlled trials</u> None	Corroborative evidence from 5 UK studies is presented in the text of the review Anderson 2001 Alder 2004 Bolling 2005 Hoare 2002 Sritharan and Morgan 2002

Introduction of family foods

First author Year	Research Question	Study populations	Study quality	Intervention	Main results	Applicability to UK populations and settings Comments
Elkan et al 2000 UK SR 2+	The review objective was to examine the effectiveness and cost-effectiveness of home visiting by health visitors. This also included an assessment of home visiting in improving children's diet.	1. Studies that reported home visiting outcomes relevant to British health visitors were included 2. The personnel involved in carrying out the programme had to have responsibilities that were within the remit of British health visitors, and could not be members of a professional group other than health visiting 3. At least one home visit was made 4. Studies had to include a comparison group (RCTs, non-RCTs and controlled before-and-after comparisons) Four of 102 studies in the SR were included relevant to improving	Quality of individual studies was assessed using a standardised quality checklist – an adapted Reich scale, which included randomisation, concealment of allocation, blinding, power calculation and ITT analysis. Reich scores: Gutelius 1977 0.59 RCT moderate Barker 1988 0.46 RCT borderline Barker 1994 0.46 non-RCT borderline Johnson 1993 0.25 RCT weak Additional	Gutelius The intervention in the US study was 9, 6 and 4 home visits in the 1st, 2nd and 3rd years of life, respectively (minimum 1 h per visit) by a paediatrician or nurse, using a mobile coach parked outside the home, from 7 months pregnant to 3 y old versus no home visits. Additionally, 16 group events, usually discussion sessions, for 1 year. (Advice was based on Dr Benjamin Spock's book 'Baby and Child Care') Also 8-16 mg Fe daily for ≥1st year of life. Evaluation at 6, 12, 24 and 36 months. (No details of dietary assessment given.) 6% loss to follow-up (2 infants excluded due to retardation) For the 2 Barker studies (Barker 1988 and 1994), the intervention was monthly health visitor home visits versus no home visits. Evaluation at 12 and 36 months. Maternal self report for dietary assessment. Johnson study	Elkan et al. summary and conclusion: The authors reported that 3 of the 4 studies (excluding Barker 1994) reported better nutritional outcomes among home-visited children. They also conclude that the studies relied on maternal self-reports to assess diet and may thus be subject to bias. The author's state that there is insufficient evidence to make any conclusions. (Johnson concluded that the 'community mothers' programme was effective but it was not clear whether it was as cost effective as using professionals.) Results taken from data extraction tables: Results for Gutelius 1977 and Barker 1988 and 1994 Milk/weaning related outcomes Appropriate daily milk at 12 months (%) Int 55% Con 27% p<0.01 Gutelius % with an adequate milk intake Int 95% Con 94% at 12 months Barker 1994 Int 92% Con 98% at 36 months Barker 1994 Feeding self at 24 months (%) Int 71% Con 48% p<0.05 Gutelius Results for individual foods/nutrients % with >1 daily serving of fruit or fruit juice Int 51% Con 33% p<0.05 at 24 months Gutelius Int 57% Con 38% p<0.05 at 36 months Gutelius % with an adequate fruit intake at 12 months Int 63% Con 68% at 12 months Barker 1994 Int 76% Con 76% at 36 months Barker 1994 % with an adequate vegetable intake Int 73% Con 76% at 12 months Barker 1994	The results appear to be applicable to the UK. Three of the 4 studies were in the UK. Limitations of included studies: many were too small to detect effects, some were unrandomised with unblinded or self-reported outcome assessment . The Child Development Programme for 'community mothers' implemented in the Johnson study in 1983/4 (Johnson 1993) was an extension of the CDP developed at the Early Childhood Development Unit,

[1] Int= Intervention; Con=Control

First auth or Year	Research Question	Study populations	Study quality	Intervention	Main results	Applicability to UK populations and settings Comments
		children's diet (3 RCTs and 1 non-RCT). Two studies considered children of 1st time mothers: Gutelius 1977, a Washington, US, RCT of low income black infants in the 1st 3 years born to normal unmarried schoolgirls aged 15-18 y with normal births (n=97: Int n=49; Con n=48); and Johnson 1993, an Irish RCT in Dublin of disadvantaged infants in their 1st year (n=262: Int n=141; Con n=121). Gutelius Int and Con groups only differed in 6 of >90 variables, of these 5 favoured the Con group. The 2 remaining studies concerned 3-27 month old infants on normal health	quality information: <u>Johnson 1993</u> Random allocation using consecutively numbered sealed envelopes. Group allocation known before consent sought. <u>Gutelius 1977</u> (from original paper) Randomisation using random numbers	Intervention: monthly visits by non-professional 'community mothers' for the infant's 1st year versus routine care (visit at birth, at 6 weeks and then as required by the public health nurse). Each community mother had 4 weeks' training and worked under the guidance of a family development nurse. Maternal self report for dietary assessment. 11% loss to follow-up	Int 77% Con 77% at 36 months Barker 1994 % with >1 daily serving of meat at 6 months Int 88% Con 75% p<0.05 Gutelius % with an adequate animal protein intake Int 87% Con 87% at 12 months Barker 1994 Int 92% Con 90% at 36 months Barker 1994 % with an adequate non-animal protein intake Int 82% Con 84% at 12 months Barker 1994 Int 89% Con 83% at 36 months Barker 1994 % with an adequate whole food intake Int 70% Con 79% at 12 months Barker 1994 Int 80% Con 78% at 36 months Barker 1994 % with an adequate energy intake Int 87% Con 92% at 12 months Barker 1994 Int 94% Con 88% at 36 months Barker 1994 Results for vitamins and minerals % of children with <50% of RDA Barker 1988 At age 12 months At age 36 months Int Con Int Con Iron 10 5 5 5 Zinc 5 3 22 54 Calcium 0 0 0 0 Vitamin C 21 11 36 27 Total folate 2 0 18 35 <u>Results for the Johnson 1993 study</u> Milk/weaning related outcomes Cow's milk given before 26 weeks (%) Int[1] 24% Con 49% p<0.001	Bristol and described in the 2 included studies by Barker 1988 & 1994. The Johnson study was curtailed early due to lack of funding. Review funded via the Health Technology Assessment NHS R&D HTA Programme (UK).

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		visitor caseloads: Barker 1988, in NW and NE England, W Glamorgan and Dublin (health visitors) (n=1051; Int n=678; Con n=373) and Barker 1994 (non-RCT), in Northern Ireland (public health and family development nurses (n=606:Intn=384; Con n=222,). Search of electronic databases included Medline (1966-1997), CINAHL (1982-1997), EMBASE (1980-1997), the Internet, the Cochrane Library, relevant journals and references lists. Key individuals and organisations were also contacted and advertisements made in journals.			Mean ±SD length of time on formula feeds (weeks) Int 38.1 ± 13.5 Con 28.0 ± 15.2 p<0.001 Results for individual foods/nutrients % whose mothers gave vegetables appropriately Int 88% Con 62% p<0.001 at 12 months % whose mothers gave animal protein appropriately Int 83% Con 42% p<0.001 at 12 months % whose mothers gave non-animal protein appropriately Int 84% Con 51% p<0.001 at 12 months % whose mothers gave whole foods appropriately Int 86% Con 46% p<0.001 at 12 months % who had an appropriate energy intake Int 92% Con 56% p<0.001 at 12 months Significant results were reported for the studies by Gutelius and Johnson but no estimations of significance were reported for the Barker studies. It appears that many of the results of the Barker 1994 study were unlikely to be significant.	

First author, Year,	Research Question	Study population	Study quality: Including study design and grade	Intervention	Main results	Applicability to UK populations and settings Comments Funding
Tedstone et al. 1998 UK SR 2++	To review interventions designed to promote healthy feeding of infants under one year of age	Inclusion criteria: Published or unpublished reports of interventions with evaluated outcomes that promoted healthy eating for 0-1- year old infants Exclusion criteria: Observational studies Studies published before 1984 Studies that targeted high-risk or diseased populations Childs 1997, an RCT of 6 week old children in 2 inner city areas of Birmingham with high social deprivation and low income, where 34.7% children were anaemic Characteristics: Asian 75%, Afro-Caribbean and White, low level of breastfeeding. N=1000 (Int, n=500; Con, n=500) No significant difference in socioeconomic status at baseline, iron intake or anaemia Johnson 1993, an Irish	Quality assessment included sample size and power, comparability of intervention and control groups, rates of attrition, validity of method of assessing outcome, blinding of outcome assessment, treatment of potential bias and treatment of potential confounding factors. Poorer quality studies excluded, however some poorly UK studies retained, based on relevance of setting and type of intervention Graded poor to good Childs 1997,	Interventions in the home environment: 2 studies Childs 1997 Intervention - Home visits from health visitors at 3, 6 and 9 months of age giving specific dietary advice via audiotapes in relevant language + discussion + culturally appropriate leaflets. Main focus: improved intake of iron and vitamin C - rich foods. Additionally breastfeeding encouraged and good weaning practice. Controls: current practice Follow-up until 18 months Johnson 1993 Intervention: monthly visits by non-professional 'community mothers' for the infant's 1st year versus routine care (visit at birth, at 6 weeks and then as required by the public health nurse). Each community mother had 4 weeks' training and worked under the guidance of a family development nurse. Controls – routine care (routine home visits from public health nurse at birth	Nutritional outcomes: Childs 1997 No effect on the level of anaemia, blood haemoglobin and iron intake at 9 months Int Con Anaemia at 9 months 27.7% 26.8% Johnson 1993 (moderate) showed improved intake in terms of dietary recommendations for animal protein, non-animal protein, whole foods, milk, fruit and vegetables (p<0.001) resulting from a home-based peer support 'community mothers' programme. Infants in the Con group were significantly more likely to be given cow's milk before 26 weeks (p<0.001). Griffiths 1995 Int Con Anaemia at baseline (age 6-12m) 28% 37% Anaemia after 12m (age 18-24m) 24% 50% Haemoglobin g/dL at baseline 11.2 10.0 Haemoglobin g/dL after 12m 11.6 10.9 Diet score at baseline (age 6-12m) 5.9 5.2 Diet score after 12m (age 18-24m) 5.4 4.9 Significance not given but results unlikely to be sig due to small nos. (Tedstone Comments: 24 h food frequency estimates of diet intake are considered to be unreliable) McEnery and Rau 1986 Int Con (n=16) (n=27?) Haemoglobin g/dL after 12m 11.1 11.9 Vitamin supplements given 94% 86% Intervention relatively unsuccessful.	The Child Development Programme for 'community mothers' implemented in the Johnson study in 1983/4 (Johnson 1993) was an extension of the CDP developed at the Early Childhood Development Unit, Bristol Three studies with anaemia outcomes (McEnery 1986, Griffiths 1995, Childs 1997) were undertaken in the UK Anaemia may be affected by factors other than diet Childs 1997: A shortage of resources lead to incomplete delivery of the intervention

First author, Year,	Research Question	Study population	Study quality: Including study design and grade	Intervention	Main results	Applicability to UK populations and settings Comments Funding
		RCT of first time mothers in Dublin of disadvantaged infants in their 1st year (n=262: Int n=141; Con n=121). No difference between groups in sex, mother's age, marital status, social class and housing but more parents were employed in the Int group. Griffiths 1995, a non-randomised trial of children aged 6-12 m in 2 inner city Bolton areas of mainly Asian families with high social deprivation. Int from adjacent GPs practices, n=34, Con from a GP's practice in another part of town, n=?. Groups similar for social class, ethnicity and age. McEnery and Rau 1986, an RCT of pregnant Asian women at a health clinic in Waltham Forest, East London n-69 (Int, n=35: Con, n=34) Only maternal data collected at baseline	RCT moderate 1+ Griffiths 1995, non-randomised trial moderate 2+ Johnson 1993 non-randomised trial moderate 2+ No power calculation McEnery and Rau 1986 RCT poor 1- Lapinleimu 1995, Niinikoski 1996 RCT prospective good 1+	and 6 weeks). Assessment by family development nurse at birth and 1 year. 24 h dietary recall at 1 y 11% loss to follow-up: Int 10%; Con 13% Intervention set at hospital or clinic and home in postnatal period Griffiths 1995 Intervention: health promotion display focussing on diet and prevention of anaemia. Weaning leaflets in appropriate language with advice and recipes explained by health visitor, with translation if needed. Children visited by health visitor bimonthly to reinforce message for 12 m Controls: standard health care Assessment: 24 h food frequency questionnaire bimonthly, giving a diet score. Blood samples at baseline and after 12 m Loss to follow-up: Int, 9 (27%); Con 5 Intervention set at a health	Lapinleimu 1995/Niinikoski 1996 Significant reduction in total intake of dietary fat, saturated fat intake, polyunsaturated/saturated fat ratio (P/S ratio) and cholesterol intake and increased polyunsaturated fat intake. Mean baseline adjusted serum lipids and cholesterol were only significantly reduced in boys. Boys Int Con p Energy intake (Kcal) 1234 1285 ns Fat % energy 30.8% 32.8 <0.0001 P/S ratio 0.48 0.38 <0.0001 Cholesterol intake (mg/1000Kcal) 118 137 0.002 Serum cholesterol mmol/l 0.32 0.56 <0.0001 Serum non-HDL cholesterol 0.17 0.35 <0.0001 Girls Int Con p Energy intake (Kcal) 1170 1199 ns Fat % energy 31.1% 33.7 0.001 P/S ratio 0.48 0.34 0.0001 Cholesterol intake (mg/1000Kcal) 123 137 0.008 Serum cholesterol mmol/l 0.23 0.37 ns Serum non-HDL cholesterol 0.09 0.20 ns . The 3 UK studies that intervened with high-risk groups (McEnery 1986 (poor), Griffiths 1995 (moderate), Childs 1997 (moderate)) failed to reduce their incidence of anaemia.	Griffiths 1995 Study too small to give sig results. McEnery and Rau 1986 Study seriously compromised by intervention subjects being moved to the control group i.e. a self-selected intervention group. The authors concluded that a home intervention might be a better option. Lapinleimu 1995, Niinikoski 1996 gave no details of socioeconomic status of subjects. Dietary regime of controls already shown to give a polyunsaturated/saturated fat ratio of 0.3-0.4 in young children

First author, Year,	Research Question	Study population	Study quality: Including study design and grade	Intervention	Main results	Applicability to UK populations and settings Comments Funding
		Lapinleimu 1995, Niinikoski 1996, a randomised prospective trial of infants at well baby clinics in Turku, Finland, (STRIP Baby Project) recruited at 5 month visit 1990-2. 1054 families with 1062 children (56% of eligible families) Int, n=540; Con, n=522 At baseline, age 7 months, blood samples showed no sig differences in nutrient intake or serum lipid level and similar growth measurements. Search of 17 electronic databases including Medline, Science Citation Index, Social Science Citation Index, Embase, Unicorn, ASSIA and CINAHL, plus hand-searching, searching for grey literature and contacting organisations and specialists in the field 5 of 26studies evaluated interventions designed to promote good feeding practice in the weaning and post-weaning period		clinic in prenatal period McEnery and Rau 1986 Intervention: 12 week intervention with 12 culturally specific prenatal 1.5h lectures at a health clinic from a health visitor, midwife or nutritionist – with a translator and appropriate literature. Controls: appropriate prenatal care including mothercraft classes (in English) at a hospital maternity unit Assessment: children examined at 1 y of age for growth, blood analysis and dietary history Follow-up: Only 16 women attended >4 classes so all the remaining women were moved to the control group! Data for 16+ 27 children at age 1 y. Loss to follow-up= 38% Intervention set at a health clinic in postnatal period Lapinleimu 1995, Niinikoski 1996 Intervention: intensive health education with specific dietary counselling to modify and reduce dietary		Although the Lapinleimu 1995/Niinikoski 1996 STRIP intervention reduced the total intake of dietary fat - the outcome noted by Tedstone not to be appropriate for this age group according to UK recommendations. Only the boys' blood lipid levels were affected but they are more at risk of CHD. Both HDL and LDL cholesterol were reduced, which diminished the effect of reducing LDL cholesterol. Tedstone concluded that the studies reported by Johnson 1993, and Lapinleimu 1995/Niinikoski 1996 provided an inadequate basis

First author, Year,	Research Question	Study population	Study quality: Including study design and grade	Intervention	Main results	Applicability to UK populations and settings Comments Funding
		but only 5 had follow-up data for age >6 months: Childs 1997, Griffiths 1995, Johnson 1993, McEnery and Rau 1986 and {Lapinleimu 1995, Niinikoski 1996}		fat intake (also encourage physical activity and avoid passive smoking). 10 meetings with paediatricians, dieticians and nurses at 7,8,10,13,15,18,21,24,30 and 36m Individual advice for 20-45 min at every visit related to dietary records. 3-4 day dietary records at 8, 13, 24 and 36 months. Aim: 30-35% energy from fat and a polyunsaturated/monounsaturated/saturated fat ratio of 1/1/1, a cholesterol intake of <200 mg/day, energy from protein and carbohydrate to be 15% and 55%, respectively. Breast or formula milk up to age 1y, then 0.6L skimmed milk/day. Use of vegetable oil or margarine in food preparation Controls: routine health care at well baby clinic. Breast or formula milk up to age 1y, then cow's milk with ≥1.9% fat. (No detailed discussion of dietary fat and only brief discussion of dietary issues.) Infant blood samples at 7, 13, 24 and 36 m		for planning future interventions due to design limitations and overall paucity of data Review funded by the Health Education Authority

First author, Year,	Research Question	Study population	Study quality: Including study design and grade	Intervention	Main results	Applicability to UK populations and settings Comments Funding
				Follow-up to age 36 m: 70% for blood lipids and 31% for dietary records Three UK health promotion interventions aimed to reduce the prevalence of anaemia in vulnerable groups (McEnery 1986, Griffiths 1995, Childs 1997)		

2 What interventions effectively promote uptake of recommended vitamin and micronutrient supplements

Studies to be included	Evidence type	UK studies (other than RCTs)
Systematic reviews Randomised controlled trials	Systematic reviews Tedstone 1998 (see above) Randomised controlled trials None	Corroborative evidence from 1 UK study is presented in the text of the review Cleghorn 2006

3 What dietary strategies effectively reduce the risk of food allergies and intolerance?

Studies to be included	Evidence type	UK studies (other than RCTs)
Systematic reviews Randomised controlled trials	Systematic reviews Osborn and Sinn 2006 Randomised controlled trials Kalliomaki 2001, Kalliomaki 2003 Arshad 1992, Hide 1994, Hide 1996 Odelram 1996 Oldaeus 1997 Schonberger 2005 Von Berg 2003	Corroborative evidence from no UK studies is presented in the text of the review

Probiotics

First author Year	Research Question	Study population	Study Quality Power Calculation	Intervention	Main results	Comments Applicability to UK populations and settings Funding
Kalliomaki et al. 2001; 2003 Finland RCT 1+	Are probiotics (Lactobacillus GG) effective in the prevention of early atopic disease in children at high risk?	A single study with follow-up at 12 and 24 months (Kalliomaki 2001) and 4 years (Kalliomaki 2003) Inclusion criteria: Mothers with at least one 1st degree relative (or partner) with atopic eczema, allergic rhinitis or asthma Sample size n=159 Participant characteristics: No differences in infants' mean weight at birth or gestation in 2 groups. Infants mean weight: Int 3631±483 g, Plac 3612±466 g Gestation time: Int 39±1.3 weeks Plac 39±1.4 weeks Both groups had similar numbers of boys and girls: Boys: 64% Int: 32% Plac Parental smoking	Power calculation required 159 to be randomised. Expected frequency of atopic disease 50% in placebo group. With ≥56 subjects in each group, a reduction of 25% would be detected at a 5% level of significance with 80% power. Loss to follow-up was 17%. Double-blind placebo RCT. (Treatment codes retained by the supplier until data had been collected and analysed. Randomisation	Intervention mothers (n=77) received 2 capsules of $1x10^{10}$ colony-forming units of Lactobacillus rhamnosus (Lactobacillus GG, ATCC 53103) daily for 2 weeks before delivery. After delivery, breastfeeding mothers either took the capsules or gave them to their children for 6 months, in which case the capsule contents were diluted with water and given with a spoon. Control: placebo (n=82) children examined in the neonatal period and at ages 3, 6, 12, 18 and 24 months for atopic disease. Atopic eczema was the primary study endpoint; SCORAD index used to assess eczema severity. Skin prick tests, serum total IgE and antigen-specific IgE in radioallergosorbent (RAST)	Lactobacillus GG N=64 / Placebo n=68 / p Atopic eczema At 24 months: 23% / 46% RR (95% CI) 0.51 (0.32-0.84) p=0.008 SCORAD Mean (95% CI) 9.8 (8.2—11.8) / 10.4 (9.3-11.6) p=0.60 Total IgE (kU/L) mean (95% CI) At 12 months 11.2 (8.0-15.7) / 9.7 (7.0-13.4) p=0.55 At 24 months 31.3 (22.8-43.0) / 32.7 (22.6-47.3) p=0.85 Increased RAST readings[2] At 12 months 16/62 (26%) / 15/66 (23%) p=0.68 At 24 months 17/62 (27%) / 16/64 (25%) p=0.76 Prick test reaction[3] At 12 months 17/63 (27%) / 12/68 (18%) p=0.20 At 24 months 11/61 (18%) / 9/65 (14%) p=0.52 Follow-up at 4 years N=53 / n=54 Atopic eczema At 4 years: 26% / 46% RR (95% CI) 0.57 (0.33-0.97) Prick test reaction[2] At 4 years 10/50 (20%) / 9/50 (18%) p=0.80 Seasonal	Reason for discontinuation with study was non-compliance i.e. failure to attend at study visits. Dropouts showed no signs of atopic disease before discontinuation Respiratory allergic diseases usually manifest themselves at an older age than 4 years so this is not a final assessment of any effect on such diseases The intervention is applicable to the UK population but the mode of delivery and long time of administration of

[2] Number (%) with at least one increased (by >0.35 kU/L) antigen specific IgE concentration in radioallergosorbent (RAST) assay.
[3] Number (%) with at least one positive skin prick test reaction.
[4] Marker of bronchial infection. Excluding 4 children with asthma and 19 children with signs of acute respiratory infection.

First author Year	Research Question	Study population	Study Quality Power Calculation	Intervention	Main results	Comments Applicability to UK populations and settings Funding
		characteristics: 12% Int; 21% Plac Furry pet at home: 21% Int; 11% Plac Both groups had similar mean (95% CI) times (months) of exclusive and total time of breastfeeding: Exclusive bf: Int 3.0 (2.6-3.4); Plac 2.7 (2.2-3.1), p=0.28 Total bf: Int 7.2 (6.4-8.1); Plac 6.4 (5.4-7.5), p=0.24	by computer. The number needed to treat was 4.5 (2.6-15.6).	assay also carried out. Overall 132 (83%) completed the study at 2 y Intervention 64 (83%) Placebo 68 (83%)	allergic rhinitis At 4 years 19% 9.3% 0.15 Asthma At 4 years 5.7% 1.9% 0.30 Exhaled nitrous oxide[4] (ppb) mean (95% CI) N=25 n=32 At 4 years 10.8 (8.6-13.0) 14.5 (12.0-17.1) 0.03 The frequency of atopic eczema at 24 months was significantly reduced in the infants given probiotics compared with those on the placebo but there were no significant differences in the other measured indicators of atopic disease. The number needed to treat was 4.5 (2.6-15.6). The preventive effect on atopic eczema extended to 4 years. At 4 years there was no significant effect on the development of respiratory allergic disease but exhaled nitrous oxide was significantly higher in the placebo group. This indicated the possibility of more under-diagnosis or subclinical cases of respiratory allergic disease in the placebo group Most mothers chose to give the capsules to their infants: 56% (36/64) of Lactobacillus GG group and 57% (36 of 64) of placebo group, p=0.9. The preventive effect did not depend on mode of administration; in the intervention group, where infants took the probiotic 9 of 36 (25%) developed atopic eczema at 24 months and where mothers took the probiotic 6 of 28 (21%) developed atopic eczema, p=0.74.	the probiotic should be noted Funded by the Finnish Foundation for Paediatric Research, the National Technology Agency of Finland and the Allergy Research Foundation in south west Finland.

Formula Milk and allergenic food

Authors Year Country Study Design Quality
Osborn and Sinn 2006 SR 2++
Review Question:
1) What is the effect of feeding hydrolysed formulas on allergy and food intolerance in infants and children compared to adapted cow's milk or human breast milk?
2) If hydrolysed/ partially hydrolysed formulas are effective, what type of hydrolysed formula is most effective?
3) Which infants (those at low/ high risk of allergy, those receiving early/ short term/ prolonged formula feeding) benefit?

Data Sources:

- The literature search used the Tedstone 1998 SR methods as a starting point (a review that focussed on the developed world) but further search terms were added. Searches from 1980-1999 in the following databases: The Cochrane Library, Medline, Popline, Health-Star, CAB-health, CINAHL and Lilacs and key researchers in the field also contacted.

Inclusion Criteria

- Randomised or quasi-randomised trials with at least 80% follow-up that compared the use of a hydrolysed infant formula to human milk or cow's milk formula included. No country or language limitation.
- Participants were infants aged 0-6 months without clinical evidence of allergy
- Types of intervention: hydrolysed infant formulas including hydrolysed cow's milk and soy formulas, and extensively and partially hydrolysed formulas. Hydrolysed formulas could be used for: 1) early short term supplementary feeds or sole formula feeding in infants unable to be breastfed in the 1st few days or 2) for prolonged supplementation or sole formula feeding in the 1st months. 3) weaning from the breast using infant formula. Control groups to include infants who receive: excusive human milk (either breastfed or expressed) or an adapted cow's milk formula
- Primary outcomes including clinical allergy, specific allergies and food intolerance

Quality score
Studies were assessed on adequacy of method of randomisation, allocation concealment, blinding of treatment and measurement, and losses to follow-up. Adequate methodology was prespecified as: adequate randomisation and allocation concealment and <10% losses to follow-up. Five of the 18 included studies met these criteria (Maggio 2005, Oldaeus 1997, Szajewska 2001, Tsai 1991 and Vandenplas 1993)

Studies (13) RCTs and (5) Quasi-randomised trials	Country Study type (quality score)	Sample No (High/mixed /low risk infants)	Intervention	Main results (include effect size(s)/CIs for each outcome if available) Summary of Results	Applicability to UK settings/ Comments
Chirico 1997	Italy RCT	n=35 (high)	Partially hydrolysed cow's milk whey formula (Vivena HA-Primigiorni HA) vs. Cow's milk formula (control)	Author's conclusions	Most of the studies were in Europe. Just one study was in Taiwan (Tsai 1991) and for another study the country was not specified (Lam 1992). All of the studies were post 1990.
De Seta 1994	Italy RCT	n=62 (high)	Formula only to 6 m Partially hydrolysed whey formula (Nidina HA, Nestle) vs. Adapted cow's milk formula (Nidina HA, Nestle) (control)	"There is no evidence to support feeding with a hydrolysed formula for the prevention of allergy compared to exclusive breastfeeding.	
Halken 2000	Denmark Q-rand	n=246 (high)	3 Int groups Extensively hydrolysed casein formula (Nutramigen) vs. Extensively hydrolysed whey formula (Profylac) vs. Partially hydrolysed whey formula (NAN-HA) With co-interventions	In high risk infants who are unable to be completely breastfed, there is limited evidence that prolonged feeding	

Juvonen 1996	Sweden Q-rand	n=144 (mixed)	2 Int groups Pasteurised human milk from a milk bank vs. Extensively hydrolysed casein formula (Nutramigen) vs. Cow's milk formula (Baby Semp) (control)	with a hydrolysed formula compared to a cow's milk formula reduces infant and childhood allergy and infant cow's milk allergy. In view of methodological concerns and inconsistency of findings, further large, well-designed trials comparing formulas containing partially hydrolysed whey, or extensively hydrolysed casein to cow's milk formula are needed."	The majority of the formula baby milks used in the studies or similar products should be available in the UK, since the majority of the studies were carried out in Europe. There were no UK studies in this review. Five of the 18 studies were quasi-randomised and the remainder were RCTs. Few individual studies had significant results.
Lam 1992	Not specified RCT	n=100 (high)	Partially hydrolysed whey formula (NAN HA, Nestle) vs. Cow's milk formula (Nan, Nestle) (control)		
Maggio 2005	Italy RCT (good)	n=21 (mixed)	(Preterm infants after establishing full enteral feeds) Hydrolysed cow's milk derived whey preterm formula (Humana GmbH, Herford Germany) vs. Cow's milk derived preterm formula with whey: casein ratio 51:49 (Humana GmbH) (control)		
Mallett 1992	France RCT	n=177 (high)	Sole or supplementary feeding for ≥4 m. Extensively hydrolysed casein formula (Pregestimil, Mead Johnson) vs. Adapted cow's milk formula (Galliazyme, Gallia, France) (control)		
Marini 1996	Italy RCT	n=95 (high)	Moderately hydrolysed formula (Nidina HA, Nestle) vs. Adapted cow's milk formula (Nan, Nestle) (control) With co-interventions		
Nentwich 2001	Austria Q-rand	n=72 (high)	Partially hydrolysed whey cow's milk formula (Beba HA, Nestle, Denmark) vs. Extensively hydrolysed whey cow's milk formula (Hipp HA, Hipp GnbH, Gmunden, Austria) With co-interventions		
Oldaeus 1997	Austria RCT (good)	n=155 (high)	2 Int groups Extensively hydrolysed casein formula (Nutramigen, Mead Johnston) vs. Partially hydrolysed formula whey: casein ratio 60:40 (Mead Johnston) vs. Cow's milk formula (Enfamil, Mead Johnston) (control) With co-interventions		
Picaud 2001	France RCT	n=16 (mixed)	Isocaloric trial formulas from a nutrition laboratory in Liege Partially hydrolysed preterm whey formula vs. Standard preterm cow's milk whey formula (control)		
Saarinen 1999	Finland Q-rand	n=5317 (mixed)	2 Int groups Pasteurised donor human milk vs. Extensively hydrolysed whey formula (Pepti-junior, Nutricia, Netherlands) vs. Cow's milk formula (Tutteli, Vali, Finland) (control)		
Szajewska 2001	Poland RCT (good)	n=46 (mixed)	2 Int groups Extensively hydrolysed preterm formula whey: casein ratio 60:40 (Nutricia, Holland) vs. Partially hydrolysed preterm formula whey: casein ratio 60:40 (Nutricia, Holland) vs. Standard preterm formula whey: casein ratio 60:40 (Nutricia, Holland) (control)		
Tsai 1991	Taiwan RCT (good)	n=33 (high)	Infants breastfed for 1-2 m then fed partially hydrolysed formula (Nan HA, Nestle) for subsequent 4 m vs. Regular		

			formula from birth		
Vandenplas 1992	Belgium RCT	n=67 (high)	Exclusive formula feeding for 6 m Whey partially hydrolysed formula (Nan HA, Nestle) vs. Adapted cow's milk formula (Nan HA, Nestle) (control) With co-interventions		
Vandenplas 1993	Belgium RCT (good)	n=41 (low)	Exclusive formula feeding for 13 weeks Whey 'intermediate' hydrolysed formula (Nutrilon Pepti, Nutricia) vs. Whey predominant cow's milk formula (Nutrilon Pepti, Nutricia) (control)		
Willems 1993	Belgium Q-rand	n=122 (high)	Partially hydrolysed whey formula (Nan HA, Nestle) vs. Adapted cow's milk formula (control)		
Von Berg 2003	Germany RCT	n=2254 (high)	3 Int groups Partially hydrolysed 100% whey formula (Beba HA, Nestle, Switzerland) vs. Extensively hydrolysed 100% whey formula (Hipp HA, Hipp, Germany) vs. Lactose-free extensively hydrolysed 100% casein formula (Nutramigen, Mead Johnston, Germany) vs. Adapted cow's milk formula whey: casein ratio 60:40 (Nutrilon Premium, Nutricia/Numico, Netherlands) (control) With co-interventions		
			The prespecified comparisons were: Comparison 01: Early short term feeding – hydrolysed formula vs. human milk feeding (low risk infants) 2 studies: Juvonen 1996, Saarinen 1999 Any allergy Asthma, Eczema, Food Allergy: 1 study (Juvonen 1996) no significant differences in childhood incidence at 3 years Cow's milk allergy: 1 study found no significant difference in incidence of infant cow's milk allergy up to mean age 27 months (Saarinen 1999) or childhood incidence (1 study, Juvonen 1996) Comparison 02: Prolonged feeding - hydrolysed formula vs. human milk feeding No studies Comparison 03: Early short term feeding – hydrolysed formula vs. cow's milk formula 2 studies: Juvonen 1996, Saarinen 1999 Any allergy, Asthma, Eczema, Food Allergy: Juvonen 1996: no significant differences in childhood incidence	Comparison 01: Early short term feeding – hydrolysed formula vs. human milk feeding (low risk infants) There were just 2 studies of early short-term hydrolysed formula versus exclusive human milk giving no significant difference in incidence of any childhood allergy (Juvonen 1996) or for incidence of infant cow's milk allergy (Saarinen 1999). Comparison 02: Prolonged feeding - hydrolysed formula vs. human milk feeding No studies Comparison 03: Early short term feeding – hydrolysed formula vs. cow's milk formula There were just 2 studies of early short-term hydrolysed formula versus cow's milk formula. One study found a significant reduction in incidence of infant cow's milk	

	Cow's milk allergy: Saarinen 1999: a reduction in infant cow's milk allergy of borderline significance RR 0.62, 95% CI 0.38, 1.00; RD-0.01, 95% CI -0.02, 0.00 No significant difference in incidence of childhood cow's milk allergy (1 study, Juvonen 1996) Comparison 04: Prolonged feeding - hydrolysed formula vs. cow's milk formula 10 studies: Chirico 1997, De Seta 1994, Lam 1992, Mallett 1992, Marini 1996, Oldaeus 1997, Tsai 1991, Vandenplas 1992, Von Berg 2003, Willems 1993. The authors report that only one study had allergy preventive co-interventions. Only 3 individual studies had significant results (Lam 1992, Marini 1996, Vandenplas 1992) for any allergy and/pr cow's milk allergy. Any allergy: Meta-analysis of seven studies (2514 infants) found a significant reduction in any infant allergy incidence (De Seta 1994, Lam 1992, Marini 1996, Oldaeus 1997, Vandenplas 1992, Von Berg 2003, Willems 1993). RR 0.79, 95% CI 0.66, 0.94; RD-0.04, 95% CI -0.08, -0.01 2 individual studies also showed a significant reduction: Lam 1992, RR 0.62, 95% CI 0.39, 0.99 Vandenplas 1992, RR 0.45, 95% CI 0.22, 0.94 Meta-analysis of two studies (950 infants) found no significant difference in childhood allergy incidence. However, there was a significant reduction for Marini 1996, RR 0.42, 95% CI 0.19, 0.90 but a nonsignificant reduction for Von Berg 2003, RR 0.91, 95% CI 0.73, 1.14. Asthma: Meta-analysis found no significant differences in infant asthma incidence (4 studies: De Seta 1994, Marini 1996, Oldaeus 1997, Tsai 1991), childhood incidence (Marini 1996) and childhood prevalence (Von Berg 2003). Eczema: Meta-analysis found no significant differences in infant eczema incidence (8 studies: Chirico 1997, De Seta 1994, Lam 1992, Mallett 1992, Marini 1996, Oldaeus 1997, Tsai 1991, Von Berg 2003), childhood eczema incidence (2 studies: Marini 1996, Von Berg 2003) and childhood eczema prevalence (Von Berg 2003). Rhinitis: Meta-analysis found no significant differences in infant rhinitis incidence (Marini 1996, Oldaeus 1997) or childhood rhinitis incidence (Marini 1996) Food Allergy: Oldaeus 1997 found no significant difference in infant food allergy. Cow's milk allergy: Vandenplas 1992: a reduction in infant cow's milk allergy RR 0.36, 95% CI 0.15, 0.89 Comparison 05: Prolonged feeding - hydrolysed formula vs. cow's milk formula (low risk infants) No studies	allergy, RR 0.62, 95% CI 0.38, 1.00; RD-0.01, 95% CI -0.02, 0.00 (Saarinen 1999). Comparison 04: Prolonged feeding - hydrolysed formula vs. cow's milk formula There were 10 studies of prolonged feeding - hydrolysed formula vs. cow's milk formula. Meta-analysis of seven studies found a significant reduction in any infant allergy incidence, RR 0.79, 95% CI 0.66, 0.94; RD-0.04, 95% CI -0.08, -0.01, whereas meta-analysis of 2 studies found no significant difference in childhood allergy incidence. Meta-analyses found no significant differences for infant asthma incidence (4 studies), incidence of infant eczema (8 studies), childhood eczema incidence (2 studies). Additionally, individual studies found no significant differences for childhood incidence and prevalence of asthma, incidence of childhood rhinitis, and incidence of infant food allergy. One study found a significant reduction in cow's milk allergy RR 0.36, 95% CI 0.15, 0.89 (Vandenplas 1992). Comparison 05: Prolonged feeding - hydrolysed formula vs. cow's milk formula (low risk infants) No studies	Three studies of prolonged feeding of hydrolysed formula vs. cow's milk formula confirmed various results by specific IgE test (Chirico 1997, Oldaeus 1997, Vandenplas 1992). Five studies reported assessment for allergy without knowledge of patient allocation (Halken 2000, Nentwich 2001, Oldaeus 1997, Vandenplas 1992, von Berg 2003).

	Comparison 06: Prolonged feeding - hydrolysed formula vs. cow's milk formula (high risk infants) 7 studies: De Seta 1994, Lam 1992, Marini 1996, Oldaeus 1997, Vandenplas 1992, Von Berg 2003, Willems 1993 In practice all 10 studies in Comparison 04 are in high risk infants and the authors give an exact copy of those results. Results were identical to those for comparison O4 (see above) i.e. were of high risk infants	Comparison 06: Prolonged feeding - hydrolysed formula vs. cow's milk formula (high risk infants) The authors report that seven studies were in high risk infants. These were the same studies which were used for the meta-analyses for 'all' studies of prolonged feeding - hydrolysed formula vs. cow's milk formula. In practice all 10 studies in Comparison 04 are in high risk infants and the authors give an exact copy of those results.	
	Comparison 07: Prolonged feeding – extensively hydrolysed formula vs. cow's milk formula 4 studies: Mallet 1992, Oldaeus 1997, Szajewska 2001, von Berg 2003 None of the 4 individual studies reported a significant reduction for any allergy or any specific allergy or food intolerance. Any allergy: Meta-analysis found no significant differences in infant allergy incidence (2 studies, 1561 infants) or childhood allergy incidence (1 study) Eczema: Meta-analysis found no significant differences in infant eczema incidence (3 studies, 1726 infants) or childhood eczema incidence and prevalence (1 study). Asthma: No significant differences for infant asthma incidence (1 study) or childhood asthma prevalence (1 study) Rhinitis and Food allergy: No significant differences for infant incidence of rhinitis or food allergy (1 study)	Comparison 07: Prolonged feeding – extensively hydrolysed formula vs. cow's milk formula Meta-analyses of the 4 studies of prolonged feeding – extensively hydrolysed formula vs. cow's milk formula gave no significant differences for incidence of any infant allergy (2 studies) or infant eczema incidence (3 studies). Additionally, individual studies found no significant differences for any childhood allergy incidence; childhood incidence and prevalence of eczema; infant incidence and childhood prevalence of asthma; incidence of infant rhinitis, or incidence of infant food allergy.	
	Comparison 08: Prolonged feeding – partially hydrolysed vs. cow's milk formula 9 studies: Chirico 1997, De Seta 1994, Lam 1992, Marini 1996, Oldaeus 1997, Tsai 1991, Vandenplas 1992, Von Berg 2003, Willems 1993 Only 3 individual studies had significant results (Lam 1992, Marini 1996, Vandenplas 1992) for any allergy and/or cow's milk allergy. Any allergy: Meta-analysis of seven studies (1482 infants) found a significant reduction in any infant allergy incidence (De Seta 1994, Lam 1992, Marini 1996, Oldaeus 1997, Vandenplas 1992, Von Berg 2003, Willems 1993). RR 0.79, 95% CI 0.65, 0.97 2 individual studies also showed a significant reduction: Lam 1992, RR 0.62, 95% CI 0.39, 0.99 Vandenplas 1992, RR 0.45, 95% CI 0.22, 0.94 Meta-analysis of two studies (510 infants) found no significant difference in childhood allergy incidence but there was significant and substantial heterogeneity between the studies with a significant reduction for Marini 1996, RR 0.42, 95% CI 0.19, 0.90 and a	Comparison 08: Prolonged feeding – partially hydrolysed vs. cow's milk formula There were 9 studies of prolonged feeding of partially hydrolysed formula versus cow's milk formula. Meta-analysis of 7 studies found a significant reduction for any infant allergy, RR 0.79, 95%CI: 0.65, 0.97, of which two individual studies also showed a significant reduction (Lam 1992, Vandenplas 1992). Meta-analysis of two studies (Marini 1996, Von Berg 2003) showed no significant difference in any childhood allergy – the two studies showed significant heterogeneity with only one study giving a significant difference, RR 0.42, 95%CI: 0.19, 0.90 (Marini 1996). No significant reduction was found for incidence of infant asthma (meta-analysis of four studies), childhood asthma (Marini 1996) or childhood asthma prevalence (Von Berg 2003); or infant eczema incidence	

	nonsignificant reduction for Von Berg 2003, RR 0.95, 95% CI 0.73, 1.25. Asthma: Meta-analysis found no significant differences in infant asthma incidence (4 studies), childhood incidence (1study) and childhood prevalence (1 study). Eczema: Meta-analysis found no significant differences in infant eczema incidence (7 studies), childhood eczema incidence (2 studies) and childhood eczema prevalence (1 study). Rhinitis: There were no significant differences in infant rhinitis incidence (3 studies) or childhood rhinitis incidence (1 study) Food Allergy: 1 study found no significant difference in infant food allergy. Cow's milk allergy: Vandenplas 1992: a reduction in infant cow's milk allergy RR 0.36, 95% CI 0.15, 0.89 Comparison 09: Prolonged feeding – extensively hydrolysed formula vs. partially hydrolysed formula 4 studies: Halken 2000, Nentwich 2001, Oldaeus 1997, Von Berg 2003 None of the 4 individual studies reported any significant differences for infant or childhood allergy Any allergy: Meta-analysis of 3 studies found no significant reduction in any infant allergy incidence and 1 study found no significant reduction in childhood incidence. Asthma: Meta-analysis found no significant differences in infant asthma incidence (2 studies) or for childhood prevalence (1 study). Eczema: Meta-analysis found no significant differences in infant eczema incidence (4 studies) or for childhood eczema incidence or prevalence (1 study). Rhinitis: There were no significant differences in infant rhinitis incidence (2 studies). Food Allergy: Meta-analysis of 2 studies (Halken 2000, Oldaeus 1997; 341 infants) found a significant reduction in incidence of infant food allergy. RR 0.43, 95% CI 0.19, 0.99 Cow's milk allergy: There was no significant difference in infant incidence of cow's milk allergy (1 study). Comparisons 10: Prolonged sole formula feeding – hydrolysed formula vs. cow's milk formula 6 studies: Chirico 1997, De Seta 1994, Lam 1992, Marini 1996, Vandenplas 1992, Willems 1993 3 of the 6 individual studies reported significant results (Lam 1992, Marini 1996, Vandenplas 1992). Any allergy: Meta-analysis of 5 studies (425 infants) found a significant reduction in any infant allergy incidence (De Seta 1994, Lam 1992, Marini 1996, Vandenplas 1992, Willems 1993). RR 0.61, 95% CI 0.46, 0.80	(meta-analysis of 7 studies), childhood eczema incidence (2 studies) and childhood eczema prevalence (Von Berg 2003); or infant rhinitis incidence (three studies, no meta-analysis) and childhood rhinitis incidence (Marini 1996); or incidence of food allergy (Oldaeus 1995). However one study of prolonged feeding of partially hydrolysed formula versus cow's milk formula found a significant reduction in infant cow's milk allergy, RR 0.36, 95%CI: 0.15, 0.89 (Vandenplas 1992). Comparison 09: Prolonged feeding – extensively hydrolysed formula vs. partially hydrolysed formula Comparison of prolonged feeding of extensively hydrolysed formula versus partially hydrolysed formula was made for four studies. No significant differences were found for any individual study or for meta-analyses of incidence of any infant allergy (3 studies), incidence of infant asthma (2 studies) and incidence of infant eczema (4 studies). However, there was a significant reduction in incidence of infant food allergy (2 studies), RR 0.43, 95%CI: 0.19, 0.99 (Halken 2000, Oldaeus 1997). Comparisons 10: Prolonged sole formula feeding – hydrolysed formula vs. cow's milk formula A comparison was also made for studies of prolonged feeding of hydrolysed formula versus cow's milk formula where infants were solely on formula feeding, which included 6 studies. Overall conclusions did not change. Meta-analysis of 5 studies found a significant reduction in any infant allergy incidence, RR 0.61, 95% CI: 0.46, 0.80 (De Seta 1994, Lam 1992, Marini 1996, Vandenplas 1992, Willems 1993). Meta-analysis found no significant	

	2 individual studies also showed a significant reduction: Lam 1992, RR 0.62, 95% CI 0.39, 0.99 Vandenplas 1992, RR 0.45, 95% CI 0.22, 0.94 One study (Marini 1996) also found a significant reduction in childhood incidence of any allergy, RR 0.42, 95% CI 0.19, 0.90 Asthma: Meta-analysis found no significant differences in infant asthma incidence (2 studies) or for childhood incidence (1 study). Eczema: Meta-analysis found no significant differences in infant eczema incidence (4 studies) or for childhood eczema incidence (1 study). Rhinitis: One study found no significant differences in childhood rhinitis incidence. Cow's milk allergy: One study (Vandenplas 1992, 67 infants) found a significant reduction in incidence of infant Cow's milk allergy, RR 0.36, 95% CI 0.15, 0.89. Comparisons 11: Prolonged sole formula feeding – hydrolysed formula vs. cow's milk formula - Allergy/food intolerance confirmed by a test For some studies allergy/ food intolerance was confirmed by specific IgE test. 3 studies: Chirico 1997, Oldaeus 1997, Vandenplas 1992) Overall conclusions remained unchanged. Comparisons 12: Prolonged sole formula feeding – hydrolysed formula vs. cow's milk formula - Blinded measurement Five studies reported assessment for allergy without knowledge of patient allocation 5 studies: Halken 2000, Nentwich 2001, Oldaeus 1997, Vandenplas 1992, Von Berg 2003. Overall conclusions remained unchanged Comparison 13: Prolonged feeding – hydrolysed formula vs. cow's milk formula (studies of adequate methodology) 4 studies: Maggio 2005, Oldaeus 1997, Szajewska 2001, Tsai 1991 No significant differences found for the individual studies. Any allergy: No significant reduction in any infant allergy incidence (1 study) Asthma: Meta-analysis found no significant differences in infant asthma incidence (2 studies). Eczema: Meta-analysis found no significant differences in infant eczema incidence (2 studies). Rhinitis: No significant differences in infant rhinitis incidence (2 studies), meta-analysis not possible. Food Allergy: No significant reduction in food allergy incidence (1 study)	differences in infant asthma incidence (2 studies) or incidence of infant eczema (4 studies). Comparisons 11: Prolonged sole formula feeding – hydrolysed formula vs. cow's milk formula - Allergy/food intolerance confirmed by a test Overall conclusions remained unchanged. Comparisons 12: Prolonged sole formula feeding – hydrolysed formula vs. cow's milk formula - Blinded measurement Overall conclusions remained unchanged Comparison 13: Prolonged feeding – hydrolysed formula vs. cow's milk formula (studies of adequate methodology) Further analysis using the two of the studies of hydrolysed formula versus cow's milk formula which were of adequate methodology (Oldaeus 1997, Tsai 1991) found no significant differences for the only two possible meta-analyses for incidence of infant eczema and infant asthma.	

	Comparison 14: Prolonged feeding – partially hydrolysed whey formula vs. cow's milk formula 8 studies: Chirico 1997, De Seta 1994, Lam 1992, Marini 1996, Tsai 1991, Vandenplas 1992, Von Berg 2003, Willems 1993 Three individual studies had significant results (Marini 1996, Lam 1992, Vandenplas 1992) Any allergy: Meta-analysis of 6 studies (1391 infants) found a significant reduction in any infant allergy incidence (De Seta 1994, Lam 1992, Marini 1996, Vandenplas 1992, Von Berg 2003, Willems 1993). RR 0.73, 95% CI 0.59, 0.90 2 individual studies also showed a significant reduction: Lam 1992, RR 0.62, 95% CI 0.39, 0.99 Vandenplas 1992, RR 0.45, 95% CI 0.22, 0.94 Meta-analysis of 2 studies (510 infants) found no significant reduction in any childhood allergy incidence (Marini 1996, Von Berg 2003). There was significant, p=0.04, and substantial heterogeneity (I^2=75.2%). One individual study (Marini 1996) found a significant reduction in childhood incidence of any allergy, RR 0.42, 95% CI 0.19, 0.90 Asthma: Meta-analysis found no significant differences in infant asthma incidence (3 studies) or for childhood incidence or prevalence (1 study). Eczema: Meta-analysis found no significant differences in infant eczema incidence (6 studies) or for childhood eczema incidence (2 studies) or for childhood eczema prevalence (1 study). Rhinitis: Two studies found no significant differences in childhood rhinitis incidence; meta-analysis was not possible. One study found no difference in childhood rhinitis incidence. Cow's milk allergy: One study (Vandenplas 1992, 67 infants) found a significant reduction in incidence of infant cow's milk allergy, RR 0.36, 95% CI 0.15, 0.89	Comparison 14: Prolonged feeding – partially hydrolysed whey formula vs. cow's milk formula A further comparison was made for studies of prolonged feeding of partially hydrolysed whey formula versus cow's milk formula, which in practice included eight of the nine studies above (Comparison 8) with the omission of the study by Oldaeus et al (1997). Overall conclusions were not changed. The significant reduction found for the meta-analysis of six studies of any infant allergy became, RR 0.73, 95%CI: 0.59, 0.90 (De Seta 1994, Lam 1992, Marini 1996, Vandenplas 1992, Von Berg 2003, Willems 1993).	
	Comparison 15: Prolonged feeding – partially hydrolysed casein containing formula vs. cow's milk formula One study: Oldaeus 1997 No significant differences reported for infant incidence of any allergy, asthma, eczema, rhinitis or food allergy	Comparison 15: Prolonged feeding – partially hydrolysed casein containing formula vs. cow's milk formula The study by Oldaeus et al (1997) was of prolonged feeding of partially hydrolysed casein containing formula versus cow's milk formula and reported no significant differences for incidence of any allergy.	
	Comparison 16: Prolonged feeding – extensively hydrolysed whey formula vs. cow's milk formula One study: Von Berg 2003 One study (Von Berg 2003) reported no significant difference in incidence of infant or	Comparison 16: Prolonged feeding – extensively hydrolysed whey formula vs. cow's milk formula Only one study was of extensively hydrolysed whey formula versus cow's milk formula (Von Berg 2003) and	

	childhood allergy, incidence of infant eczema, incidence or prevalence of childhood eczema, or prevalence of childhood asthma Comparison 17: Prolonged feeding – extensively hydrolysed casein containing formula vs. cow's milk formula 3 studies: Mallet 1992, Oldaeus 1997, Von Berg 2003 Von Berg 2003 was the only study to report individual significant results (for any allergy and eczema). Any allergy: Meta-analysis found no significant reduction in any infant allergy incidence (1072 infants) (2 studies) Von Berg 2003 showed a significant reduction for infant incidence, RR 0.72, 95% CI 0.53, 0.97 Asthma: Oldaeus 1997 found no significant result for infant incidence of asthma and Von Berg 2003 found no significant result for childhood prevalence. Eczema: Von Berg 2003 reported a significant reduction in infant eczema, RR 0.69, 95% CI 0.47, 1.00; childhood incidence of eczema, RR 0.66, 95% CI 0.44, 0.98; and childhood prevalence of eczema, RR 0.50, 95% CI 0.27, 0.92 Meta-analysis (3 studies) found a significant reduction in incidence of infant eczema: RR 0.71, 95% CI 0.51, 0.97 Rhinitis: One study found no significant differences in infant rhinitis incidence Food Allergy: One study found no significant differences in infant food allergy incidence Adverse effects of hydrolysed formulas	had no significant outcome differences. Comparison 17: Prolonged feeding – extensively hydrolysed casein containing formula vs. cow's milk formula Comparisons were also made for 3 studies of extensively hydrolysed casein formula versus cow's milk formula (Mallet 1992, Oldaeus 1997, Von Berg 2003) where overall results were different from those for extensively hydrolysed formula per se. No significant reduction was found for incidence of any infant allergy (meta-analysis of 2 studies); incidence of infant asthma (Oldaeus 1997) and prevalence of childhood asthma (Von Berg 2003); or infant rhinitis incidence (Marini 1996); or incidence of food allergy (Oldaeus 1995). Von Berg et al (2003) found with extensively hydrolysed casein formula versus cow's milk formula a significant reduction in incidence of any childhood allergy, RR 0.72, 95%CI: 0.53, 0.97; incidence of infant eczema, RR 0.69, 95%CI: 0.47, 1.00; incidence of childhood eczema, RR 0.66, 95%CI: 0.44, 0.98; and prevalence of childhood eczema, RR 0.50, 95%CI: 0.27, 0.92. Meta-analysis for incidence of infant eczema (all three studies) also showed a significant reduction for extensively hydrolysed casein formula versus cow's milk formula, RR 0.69, 95%CI: 0.47, 1.00, but the study by Von Berg et al (2003) contributed 75% weight to the meta-analysis. Adverse effects of hydrolysed formulas No study reported serious adverse events or mortality Seven studies reported growth (5 found no difference in weight between groups and 2 found significantly less growth in groups receiving hydrolysed formula) Three reported infant refusal of hydrolysed formula Additional results were presented for weight gain, length gain, and head circumference change.	

First author, Year	Research Question	Study population	Study quality	Intervention	Main results	Comments Applicability to UK populations and settings Funding
Arshad et al. 1992 & Hide et al. 1994 & Hide et al 1996 Isle of Wight, UK RCT 1+	To assess whether avoidance of food and inhaled allergens in infancy protects against the developme nt of allergic disorders in high-risk infants	Inclusion criteria: Infants with a family history of atopy and high (>0.5 kU/l) total IgE cord-blood concentrations were allocated randomly to prophylactic and control groups. Exclusion criteria: Not stated Sample size n=120 Participant characteristics The two groups were similar in hereditary characteristics, cord blood IgE distribution, home environments, rates of breastfeeding, formula feeding and introduction of solid foods	Power calculation not reported Mothers were prenatally randomised via computer-generated random numbers. The allergy specialist was not aware of the allocation group. Loss to follow-up 12%. All subjects were used in the final analysis.	Intervention group (I) (n=58) A dual approach was used: breastfeeding mothers avoided allergenic foods (milk, egg, fish and nuts) Infants' diets were free of dairy, egg, wheat, unhydrolysed soya, orange, fish and nuts up to 12 months. Up to 9 months breastfeeds were supplemented if necessary with a soya-based protein hydrolysate (Aptamil HA). Formula fed infants received Aptamil HA from birth. Cow's milk and soya were introduced at 9 months, wheat at 10 months, and egg at 11 months. A dietitian explained the dietary restriction in detail to all intervention mothers at birth. Written instructions were also given to mothers with a list of foods to take. In addition, the infants' bedrooms and living rooms were treated with an acaricidal powder and foam (benzyl benzoate, a chemical agent used to kill mites) in the first week of life	<u>Follow-up at 10-12 months</u> (reported in both Arshad 1992 and Hide 1994) One or more allergic symptoms: p<0.005 I: 8/58 (14%), C 25/62 (40%) OR: 6.34, 95% CI: 2.0, 20.1 Asthma: p<0.05 I: 4/58 (7%), C: 12/62 (19%) OR: 4.13, 95% CI: 1.1, 15.5 Eczema: p<0.05 I: 4/58 (7%), C 12/62 (19%) OR: 3.6, 95% CI: 1.0, 12.5 Food intolerance: not significant I: 2/58 (3%), C: 7/62(11%) OR: 3.29, 95% CI: 0.6, 17.3 Parental smoking was a significant risk factor for total allergy at 12 months whether only one parent smoked or both parents smoked (OR: 3.97, 95% CI: 1.2, 13.6, p<0.05 and OR: 4.72, 95% CI: 1.2, 18.2, P<0.05, respectively). At 12 months, infants from a low socio-economic group had a higher risk of developing allergy than infants from high socio-economic group (OR: 3.30, 95% CI: 1.1, 10.2, p<0.05). <u>Follow-up at 2 years</u> (reported in Hide 1994) One or more allergic symptoms: I: 15/58 (26%) asthma 9, eczema 8, food intolerance 7, allergic rhinitis 2 C: 29/62 (47%) asthma 17, eczema 15, food intolerance 11, allergic rhinitis 7 At 2 years infants in the control group remained more likely to manifest any allergy (p<0.005), and eczema (p=0.008), but the enhanced risk of asthma shown at 1 year was no longer significant The authors concluded that the intervention (reduced exposure to allergens in food and in house dust) lowered the frequency of allergic disorders in the first years of life. Passive smoking is an important risk factor that should also be addressed in any prophylactic programme	301 women were randomised before the birth of the infant. 136 met the inclusion criteria. 16 of the infants did not complete follow-up (11 in the intervention group and 5 in the control group) Of the 120 remaining, 8 mothers gave up the diet, and 3 infants were introduced to cow's milk. These infants were included in the final analysis It appears that this study was conducted in the UK (not explicitly stated) and is therefore directly applicable Supported by Milupa (UK),

First author, Year	Research Question	Study population	Study quality	Intervention	Main results	Comments Applicability to UK populations and settings Funding
				and then every 3-9 months, and all infants used polyvinyl-covered mattresses with vented head area Control group (C) (n=62): the diet of the mothers was unrestricted and presumed to be the normal diet as recommended by health workers There was no acaricidal treatment All lactating mothers were given 1000 mg calcium/day supplementation and vitamin supplements. Assessment Data on allergic manifestations were compared. The same paediatric allergy specialist examined all children for allergic diseases and was unaware of the allocation group. Skin prick tests were also carried out. Dermatophagoides pteronyssimus antigen (Der p 1) in house dust was measured at 9 months in both groups and during the first week after birth for the	<u>Follow-up at 4 years</u> (reported in Hide 1996) More total allergy in the control group (OR 2.73, 95% CI 1.21 to 6.13, p<0.02) More definite allergy (allergic symptoms with positive skin prick test) in the control group (OR 5.6, CI 1.8 to 17.9, p<0.005) More positive skin prick tests in the control group (OR 3.7, CI 1.3 to 10.0, p<0.02) More eczema in the control group (OR 3.4, CI 1.2 to 10.1, p<0.05) The authors concluded that the intervention significantly reduced the risk of atopic disease among infants at very high risk of atopy. They state close medical and dietetic supervision must be available.	Crawford Chemicals (UK), the Isle of Wight Health Authority Trustees, the Wessex Medical Trust and the National Asthma Campaign (Isle of Wight Branch)

First author, Year	Research Question	Study population	Study quality	Intervention	Main results	Comments Applicability to UK populations and settings Funding
				Intervention group. Follow up of 120/136 (88%) (see comments) at 10-12 months and 2 years (100%)		

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Odelram et al. 1996 Sweden and Finland RCT 1-	To compare ultra filtered whey hydrolysate formula (eH) with cow's milk formula (CMF) to prevent atopy developme nt in infants at high risk of developing atopy	Inclusion criteria Infants were recruited if there were at least two atopic family members, or one atopic parent, and cord blood total IgE >0.5 kU/l Exclusion criteria Gestational age below 37 weeks, complicated delivery, neonatal illness, severe birth defects, and documented non-compliance with diet prescriptions were reasons for exclusion Study population N=91 (71 randomised) Recruited at well-mother clinics in Turku, Finland and Motala, Sweden Participant characteristics Turku 72; Motala 19 48 boys, 43 girls Mean birth weight: 3542g (2280-4700 g) No significant differences between groups with regard to family members with atopy, age of introduction of solid foods,	Power calculation not reported Randomisation of 82 infants after breastfeeding for 0-12 months only for 2 intervention groups in blocks of 4, separately for infants at the 2 centres. 71 of these infants were exclusively breastfed for ≤9 months and included in the study analysis. 3rd group created due to its high level of long >9 months breastfeeding. Concealment was not addressed. Blinding was only addressed at the physical examination at 18 months	Intervention A: infants were given hydrolysed ultra filtered cow's milk whey formula (Profylac) (n=32) Intervention B: infants were given ordinary cow's milk formula (n=39) Control: infants who were exclusively breast-fed for more than 9 months (n=20) For all families, allergy prophylactic advice was given, including discouraging tobacco smoke, and pets. No fish or egg products were advised for the first 12 months of life, and all cow's milk products were to be avoided. Mothers were advised to avoid cow's milk, egg and fish from 10 days before expected day of delivery and throughout breastfeeding. Breastfeeding was encouraged, with other foods to be introduced from about 4 months. Mothers given a calcium carbonate supplement, 1000 mg Ca daily	At 18 months. Atopy before/after formula introduction . n/n %after Int A 7/10 31% Int B 7/15 39% 'Control' 7/3 35% These differences were not statistically significant, nor were those for skin prick tests or elevated levels of serum total-IgE and CM IgE	Study methodology was well reported but outcome data/results were less clearly reported Duration of breastfeeding in the Swedish/Finnish families was higher than in Britain Funded by the Swedish Medical Research Council, the Swedish National Association of the Prevention of Asthma and Allergy, the Medical Research Fund of the County of Ostergotland, the King Gustav Vth 80-year Anniversary Fund, the Odd Fellows Foundation, and the Swedish

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		environmental tobacco smoke exposure or house pets		When women decided to stop breastfeeding (before 9 months), they were randomised to one of the intervention groups The families completed questionnaires on symptoms of atopic disease and allergy when the infants were 3, 6, 9, 12 and 18 months old, including skin prick tests and determination of serum total IgE and cow's milk specific IgE. Parents also completed daily diaries recording symptoms and feeding changes including dietary mistakes. The infants had a blinded physical examination at 18 months,		Association for Allergology

First author Year	Research question	Study population	Study quality	Intervention	Main results	Comments Applicability to UK populations and settings Funding
Oldaeus et al. 1997 Sweden RCT 1-	To compare the incidence and severity of atopic disease and allergic sensitisation during the first 18 months of life in infants at risk who were fed either an extensively hydrolysed formula milk a partially hydrolysed formula milk or a standard formula milk from the start	Inclusion criteria Infants of pregnant women attending well mother clinics in three towns in southeast Sweden. Infants with two or more family members with significant atopic disease (asthma, allergic rhinitis, or atopic dermatitis, diagnosed by a doctor) or one family member and cord blood IgE concentration of at least 0.5 kU/l (or food allergy with an immediate reaction or a positive oral challenge), were included Exclusion criteria Clear maternal risk of non-compliance with diet or follow-up, birth defects, severe chronic disease, birth at <35 weeks, mechanical ventilation, single heredity, breastfed for >9 months. Urticaria alone not accepted. 155 infants were randomised as weaning began Study population	Power calculation: 55 per group for 80% power to detect a 25% reduction of allergic disease in the intervention group from the expected 40%. The cumulative incidence of atopic disease was also higher than expected: 60% in RM cf 40% in N group and the reduction smaller (20%). The study was therefore underpowered as it would require 107 instead of 55 subjects in each group to have 80% power Randomisation at weaning stage, stratified	One of 3 formulas to be given from start of weaning to age 9 months: N (n=55): extensively hydrolysed casein formula (Nutramigen) PH (n=51): partially hydrolysed formula whey: casein ratio 60:40 RM (n=49): standard formula milk (Enfamil) For all families, allergy preventive measures recommended, including discouraging smoking and furry animals in the home. All mothers were asked to eliminate cows' milk, eggs and fish from their diet from one week before the birth was expected until breastfeeding ended. Mothers were asked to exclude the following from their infants' diet: milk (to 9m), eggs, fish and citrus fruits (to 1y), other solid foods (to 4m). All mothers were given a 1 g/day calcium supplement during the diet period.	Wheezing during first 18 months: N 13%, PH 16% and RM 33% Significantly higher rates in RM than N group (p=0.031). Differences at 6, 9 and 12 months, and differences between N and PH group, not significant Atopic dermatitis in first 9 months: Significantly higher rates in PH 44% (p=0.004) and RM 41% (p=0.006) than N group 17%. Intergroup differences not significant at 6, 12 and 18 months Cumulative atopic symptoms: Significantly less in N than RM at 6, 9, 12 and 18 months (p=0.013-<0.001) Significantly less in N than PH group at 6 months (p=0.025) and 9 months (p=0.018) Significantly less in PH than RM group at 18 months (p=0.039) At 18 months: N 51%, PH 64% and RM 84% Yet non significant data also given for final cumulative diagnosis of atopy and obvious atopic disease at 18 months: N 29%, PH 44% and RM 33% Positive skin prick test for eggs: At 9 months, significantly fewer in N group (10%) than in PH group (33%) (p=0.006) otherwise no sig result. Other results are reported. Summary The extensively hydrolysed formula (N) had an allergy preventive effect but not the partially hydrolysed formula (PN) during the first 18 months of life of high risk infants.	Most of the differences in morbidity emerged at 3-6m, in line with other studies Authors report that analysis of confounding factors gave no difference between the groups or study sites. These conclusions may be applicable in the UK Funded by Bristol-Myers Inc, the Swedish Medical Research Council, the National Association for the Prevention of Asthma and Allergy, the Queen Sylvia's Jubilee Fund, and the Division of Research, Jonkoping City Council.

	of weaning until 9 months of age	There were no sig differences between the groups for: Birthweight, sex ratio, Furry animals in the home initially: N 22%, PH 6%, RM 16% and at the end of 1 year: N 27%, PH 8%, RM 16% Mean age at formula introduction (months) N 3.6, PH 3.8, RM 3.3 Mean age when weaning completed (months): N 5.1, PH 5.6, RM 5.1	according to age at starting weaning/giving formula – method not given. The formula tins had the same design but the RM formula was not masked. Authors report the challenge testing as being double blind. Follow-up 91% overall. ITT analysis - not clear	Infants seen by a nurse at 3,6,9,12 and 18 months, who recorded growth, formula acceptance, clinical symptoms (using a scoring system for atopic dermatitis) and challenge procedures e.g. skin prick tests, specific IgE RAST at 9,12, 18 months. Follow-up 50/55 (91%) N, 45/51 (88%) PH, 46/49 (94%) RM 141/155 (91%) overall Results are also given in the paper for the group which continued breastfeeding after 9 months, which were not randomised.		The three formulae were provided by the manufacturer, Mead Johnson USA.

Formula Milk and allergenic food

First author Year	Research Question	Study population	Study Quality Power Calculation	Intervention	Main results	Comments Applicability to UK populations and settings Funding
Schonberger et al. 2005 The Netherlands RCT 1+	What is the clinical effectiveness of a multifaceted educational preventive strategy to prevent childhood asthma up to the age of 2 y?	PREVASC study 1997-2000 Dutch primary care setting Pregnant mothers recruited by GPs and midwives during the 1st 2 trimesters of pregnancy. Only babies considered to be at risk of developing asthma – asthma present at least in mother, father or sibling(s) 476 families recruited No difference in baseline socio-demographic characteristics except for mite allergens at base line and enrolment season Int Con n 222 221 Male 118 111 Female 104 110 Age mother y 30.9 31.0 Low education (mother) 2 20 Family history of asthma Father 84 80 Mother 118 111 Siblings 83 95 Birth weight g 3387 3475 Pregnancy	Randomisation: blinding not possible so families allocated to Int or Con groups by pre-randomisation, with information about their trial arm but not the other. Pre-randomisation performed in clusters, taking account of the post code of the family and the location of their GP's practice. Once a GP's practice was allocated, all the families at that practice allocated automatically to the same group Some data on smoking and	Intervention: n=242 3 home visits by specially trained nurses at 4-6 m pregnant, 8 months pregnant and 1-3 weeks after the birth with 4 instructions 1. Reduce mite allergens by daily floor washing, washing bedclothes on hot cycle (≥60˚C), removing textile floor coverings, reducing air humidity by ventilation/airing and heating, using mite impermeable bedding for both parents and infant. Informed at 2nd visit, asked to apply measures before birth and for 1st 2 y of life 2. Reduce pet allergens by disposing of pets or keeping them outside the house and washing them ≥1 time/month Informed 1st, 2nd and 3rd visits, asked to apply ≥3 m before birth and for 1st 2 y of life 3. Reduce food allergens by breastfeeding for ≥6 months. If breastfeeding stopped before 6 months or supplementation was	Occurrence of asthma symptoms and allergic morbidity at 0-2 y and at 2 y resulting from the complete intervention Intervention % n/N Control % n/N OR (95% CI) Symptoms reported by parents at 0-2 y Wheezing at least once 64 (127/200) 57 (113/200) 1.4 (0.83-2.4) Wheezing with awakening at least once 14 (26/188) 17 (30/182) 0.88 (0.45-1.7) Recurrent wheezing ≥4 times 26 (49/189) 26 (47/184) 1.1 (0.61-2.0) Night-time cough without a cold at least once 48 (95/197) 53 (101/190) 0.78 (0.46-1.3) Current symptoms reported by parents age 2 y Wheezing 8 (15/187) 15 (25/171) 0.73 (0.56-0.96)* Shortness of breath 16 (30/187) 25 (43/171) 0.76 (0.61-0.96)* Night-time cough 44 (57/184) 56 (72/168) 0.72 (0.55-0.95)* GP recorded morbidity at 0-2 y Wheezing without fever at least once 34 (72/212) 40 (80/200) 0.87 (0.72-1.1) Shortness of breath at least once 27 (57/212) 31 (62/200) 0.90 (0.73-1.1) Coughing at least once 68 (144/212) 70 (139/200) 0.96 (0.72-1.2) Diagnosis of asthma 26 (54/212) 31 (61/200) 0.88 (0.72-1.1) Diagnosis of atopic eczema 27 (58/212) 23 (46/200) 0.88 (0.72-1.4) * p<0.05 Conclusion: The intervention was not effective in reducing asthma-like symptoms in high risk children during the 1st 2 years of life, although it was modestly effective at 2 years However, during the 1st 2 y of life a sub-analysis showed that there was a significant reduction in asthma symptoms for females in the intervention group but not for males. Significant outcomes for girls included:	The intervention is applicable to the UK It is difficult to separate results for the different parts of the intervention. Multiple logistic regression analyses revealed that exposure to mite allergens and food allergens and passive smoking all contributed, independently of each other to asthma symptoms Funded by The Dutch Asthma Foundation, Prevention Fund and Royal Academy of Science (KNAW)

First author Year	Research Question	Study population	Study Quality Power Calculation	Intervention	Main results	Comments Applicability to UK populations and settings Funding
		Duration w 39.7 39.7 Uncomplicated Delivery 172 168 Age house≤20y 101 120 First-born 87 85 Born spring/summer 108 112 Baseline exposure in dust (ng/m^2) Mite Der p1 148 79* Fel d1 94 73 Can f1 34 39 Presence of cat or dog 62 71 Smoking: Mother 28 32 father 46 46 * p<0.001 After intervention Smoking 23 17 Breastfeeding 14 2	breastfeeding frequencies was missing. Analyses therefore performed considering missing data as such and considering cases with incomplete data as passive smokers and those with missing data on breastfeeding as not being breastfed. GPs were not blinded for the intervention No further details were given. No power calculation performed	necessary then use an extensively hydrolysed formula milk (Nutrilon Pepti®; Numico, Zoetermeer, the Netherlands). Recommended postponing introduction of solid foods until after 6 m. Informed 2nd and 3rd meeting 4. Reduce passive smoking during pregnancy but maternal abstention and postnatally by abstention by both parents in 1st 2 y of life. Informed 1st, 2nd and 3rd meetings Controls: n=234 Usual care by GP. Present Dutch guidelines only recommend preventative measures when children are already asthmatic Assessment: asthma symptoms during the 1st 2 y and during the last month of the 2nd year Questionnaires from the International Study of Asthma and Allergies in Childhood (ISAAC) at ages 6m, 1 and 2 y Parental reports of asthma-like symptoms in month 24	Symptoms reported by parents of girls in ISAAC questionnaire at 0-2 y: wheezing with awakening at least once, p=0.04; recurrent wheezing ≥4 times, p=0.03 GP recorded morbidity at 0-2 y: wheezing without fever at least once, p=0.02; Shortness of breath at least once, p=0.01. GP diagnosis of asthma was less likely in the intervention group but the result was not significant, p=0.08 OR (95% CI) for infant feeding and asthma symptoms Ever Breastfed / Ever hypo-allergenic formula fed / Introduction of 1st solid foods <6 months Recurrent wheezing at 0-2 y: 0.32 (0.19-0.56)* / 1.3 (0.72-2.3) / 1.1 (0.59-2.0) Ever wheezing with awakening 0-2 y: 0.35 (0.19-0.66)* / 0.72 (0.38-1.4) / 1.3 (0.63-2.7) Current wheezing at 2 y: 0.42 (0.18-0.97)* / 0.66 (0.27-1.6) / 1.4 (0.61-3.2) Current shortness of breath at 2 y: 0.61 (0.34-1.1) / 0.95 (0.53-1.7) / 0.77 (0.41-1.5) * p<0.05 After the intervention, infants in the intervention group were more likely to be exclusively breastfed, received more hypoallergenic bottle feeds and were less likely to be given solid food before the age of 6 months Conclusion: Feeding hypoallergenic formula (extensively hydrolysed formula) or the introduction of solid foods at <6 m were not significantly associated with asthma symptoms at age 2 y or earlier but breastfeeding was significantly negatively correlated with wheezing at age 2 y or earlier. There were no significant differences in total and specific immunoglobulin E between the 2 groups. Additional results were given in the article	

First author Year	Research Question	Study population	Study Quality Power Calculation	Intervention	Main results	Comments Applicability to UK populations and settings Funding
				GP reports after consultations during the 1st 2 y of life At age 2 y IgE for dust mite, cat and dog allergens measured Mite and pet allergens also measured in house dust at baseline (3-5 m before birth) and 1 y later (7-9 m after birth) Weekly diary records made for breastfeeding and formula feeding. At age 6 m a questionnaire on the introduction of solid foods Questionnaire on parental smoking when child aged 1 y Follow-up: 443/476 Follow-up for Int n=222 Con=221 Loss to follow-up: 7%		

First author Year	Research question	Study population	Study quality	Intervention	Main results	Comments Applicability to UK populations and settings Funding
Von Berg et al. 2003 Germany RCT 1-	To investigate the allergy-preventive effect of 3 differently hydrolyzed infant formulae compared with a conventional cow's milk formula	Inclusion criteria Healthy newborn infants with at least one family member (mother, father, or biological sibling) with an allergic disease recruited in obstetric units in 2 areas of Germany (Wesel, North Rhine Westphalia, and Munich, Bavaria) Exclusion criteria Severe acquired or congenital diseases, gestational age <37 weeks, birth weight <2500g, age >14 days, intake of any cow's milk based formula before inclusion, incapability of the parents to comply with the study protocol 2252 randomised to four groups Control (C) (n=556) Conventional cow's milk formula (Nutrilon Premium) casein: whey ratio 40:60	Power calculation: A loss caused by drop out and exclusive breastfeeding of 50% was expected Prevalence of allergic disease in the cow's milk group was expected to be 30% A sample size of at least 313 infants per formula was needed. Infants randomised with a computer-generated list stratified by single or double (parents only) heredity of atopy and study region. Blinding of parents and study team by	Infants randomised at birth to one of four standard formula milks. Study formula provided until infant 6 months old All mothers received written recommendations for feeding the infants – encouraged to exclusively breastfeed for 4 months (strict intervention period) and preferably 6 months No dietary restrictions during lactation were recommended The time of weaning and introduction of study formula was left to the mother Mothers were asked not to feed solid food during the first 4 months and thereafter to add not more than one food per week and to avoid milk and dairy products, hen's eggs, soy products, fish, nuts, tomatoes and citrus fruits in the first year Mother's kept a weekly infant feeding diary, which included health problems. Infants examined at 1, 4, 8 and 12 months with a	First year incidence of AD, allergic urticaria, FA-GIT and AM C pHF-W eHF-W eHF-C No of infants 256 241 238 210 AD n 38 22 31 15 % 14.8 9.1 13.0 7.1 Urticaria n 1 0 1 3 % 0.4 0 0.4 1.4 FA-GIT n 1 5 2 4 % 0.4 2.1 0.8 1.9 AM n 40 26 34 19 % 15.6 10.8 14.3 9.1 Crude OR 1 0.65 0.90 0.54 95%CI (0.39-1.1) (0.55-1.5) (0.30-0.96) P value 0.114 0.677 0.036 AD: atopic dermatitis FA-GIT: food allergy with manifestation in gastrointestinal tract AM: allergic manifestation Outcomes are reported at one year for infants who received formula according to protocol (n=945) The incidence of allergic manifestation was significantly reduced by using eHF-C compared with conventional cow's milk formula. The reduction in incidence of AM in both groups fed whey hydrolysate was not statistically significant.	This intervention was only for mothers who gave formula to their infants before 4 months 42% of infants randomised were exclusively breastfed for 4 months so were excluded from the study post-randomisation 15% of infants randomised were exclusively formula fed Family history of AD was a significant risk factor and modified the preventive effect of the hydrolysates Male infants were significantly more likely to develop AMs than female infants.

First author Year	Research question	Study population	Study quality	Intervention	Main results	Comments Applicability to UK populations and settings Funding

		pHF-W (n=557)
		Partially hydrolysed whey formula (Beba HA) casein: whey ratio 0:100
		
		eHF-W (n=559)
		Extensively hydrolysed whey formula (Hipp HA) casein: whey ratio 0:100
		
		eHF-C (n=580)
		Extensively hydrolysed casein formula (Nutramigen) casein: whey ratio 100:0
		
		Baseline characteristics for infants remaining at end of follow-up:
		C, n=256; pHF-W, n=241; eHF-W, n=238; eHF-C, n=210
		
		Male n (%)
		C=139(54);
		pHF-W=129(54);
		eHF-W=128(54);
		eHF-C=103(49)
		p=0.669
		
		Mean (SD) birthweight (g)
		C=3469(515);
		pHF-W=3465(473);
		eHF-W=3511(479);
			using identically labelled tins of formula coded with 4 different letters.
			At 4 weeks, 114 (5%) were lost to follow-up and 889 (42%) of the remainder exclusively breastfed and data was not reported for this group. Of the remainder (1249), 166 (13%) dropped out and a further 138 (13%) did not comply with the study. i.e. total loss to follow-up, 58%, or 31% excluding those exclusively breastfed
			Data for a total of 945 infants
			There were sig more dropouts in the eHF-C group: 18% vs.
				structured interview on health problems carried out by study physician
				
				Follow-up 945/2252 (42%) (see note in comments column about post-randomisation exclusions)
						Neither parental education, nationality nor study centre influenced the incidence of AM
						
						Funding:
						Federal Ministry for Education, Science and Research.
						Child Health Foundation.
						Formulae provided by Nestle, Hipp, Milupa, Numico, Mead Johnson

First author Year	Research question	Study population	Study quality	Intervention	Main results	Comments Applicability to UK populations and settings Funding
		eHF-C=3441(454) p=0.502 Mean (SD) length (cm) C=52.4(2.6); pHF-W=52.3(2.6); eHF-W=52.2(2.4); eHF-C=52.1(2.4) p=0.552 Study formula during 1st 4 weeks C=168(66); pHF-W=160(66); eHF-W=165(69); eHF-C=149(71) p=0.576 13-16 week of study formula feeding C=126(49); pHF-W=113(47); eHF-W=123(52); eHF-C=96(46) p=0.589 Exclusive study formula feeding C=45(18); pHF-W=32(13); eHF-W=32(13); eHF-C=30(14) p=0.493 One family member with history of allergy n (%) C=188(73);	10-12%, p=0.02 ITT analysis not described in detail but authors reported that an ITT analysis carried out on those with a 4 week follow-up (2138 (95%)) confirmed the results although they were less prominent.			

First author Year	Research question	Study population	Study quality	Intervention	Main results	Comments Applicability to UK populations and settings Funding

		pHF-W=168(70);
		eHF-W=164(69);
		eHF-C=147(70)
		NS
		Two family members with history of allergy n (%)
		C=68(27); pHF-W=73(30);
		eHF-W=74(31);
		eHF-C=63(30)
		NS
		
		Parental education <10y n(%)
		C=32(13); pHF-W=20 (8);
		eHF-W=25(11);
		eHF-C=18(9)
		NS				

4 What dietary interventions help to prevent diet-related dental caries, tooth loss and dental erosion in infants and young children?

Studies to be included	Evidence type	UK studies (other than RCTs)
Systematic reviews Randomised controlled trials	<u>Systematic reviews</u> SIGN 2005 Holm 2002 <u>Randomised controlled trials</u> None	Corroborative evidence from 1 UK study is presented in the text of the review Blinkhorn and Davies 1999

Dietary interventions and dental caries

<table>
<tr><th>First author Year</th><th>Research Question</th><th>Study population</th><th>Study quality</th><th>Intervention</th><th>Main results</th><th>Applicability to UK populations and settings Comments</th></tr>
<tr>
<td>Holm et al.

2002

Sweden

SR

2-</td>
<td>What interventions prevent dental caries?</td>
<td>1. RCTs and CCTs were included. Retrospective studies were excluded
2. Studies with follow-up times <2 y (for permanent teeth) were excluded. The follow-up time was less stringent for primary teeth, root surfaces or caries in patients receiving radiotherapy
3. Studies that did not use caries as an endpoint were excluded

The authors searched Medline (1966-2001)

A total of ~900 articles were reviewed but no details of those related to individual exposures were provided

The studies included data from children and adults</td>
<td>Evidence was graded from 1 to 4, i.e. from strong to insufficient scientific support (detailed criteria of these grades were not reported)</td>
<td>Many interventions were discussed but most related to the use of fluoride and there were no included studies giving dietary information.</td>
<td>Data are not provided in the English summary of the review. The conclusions were summarised in table format. Relevant data included:

Effects of interventions to prevent caries

<table>
<tr><th>Intervention</th><th>Effect</th><th>Grade</th><th>Comments</th></tr>
<tr><td>Sorbitol in sweets and chewing gum</td><td>Uncertain effect</td><td>Insufficient scientific support</td><td>Insufficient documentation</td></tr>
<tr><td>Xylitol in sweets and chewing gum</td><td>Uncertain effect</td><td>Insufficient scientific support</td><td>Insufficient documentation</td></tr>
<tr><td>Dietary information</td><td>Uncertain effect</td><td>Insufficient scientific support</td><td>No studies</td></tr>
</table>

Sorbitol and xylitol are sugar substitutes. The authors note that the dietary interventions reviewed chiefly related to a reduction of sugar in the diet.</td>
<td>This report is an English language summary of a Swedish SR.

Evidence is insufficient to be applicable

High risk groups for caries in children and adolescents in Sweden include many immigrants and refugees and families with low educational level and no cash margin. Insufficient evidence indicated that there were too few studies of suitable quality to draw reliable conclusions not that the intervention had no clinical effects. Swedish sugar consumption is relatively high. For the previous 10 y it</td>
</tr>
</table>

First author Year	Research Question	Study population	Study quality	Intervention	Main results	Applicability to UK populations and settings Comments
						was 40 kg/person/year. The review was carried out by the Swedish Council on Technology Assessment in Health Care (SBU) which appears to be government funded

First author, Year,	Research Question	Study population	Study quality	Intervention	Main results	Applicability to UK populations and settings Comments
SIGN[5] 2005 UK SR 2+ included Valaitis et al. 2000 SR 2+ Reisine & Psoter 2001 SR 2+	To provide guidelines for the prevention and management of dental decay in the pre-school child including those relating to dietary factors	Inclusion/exclusion criteria not supplied - apparently all relevant material including studies of adults and children. Included studies (only those studies that were used to develop guidelines relevant to the 6-24 m and 2-5 y NICE reviews are described and results that apply to children aged 6 to 24 m) Systematic reviews: Burt & Pai 2005, Lingstrom 2003, Reisine & Psoter 2001, Valaitis 2000 RCTs: Gedalia 1994 Intervention studies: (Rodrigues & Sheiham 2000); Other studies: Gibson & Williams 1999 (large cohort study), cross-sectional study Hallett 2002, retrospective study Mohan 1998, a large US prospective study (Marshall 2003, Levy 2003) Initial search for guidelines: Embase and Medline (1996-	Levels of evidence (1++ to 4 (expert opinion)) and grades of recommendation (A-D) were presented (see results) No other information on quality reported.	Few details given of specific interventions in review. Additional information includes the following: Reisine & Psoter 2001: Rodrigues & Sheiham 2000: conducted in Brazilian children in nurseries with and without guidelines restricting the sugar consumption Burt & Pai 2005: a systematic review of observational studies Gibson & Williams 1999: large NDNS UK study of children aged 1.5-4.5 y Mohan 1998: Low income US children (n=122) attending a WIC supplement programme. Hallett 2002: Cross-sectional Australian study of 3375 children (4-6 y old)	The SIGN Guidelines were developed using studies of subjects of any age. Data from individual studies was not provided in SIGN review and some additional data from original papers is presented in this table. Guidelines given a grade B None relevant to this review Guidelines given a grade C Milk feeding and caries • A SR (2+) gave inconsistent evidence of an association between breastfeeding beyond one year and the development of early caries. (Valaitis 2000) • A SR (2+) based on poor quality studies found weak evidence that the duration of bottle use was not related to caries risk (Reisine and Psoter 2001) Relevant guidelines: Members of the dental team should support and promote breastfeeding according to current recommendations. Parents and carers should be advised that drinks containing free sugars, including natural fruit juices, should never be put in a feeding bottle. Bottle feeding with sweetened drinks • A large US prospective study (graded 3) of infants aged 6-24 m found a high risk of colonisation by streptococci mutans with having sweetened bottle contents. (Mohan 1998) • A large cross-sectional study of Australian children aged 4-6 y (graded 3) found an increased risk of early childhood caries (at <6 y of age) with (OR=4.29, CI 2.9-6.38) for sweetened bottle content, (OR=1.73, CI 1.49-2.0) for sleeping with a bottle, (1.58, CI 1.49-2.0) for sipping from the bottle during the day (Hallett 2002). NB This result is relevant to the 2-5 y review Neither of the 2 studies (Mohan 1998 and Hallett 2002) adjusted for	The Guidelines were directly applicable to the UK The guidelines were developed because pre-school children in Scotland have the highest rates of tooth decay in Europe. The intention is to consider the guidelines for review in 2008. The Brazilian study (Rodrigues & Sheiham 2002) adjusted for many confounders e.g. tooth brushing, fluoride use, home sugar consumption. The review acknowledged that chewing gum

[5] SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland.

First author, Year,	Research Question	Study population	Study quality	Intervention	Main results	Applicability to UK populations and settings Comments
		2003), the following websites: American Dental Association, Canadian Dental Association, Canadian Practice Guidelines Info Base, National Guidelines Clearinghouse, New Zealand Guidelines Group, National Health and Medical Research Council – Australia, Swedish Council on Technology Assessment in Health Care (SBU), UK Health Technology Assessment Programme and US Agency for Healthcare Research and Quality. Searches for systematic reviews, RCTs, meta-analyses and observational studies 1999-2004 on Embase, Medline and the Cochrane Library. Grey literature not included. Additional material from members of the group.			confounding factors like social class or toothbrushing. A SR (Reisine and Psoter 2001, 2+) found only weak evidence of an association of bottle contents (e.g. sweetened milk or juice) with caries but the reviewers noted the very poor quality of most studies. Relevant guideline: Parents and careers should be advised that drinks containing free sugars, including natural fruit juices, should never be put in a feeding bottle Results for children aged 2-5 years are given in the 2-5 year review.	should not be applicable to pre-school children but that chewable sweets would be applicable. The SIGN review suggests that the results of the Burt & Pai review 2005 should not give false reassurance about the role of sugars in dental caries.

5 What interventions effectively help mothers continue breastfeeding after 6 months, both at home and out of home? (e.g. to return to paid employment)

Studies to be included	Evidence type	UK studies (other than RCTs)
Systematic reviews Randomised controlled trials	Systematic reviews None Randomised controlled trials Jones 2004	Corroborative evidence from 4 UK studies is presented in the text of the review Bolling 2007 Fulton 1998 Hoddinott 2006 Kosmala-Anderson 2006

Continuing Breastfeeding after 6 Months

First author, Year,	Research Question	Study population	Study quality	Intervention	Main results	Confounders/ Comments Applicability to UK populations and settings Funding
Jones 2004 Stone and Stoke-on-Trent, Staffordshire, UK RCT 1-	Objective: to support continued breastfeeding for mothers who plan to return to work and to ascertain the numbers of mothers who continued to breastfeed exclusively after returning to work	Inclusion Women who wished to breastfeed and planned to return to work were invited to participate Women who were successfully breastfeeding at 2 – 4 weeks and still planned to return to work were randomised. Exclusion Antenatal or postnatal complications Mothers contacted antenatally for consent, then 2-4 weeks post partum 75 randomised Mainly first time mothers, all singleton pregnancies Participant characteristics not reported	Randomisation using random permuted blocks gave rise to unbalanced numbers. 61% lost to follow-up. Reasons: did not or delayed return to work, weaned before work, postnatal depression, Blinding/concealment not addressed Power calculation not reported	Intervention group (I) n=44 Intervention 2001-2003 Specialist lactation advice by the researcher regarding return to work and milk expression: One hour evidence-based session and written leaflet (content included principles and technique of expression, handling and storage of breast milk, management of milk supply, emphasis on eliciting the milk ejection reflex and managing milk leakage and preventing mastitis; 'back to work' set (breast pump, storage bottles, gel pack, breast pads and shoulder bag) Control group (C) n=31 Standard support from community midwives and health visitors: Advice (ad hoc, some given leaflets, information not comprehensive); 'back to work' set (as above) Follow-up: mothers were contacted at the time they	Mothers returned to work 2-6 months after the birth (not reported by intervention group) Full time work: I 47%, C 40% I (n=19) C (n=10) p value Expressed at work 12 5 NS Infant exclusively fed expressed milk while at work 9 7 NS (Infant fed breast milk and formula 10 3 Worked full time 9 4 NS Practised milk expression prior to returning to work 12 5 (p=0.04) Stockpiled expressed milk prior to returning to work 15 4 NS Lactation problems at work Engorged 4 2 NS Leaked 4 3 NS None 11 4 NS No refrigerator available for milk storage at work 4 4 NS NS: not statistically significant (Women who were still breastfeeding at 2-4 weeks post partum received significantly more support from health professionals and family than those who had not (p<0.001).)	This was a pilot study Authors state women reported practising how to express their milk prior to returning to work was beneficial to their success Many found the barriers they experienced at work insurmountable and were unable to express milk while at work Funded by the North Staffordshire Medical Institute. Cannon-Avent donated the 'Back to Work' milk expression sets

First author, Year,	Research Question	Study population	Study quality	Intervention	Main results	Confounders/ Comments Applicability to UK populations and settings Funding
				originally anticipated returning to work, and received postal questionnaires one month and three months after returning to work Follow-up rates: I 19/44 (43%), C 10/31 (32%) Overall 29/75 (39%)		

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