Systematic review of literature on early life patterns of exposure to, and avoidance of, food allergens and later development of sensitisation and clinical food allergy.

Document 2: Tables of evidence (Human Studies)

Research question 1 (Allergen exposure in the mother)
1. All allergens (7 studies)

Author year (study name)	Study type	Qua-lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Hattevig *et al.* 1999	Non-randomis-ed clustered trial	3/13 (-)	Baseline: 140 infants Follow-up Authors' report a 100% follow-up after 3 months. This article is based on 115 with outcome data at 10 years (82%). 65 – Diet group 50 – Non-diet group Included in analysis Food allergy – 115 Food sensitisation IgE – 110 (79%) SPT – 114 (81%)	High risk group Between Aug 1984 and Mar 1986 all pregnant women visiting ante-natal clinics in Skovde and Boras, Sweden were asked about family history of atopy. 177 had a history of atopy (atopic dermatitis, allergic rhinoconjunctivitis, asthma.) in themselves, husband or children. Included Inclusion criteria: Double heredity for atopic disease (both parent, or one parent and one sibling) or single heredity and cord blood IgE ≥0.9 kU/L, no smokers and no indoor furred pets.	Boras (non-diet group). After birth of infant mother to follow an unrestricted diet Dietary advice for infants was the same in both groups: Breast feed or hydrolysed casein-based formula for 6 months. Cows' milk after 6 months and eggs after 9 months.	Skovde (diet group) After birth of infant mother to follow diet free from eggs, cows' milk, fish from delivery for 3 months Women were instructed by a dietitian during last trimester	10 years	Parental report of food reactions (within 1hr on at least 2 occasions). These were not confirmed by challenge IgE – RAST (+ve ≥0.35kU/L) SPT - Wheal ≥ 3mm =+ve	**Food allergy -% (n)** **Parental reports at 10 y** **Diet** –11%(7) and **Non-diet** –16%(8) NS **Food sensitisation % (n)** **(**all NS unless indicated otherwise**)** **Any food allergen** IgE- Diet – 18%(11); Non-diet 23%(11) SPT- Diet – 14%(9); Non-diet 24%(12) **Egg white** IgE - Diet – 3%(2); Non-diet 10%(5) SPT – Diet – 2%(1); Non-diet 8%(4) **Cows' milk** IgE - Diet – 2%(1); Non-diet 4%(2) SPT – Diet – 2%(1); Non-diet 2%(1) **Cod fish** IgE - Diet – 2%(1); Non-diet 0% **Wheat** IgE - Diet – 6%(4); Non-diet 21%(10) **Peanut** (P=0.02 for SPT) IgE - Diet – 8%(5); Non-diet 19%(9) SPT – Diet – 2%(1); Non-diet 14%(7) **Soy** (P=0.02 for IgE) IgE - Diet – 3%(2); Non-diet 17%(8) SPT – Diet – 3%(2); Non-diet 4%(2) **Hazelnut** IgE - Diet – 5%(3); Non-diet 15%(7) SPT – Diet – 9%(6); Non-diet 18%(9)
Notes	**Overall finding: Excluding eggs, cows' milk and fish from the mothers' diet during the first 3 months after birth did not affect food allergy or food sensitisation in the child at 10 years of age.** The groups were not randomised it is not sure how or why the locations were chosen as intervention or control. There was a good rate of follow-up for a study of this length; however there is no information on follow-up rates for Boras and Skovde separately. There was no information on dietary habits in the child up to 10 years. There was no information on compliance with the advice either for mothers or infants. Results were not adjusted for other factors. Parental reported were not confirmed by challenges. It is unclear why two methods of food sensitisation are used. The results for both measures were consistent for most allergens except for peanuts and soy.								

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Sausent -haler *et al.* 2007 LISA	Cohort	7/13 (+)	Baseline: 3097 newborns were enrolled with a 52-58% response rate depending on centre. Follow-up: At 2 years 2641(85%) completed all questionnaires. Included in the analysis: 2122 (69%) with IgE at 2 years.	Population group Infants delivered between Nov 1997 and Jan 1999 in 4 cities in Germany Exclusion criteria: Preterm (<37 weeks gestation, low birth weight (<2500g), congenital malformation, antibiotic medication, in hospital or in intensive care during neonatal period. Non-German parents. Mothers had immune related diseases (autoimmune disorders, diabetes, hepatitis B)	High intake food allergen Maternal diet assessed by FFQ 3days after delivery to reflect diet over previous 4 weeks. FFQ included 26 food items with more information on milk and yogurt. Relatively crude measure (no portions). No information on validity. Compared low (bottom 2 tertiles) vs. high intakes (upper tertile)	Low intake of food allergen	2 years	IgE (+ve 0.35kU/L) in infant at 2 years using FX5 (combined egg cows' milk, wheat, peanut, soybean and codfish). A positive result was followed by a single allergen test (egg, cows' milk, peanut) Adjusted for study area, sex, maternal age at delivery, smoking in 2/3 trimesters, parental education, exclusive breastfeeding for ≥ 4 months, family history of atopy, season of birth, all dietary variables	**Food sensitisation** **% sensitised to food allergens (not specific) by maternal diet (low/high intakes) (unadjusted)** **Milk** Low – 10.1%; High – 8.9% **Yogurt** Low – 9.7%; High – 9.0% **Cheese** Low- 9.6%; High – 8.9% **Cream** Low – 8.7%; High – 10.9% **Eggs** Low- 9.0%; High – 9.4% **Nuts** Low – 9.4%; High – 9.1% **Fish** Low- 9.1%; High – 9.9% No result was statistically significant **Odds ratios (High intakes vs. low intakes in maternal diet and food sensitisation) (adjusted)** **Milk** 0.95 (0.66, 1.37) **Yogurt** 0.89 (0.62, 1.27) **Cheese** 0.97 (0.68, 1.39) **Cream** 1.26 (0.87, 1.83) **Eggs** 0.93 (0.63, 1.38) **Nuts** 1.10 (0.72, 1.67) **Fish** 1.01 (0.69, 1.48) No result was statistically significant
Notes	**Overall finding: There were no associations between maternal diet and sensitisation for dairy foods, eggs, fish or nuts and food sensitisation**. The study aimed to carry out IgE tests on all children (not just those who reported symptoms); however not all parents agreed. The response rate at baseline was not good; there was a good follow-up for completing the questionnaires at 2 years; however only two thirds of children had IgE tests. Children with atopy, male gender and high parental education were all factors associated with having blood tests and thus the results may not be representative of the general population. It is not clear whether the dietary questionnaire was validated. Results were adjusted for other factors (as shown in the table). The authors did report that they had carried out further analyses on specific IgE for cows' milk and egg. They reported an increased risk of cows' milk sensitisation in the child with a maternal intake of cream. There was no association between maternal egg intakes and egg sensitisation in the child.								

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Wetzig *et al.* 2000	Cohort	6/12 (+)	Baseline: 475 out of all 3540 newborns identified as high risk Follow-up at 1 year 323 (68%) examined Follow-up at 2 years 265 (56%) examined	All newborns were registered by level of cord blood IgE measured and family history of atopic disease in Leipzig, Germany High risk group: A)Healthy, appropriate for gestational age, Increased cord IgE (>0.9kU/L) OR B)double positive atopic family history (adults, siblings) independent of cord IgE	Hen's egg or cows' milk in diet of nursing mother Information collected annually by questionnaire.	Avoidance or reduced exposure to hen's egg or cows' milk in diet of nursing mother	Two years	Specific IgE RAST ≥ 1 = positive	**Food sensitisation** No statistically significant difference in atopy in child and maternal egg or milk consumption
Notes	**Overall finding: No significant differences detected in sensitivity to hen's egg or cows' milk in infants.** This result was reported in the discussion of the paper. Identification of high risk group appears complete at baseline; however only two thirds were followed-up at 1 year and just over half at two years. There is no information on weaning or types of formula used. A RAST test result of 1 was considered positive. Results were not adjusted for other factors. It is unclear how the information on the mother's diet during lactation was ascertained from the questionnaire i.e. how the question(s) was/were phrased.								

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Calvani *et al.* 2006	Case-control	7/10 (+)	1044 enrolled (not sure if any declined to take part) <u>77 cases</u> with fish sensitivity <u>869 controls</u> with no sensitivity to fish <u>Included in the analysis</u> 946 (91% of those enrolled)	<u>High risk population</u> Enrolled consecutively when attending outpatients' allergy clinics in 6 hospitals in Italy between September 2001 and March 2002. Median age of child was 5 years (range < 2 to > 7 years) 744 had atopic disease (asthma, rhinitis or eczema) and 244 had respiratory symptoms, gastrointestinal symptoms or skin disease <u>Exclusion criteria:</u> immunodeficiency, connective tissue disease or chronic respiratory tract disease other than asthma	Higher maternal intake of fish during pregnancy ≥ once a week Mother completed a self-administer questionnaire on maternal intake of fish, butter and margarine during pregnancy. Five frequency choices from never to almost daily.	Lower maternal intake of fish during pregnancy < once a week	Up to 18 years	SPT Wheal ≥ 3mm =+ve	**Food sensitisation** **<u>Fish sensitisation – allergic mothers</u>** 1/week vs. 1 /month or less Odds ratio 1.15 (0.38, 3.47) NS 2-3 /week or more vs. 1/month or less Odds ratio 1.13 (0.31, 4.1) NS *Adjusted for age, occupation and eczema* **<u>Fish sensitisation – non-allergic mothers</u>** 1/ week vs. 1/month or less Odds ratio 0.22 (0.08, 0.55) Sig 2-3 /week or more vs. 1 /month or less Odds ratio 0.23 (0.08, 0.69) Sig P trend = 0.002 *Adjusted for age, age of gestation, maternal occupation, oculorhinitis and eczema* Additional adjustment for butter, margarine, gender, maternal smoking, and paternal atopy did not substantially change the results. Results presented below are for maternal fish intake and milk and egg sensitisation. It is unclear whether they relate to the whole population and which factors are adjusted for **<u>Milk sensitisation (adjusted)</u>** Fish 2-3 /week or more vs. 1 /month or less Odds ratio 0.05 (<0.01, 0.54) Sig **<u>Egg sensitisation (adjusted)</u>** Fish 2-3 /week or more vs. 1 /month or less Odd ratio 0.33 (0.10, 1.07) NS
Notes	**Overall finding: A higher intake of fish during pregnancy was associated with a reduction in risk of sensitisation to fish in children of non-atopic mothers of a wide age range. No reduction in risk was seen for children of atopic mothers.** Retrospective assessment of diet in some cases was a long time in the past (up to18 years). It is unclear whether the dietary questionnaire was validated. Children's diet may also have influenced development of food sensitisation. Fish intake was similar in atopic and non-atopic mothers. Many confounding factors were adjusted for in the analysis; however breast feeding was not considered. The hypothesis is that dietary fatty acid can influence the development of atopic disease. This is outside the remit of this review but provides a reason for the protective effect of a possible food allergen. There is no detailed information about the type of fish consumed and level of fatty acids.								

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Frank *et al.* 1999	Case-control	6/10 (+)	25 cases with peanut sensitivity 18 controls With milk or egg sensitivity No information on response rate Included in the analysis 1. Pregnancy 23 cases (92%) 16 controls (89%) 2. Lactation 23 Cases (92%) 18 controls (100%)	High risk group Children referred from hospital in South Africa with suspected food allergy aged between 0 and 3 years of age at time of diagnosis.	Higher intake of peanuts and peanut products in the maternal diet during pregnancy and lactation. > once a week Mother completed a standardized questionnaire. To avoid bias the questionnaire asked about intake of a variety of foods (not only peanuts)	Lower intake of peanuts and peanut products in the maternal diet during pregnancy and lactation. < once a week	Up to 3 years and 9 months	Peanut specific IgE RAST (> 0.35 kU/l = +ve) No food challenge tests	**Food sensitisation** **Peanut sensitisation** **Peanut consumption by mothers during pregnancy** Odds ratio 3.97 (0.73, 24.0) NS for > 1/week vs. <1/week (unadjusted) **Peanut consumption by mothers during lactation** Odds ratio 2.19 (0.39, 13.47) NS for > 1/week vs. <1/week (unadjusted) Paper states that there was no significant different between cases and controls for age, weight, height, allergic disease in mother, grandparents or index child's siblings
Notes	**Overall finding: Consumption of peanuts by mothers during pregnancy or lactation was not associated with childhood sensitisation to peanuts.** The sample size is small and there is no power calculation. There is no information on response rate. It is unclear whether there were any mothers who consumed peanuts once a week and if so which category they were placed in. The study did not account for inadvertent exposure to peanut in the child's diet by other caregivers or exposure outside the home. Cases were not confirmed by food challenges. Results were not adjusted for other factors. It is unclear whether the dietary questionnaire was validated.								

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Lack *et al.* 2003 ALSPAC	Case-control	6/11 (+)	Baseline 14541pregnant women invited and 13971 agreed to take part (96%) Follow-up: children up to age 38 months 12090 responded to at least one question on food avoidance and reactions to foods 86.5%). Plus children identified from questions regarding previous clinical history. Total number unclear. 23 cases +ve peanut challenge 70 atopic controls Random sample of children with eczema in first 6 months of life 140 normal controls Random sample of children with no peanut allergy	Population and high risk groups Study enrolled pregnant women from Avon, UK (ALSPAC study birth cohort) with expected delivery date between April 1 1991 and Dec 31 1992. Inclusion criteria: Resident in Avon when pregnant and on expected date of delivery. Exclusion criteria: Infant died before 1 year. If moved before the 3rd trimester.	Consumption of peanuts whilst pregnant and during lactation Interviewed by telephone	Did not consume peanuts whilst pregnant or during lactation	5-7 years	SPT Peanut (+ve 3mm) followed by DBPCFC 49 reports of reactions to peanuts 36 (73%)– went for further tests of which 29 had +ve SPT and 23 +ve DBPCFC	**Food allergy** **Peanut allergy** **% mothers not consuming peanuts during pregnancy** Peanut allergy cases – 65% Atopic controls – 61% Normal controls – 71% NS **% mothers consuming peanuts at least 7 times per week during lactation** Peanut allergy cases – 17% Atopic controls – 5% Normal controls – 5% Sig (P=0.03) The paper states that this association was no longer statistically significant after adjustment (no figures reported). It is not clear from the paper which variables were adjusted for.
Notes	**Overall finding: This study does not show an association between consumption of peanuts during pregnancy or lactation and development of peanut allergy in the child.** Although the ALSPAC study is a birth cohort, this part of the study was analysed as case-control study. Key questions had not been included in the prospective interviews. Asking mothers about consumption of peanuts during pregnancy especially if their child has peanut allergy is prone to bias. No sample size calculation is presented in the paper so we do not know if the study was adequately powered. The results for pregnancy and lactation are presented differently and it is unclear why. We do not know how many mothers breast-fed or how many eliminated peanuts during lactation. We also do not know if there was any difference by family history of atopy. Cases and controls were not matched and it is unclear what factors were adjusted for in the analysis.								

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Ushiyama *et al.* 2002	Case-control	5/11 (+)	32 cases With reported food allergy 1824 controls With no reported food allergy Survey carried out on 2070 (94.7%). Data presented on 1856 (85% of total)	Mothers who participated in a regular infant health examination held by Pediatric Association of Kochi Prefecture between April 2000 and April 2001 in Japan. Mean age of child was 7.6 months. All children were aged <1 year. General Population No exclusion criteria	Consumption of fish, egg, tofu/natto, milk and milk products during late pregnancy Mother completed an FFQ with 3 or 4 frequency categories. Portion size was ascertained. This questionnaire was validated previously – published in 1977.	Unclear whether reduced intake or avoidance	Most less than one year	Reported food allergy in child in questionnaire completed by mother Adjusted for family history of allergic diseases, sex, order of birth and age.	**Food allergy** **Parental reports of food allergy** **Unadjusted odds ratios (high versus low maternal intake)** (95% confidence intervals not presented) Fish – 0.82 Egg – 0.58 Tofu/natto – 1.14 Milk & milk products – 1.13 **Adjusted odds ratios (high versus low maternal intake)** Fish - 0.81 (0.30, 2.20) Egg - 0.62 (0.20, 1.88) Tofu/natto – 1.05 (0.61, 1.83) Milk & milk products – 1.16 (0.91, 1.49) No result was statistically significant
Notes	**Overall finding: This study does not show any association between intakes of fish, egg, milk or tofu/natto during late pregnancy and reported food allergy in the child before the age of one year.** Details of the food frequency questionnaire are not clear. It is reported to be validated, however the reference is from 1977 and it is unclear whether it has been modified. Food allergy in the child was reported by the mother and not confirmed by challenge. There was a good response rate. Unclear why only 1856 of 2070 mother-child pairs were included.								

Research question 2 (Allergen exposure in childhood)
Allergen: cows' milk (6 studies)

Author year (study name)	Study type	Qua-lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
de Jong *et al.* 2002	RCT	6/9 (+)	Baseline: 1533: 1. Brief early exposure to cows' milk – 758; 2. Placebo – 775 Followed-up at 5years 1. Brief early exposure to cows' milk – 542 (72%) 2. Placebo – 566 (73%) Included in analysis at 5 years 1. Brief early exposure to cows' milk – 470 (62%) 2. Placebo – 467 (60%)	Infants from birth were recruited by midwives in the Netherlands. Inclusion criteria: Healthy, full term newborns, birth weight ≥ 2750g whose mother's intended to breast feed for at least 6 weeks. Parents understood Dutch General population group	Cows' milk formula provided as a supplement to be fed to infants at least 3 times in first three days after randomisation	Placebo (visibly indistinguishable from intervention) to be provided in same way as cows' milk formula	5 years (note previous data had been published on 2 year follow-up in 1998)	Cows' milk and egg specific IgEs by radioallergosorbent test (RAST) RAST 2+ to 5+ were considered positive [where negative= normal, 1+= dubious and 5+ = strongly positive]	**Food sensitisation** % (n) with +ve RAST to cows' milk at 5 years 1. **Brief early exposure to cows' milk** 5.3% (25) 2. **Placebo** 3.0% (14) Unadjusted odds ratio OR = 1.77 (0.93, 3.37) NS for brief early exposure to cows' milk vs. placebo % (n) with +ve RAST to egg at 5 years 1. **Brief early exposure to cows' milk** 0.2% (1) 2. **Placebo** 0.6% (3) Unadjusted odds ratio OR = 0.33 (0.04, 3.17) NS for brief early exposure to cows' milk vs. placebo
Notes	**Overall finding: Early brief exposure to cows' milk as a supplement to breast milk compared with placebo was not associated with food sensitisation (milk and egg) up to age 5 years.** The study was conducted as a RCT for the first two years, it was then unblinded. The intervention and placebo groups continued to be followed up for a further 3 years. Intervention feeding was given in agreement with study protocol to 935 of children (n=1422). Results on 2 year follow-up published in 1998 also reported the same result. No information on response rate at baseline. There was no other information on feeding or introduction of solids. Results were unadjusted; however there were no substantially differences at baseline.								

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Halken *et al.* 2000	RCT*	5/10 (+)	Initial response rate 595 invited, 19 declined and 26 excluded Baseline: 550: 1. Partially hydrolysed whey formula (PHF) 2. Extensively hydrolysed whey formula (EHF – W) 3. Extensively hydrolysed casein formula (EHF – C) 4. Breast fed (BF) (not randomized) (Numbers randomized to each group are not clear.) Follow-up 18 months: 514 (93%). Included in analysis 478 (80%) 1. Partially hydrolysed whey formula (PHF) - 85 4. Breast fed (BF) (not randomized) - 232	Infants were recruited during pregnancy from 4 hospitals in Denmark. Inclusion criteria: Full-term, had not received cows' milk or other formula before randomisation. High risk group: Doctor diagnosed bi-parental atopic predisposition (asthma, hay fever, atopic dermatitis, allergic urticaria, food allergy)or severe single and raised cord blood IgE (≥ 0.3kU/L)	Partially hydrolysed whey formula (PHF) All mothers had an unrestricted diet during pregnancy and were encouraged to breastfeed. If breastfeeding was not sufficient formula randomised to be used for first 4 months. After 4 months infants were allowed an unrestricted diet (including cows' milk formula) Mothers' were asked to avoid exposure of the infant to tobacco smoke, furred pets and damp housing	Breastfed (not randomised)	18 months	Parental reports of food allergy Confirmed food allergy was defined as reproducible reactions diagnosed by controlled elimination/challenge procedures. Challenges were open, but with equivocal results the challenge was repeated and blinded	**Food allergy** Parental reports at 18 months- cumulative incidence- % (n) **Milk** PHF – 7.1% (6) BF – 2.6% (6) **Egg** PHF – 1.2% (1) BF – 1.7% (4) **Fish** PHF –1.2% (1) BF – 0.9% (2) **Peanut** PHF – 0% (0) BF – 0% (0) Confirmed food allergy- % (n) **Milk** PHF – 4.7% (4) BF – 1.3% (3) **Egg** PHF – 0% (0) BF – 1.7% (4) **Wheat** PHF – 0% (0) BF – 0.4% (1) No result was statistically significant. All analyses were unadjusted
Notes	**Overall finding: Partially hydrolysed whey formula compared with breastfeeding for four months was not associated with food allergy either parental reports (milk, egg, fish, peanut) or challenge confirmed food allergy (milk, egg, wheat) up to 18 months of age.** The study was designed as a randomized controlled trial comparing different formulas. However, not all mothers chose to introduce formula before the age of 4 months and data were also presented on children who were exclusively breastfed. The breastfed group were not randomised. There was a good rate of follow-up and compliance (36 subjects were excluded due to poor compliance). There was a high rate of breast feeding and few infants were exclusively fed formulas. There was a low incidence of allergy and results should be interpreted with caution. Food allergy was confirmed by open challenge. Results were not adjusted for other factors.							

All confidence intervals refer to 95% confidence intervals. Values P≤0.05 are considered statistically significant (Sig) and values of P>0.05 are not considered statistically significant (NS) for this report. If reported in papers P values have been included for statistically significant results only.
RCT* indicates studies set up as RCTs where the breastfeeding arm of the trial was not randomised.

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Saarinen *et al.* 1999	RCT	6/10 (+)	15400 invited, 6267 (41%) agreed, 58 lost leaving 6209. Of these 5385 (87%) required supplementary feeding (due to insufficient secretion of breast milk) in hospital. Baseline: 5385 1. Cows' milk formula (CMF) – 1789 2. Extensively hydrolysed – whey formula -EHP-W – 1737* 3. Pasteurised human milk (mixed donors) HM – 1859 Follow-up 18-34 months: 1. Cows' milk formula (CMF) – 1758 (98%) 3. Pasteurised human milk (mixed donors) HM – 1844 (99%) (All were included in the analyses)	Infants were, recruited from birth from maternity hospitals in Finland Inclusion criteria: Healthy, full term newborns General population group	Cows' milk formula (CMF) Mothers were advised to give supplementary feed when required and to start introducing solids at 4-6 months.	Pasteurised human milk (mixed donors) HM	18-34 months Primary endpoint was adverse reaction to challenge with cows' milk	Parental report of symptoms followed by open challenge 622 mothers reported infants had symptoms at home. Cows' milk allergy was confirmed by challenge in 118 children	**Food allergy** % (n) with confirmed cows' milk allergy **Cows' milk formula** – 2.4% (43/1758) **Pasteurised human milk** – 1.7% (32/1844) Unadjusted odds ratio Human milk vs. cows' milk 0.70 (0.44, 1.12) NS The paper also reports results for cows' milk formula versus human milk and extensively hydrolysed formula Adjusted odds ratio was 1.54 (1.04, 2.30) Sig (P=0.03) Adjusted for parental atopy
Notes	**Overall finding: Cows' milk formula compared with pasteurized human milk given as a supplementary feed to breastfeeding was not associated with food allergy (cows' milk) in children up to 18-34 months old** If data from the cows' milk formula group was compared with the other two groups there was a significant difference – there was an increased risk of cows' milk allergy. Food allergy was confirmed by open challenge. Only 41% of mothers agreed to take part. Data are presented for virtually 100% at follow-up; however it is not clear whether contact was made with all the children. The trial endpoint was food allergy and it is not clear whether any further data were collected on children whose mothers did not report symptoms. Randomization to intervention group depended on month of birth and hospital attended and was not purely random.							

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Schoetzau *et al.* 2002 **Von Berg *et al.* 2003 (GINI)**	RCT*	6/9 (+)	Initially randomised: 2252: 1. Cows' milk formula (CMF)– 556; 2. Partially hydrolysed whey formula (PHF) –557 3. Extensively hydrolysed whey formula (EHF-W)-559 4. Lactose free extensively hydrolysed casein formula (EHF-C)– 580 Actual feeding method for first 4 months: 1121 Exclusively breast fed for 16 weeks (i.e. did not use formula randomised to) formed an non-randomised additional control group - 865 CMF - 256 Included in analysis at 4 months CMF – 215 (84%) Breastfed – 698 (81%) Included in analysis at 4 months CMF – 197 (77%) Breastfed – 632 (73%)	Infants recruited from birth from 16 obstetric units in Germany Inclusion criteria: Healthy full term newborn, birth weight ≥ 2500g. Parents able to comply with protocol High risk group: 1st degree relative with food allergy, asthma, atopic dermatitis or allergic rhinitis, allergic urticaria	Cows' milk formula (CMF) Guidance To exclusively breast feed for ≥ 4 months and preferably for months. No dietary restrictions for mother. Timing of weaning and use of randomised formula left to mother. Study formula provided until infant months old. Solid foods to be introduced at 4 months at earliest and only one per week. No milk, dairy products, hen's egg, soy products, fish, nuts, tomatoes and citrus fruits for first year.	Exclusive breastfeeding for 16/52 (not randomised) See guidance under cows' milk formula	12 months	Serum IgE – α lactabumin, β lactoglobulin and casein at 4 months and one year [RAST >0.35 kU/L positive]	**Food sensitisation** Sensitisation to milk allergens at 4 months - % (n) CMF - 0.9% (2) Breastfed - 2.9% (20) NS Sensitisation to milk allergens and/or ovalbumin at one year CMF – 9.6% (19) Breastfed – 11.6% (73) NS Odds ratio (Breastfed vs. CMF) 1.30 (0.74, 2.28) NS Adjusted for atopic risk level, cord blood IgE, gender, pets at home, parental school education
Notes	**Overall finding: Cows' milk formula compared with breastfeeding was not associated with food sensitisation (milk or egg) up to age one year.** Initially 2252 infants were randomised to 4 different formulas; however all mothers were encouraged to breastfeed and as a result 865 infants were exclusively breastfed for 4 months and 256 infants received cows' milk formula (only 45 of these were exclusively bottle-fed). Hence infants were randomised to CMF, however those who breastfed exclusively were self selected. There is no information on response rate at baseline. Also it is not possible to separate the effect of breastfeeding or weaning. Follow-up rates at 4 months were about 80% and likely lower at one year.								

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RCT* indicates studies set up as RCTs where the breastfeeding arm of the trial was not randomised.

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Szajewska *et al.* 2004	RCT*	5/10 (+)	Baseline: 122: 1. Cow's milk preterm formula (CMF) -32 2. Partially hydrolysed preterm whey formula (PHF)– 32; 3. Extensively hydrolysed preterm formula (EHF) – 26 4. Fortified breast milk (not randomised) -32 Follow-up one year: 1. Cow's milk preterm formula – 24 (75%) 2. Partially hydrolysed preterm whey formula (PHF) – 20 (63%) 3. Extensively hydrolysed preterm formula (EHF – 19 (73%) 4. Fortified breast milk (not randomised – 26 (81%) Included in analysis at one year (sensitisation) 1. Cow's milk preterm formula – 22 (69%) 2. Partially hydrolysed preterm whey formula (PHF) – 20 (63%) 4. Fortified breast milk (not randomised – 26 (81%)	Infants recruited from birth from 5 neonatal departments in Poland. Inclusion criteria: Pre-term, birth weight <2500g, but appropriate for gestational age. Had not received cows' milk formula before randomisation. High risk group: 1st degree relative with asthma, atopic dermatitis, allergic rhinitis or conjunctivitis	Standard preterm cows' milk formula. *OR* Partially hydrolysed preterm whey formula (PHF) All mothers had unrestricted diets during pregnancy and lactation. All groups were asked to avoid cows' milk products and supplementary foods until 5th month when foods were gradually introduced according to Polish recommendations Non-acceptance formula – CMF- 1/24 (4%) PHF - 0	Fortified breast milk - not randomised See guidance under cows' milk formula Non-acceptance BF - 0	One year	**Sensitisation** Cows' milk specific IgE (CAP FEIA ≥5 kU/L positive) **Allergy** GI symptoms related to food and resolved after elimination of this food, but reappeared when food reintroduced	**Food allergy** % with GI symptoms % (n/total) 4-5 months CMF 4% (1/26) PHF 0% (0/22) BF 3% (1/29) One year CMF 4% (1/24) PHF 5% (1/20) EHF 11% (2/19) BF 4% (1/26) **Food sensitisation** % with sensitisation to cows' milk (n/total) 4-5 months CMF 4% (1/25) PHF 0% (0/20) BF 0% (0/28) One year CMF 14% (3/22) PHF 15% (3/20) BF 8% (2/26) No result was statistically significant. All analyses were unadjusted
Notes	**Overall finding: Standard preterm formula or partially hydrolysed preterm whey formula compared with fortified breast milk was not associated with food sensitisation (cows' milk allergy) or food allergy (data on specific foods not supplied) up to age one year.** The required sample size for the study was 39 in each group, this was not achieved and hence the study was under-powered. Infants whose parents preferred that their infant should be breastfed received their mothers' fortified breast milk and were not randomised. There is no information on response rate at baseline. Food allergy was not confirmed by challenge. Results were not adjusted for other factors. Those in the formula groups were less likely to have complete sensitisation data than those fed fortified breast milk.								

All confidence intervals refer to 95% confidence intervals. Values P≤0.05 are considered statistically significant (Sig) and values of P>0.05 are not considered statistically significant (NS) for this report. If reported in papers P values have been included for statistically significant results only.
RCT* indicates studies set up as RCTs where the breastfeeding arm of the trial was not randomised.

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Hilkino *et al.* 2001	Cohort	5/13 (+)	Well-baby check-ups are municipally funded and obligatory. Actual number eligible for appointment at 4 months is not reported in paper. Follow-up- 18 months 21766 with questionnaire 20466 with complete data Follow-up – 3 years 4378 with questionnaire All had complete data Paper states that check-ups at 18 months and 3 years covered 85-90% of children at these ages. Note lower number at 3 years is because children enrolled at 4 months had not reached 3 years within the study period.	Children recruited from well-baby check-up at four months in Japan. All children were eligible General population group	Formula milk OR Mixed Formula and breast milk Feeding method at four months Information on feeding method was obtained by questionnaire at baseline (4 months of age). No information on duration of breastfeeding. No information on validity of questionnaire.	Breast milk	2 years and 8months	Parent reported whether baby had ever been diagnosed as having or had a food allergy by doctors. Odds ratios adjusted for birth weight, gestational age and sex	**Food allergy** % (n/total)reported food allergy At 18 months Unadjusted (P<0.0001) **Breast feeding** 13.5% (1384/10289) **Mixed feeding** 9.3% (556/ 5999) **Formula feeding** 8.1% (441/5178) Adjusted odds ratio **Mixed vs. breast feeding** 0.67 (0.60, 0.75) Sig **Formula vs. breast feeding** 0.58 (0.52, 0.66) Sig At 3 years Unadjusted (P= 0.0008) **Breast feeding** 10.5% (222/2110) **Mixed feeding** 7.3% (85/ 1167) **Formula feeding** 7.3% (80/1101) Adjusted odds ratio **Mixed vs. breast feeding** 0.66 (0.51, 0.86) Sig **Formula vs. breast feeding** 0.72 (0.55, 0.94) Sig
Notes	**Overall finding: Formula feeding and mixed feeding compared with breastfeeding were associated with a lower risk of food allergy at both 18 months and 3 years.** Follow-up appears to be good; however numbers seen at four months or not reported. Poor assessment of food allergy which relied on parental reports. Adjustments used to compute the odds ratio did not include parental allergy. If parents with a history of allergy were more likely to breastfeed exclusively this might explain the higher rate of food allergy in infants who are breastfed. Also no information on duration of breast feeding nature of food allergy and information on weaning.								

Research question 2 (Allergen exposure in childhood)
Breastfeeding and introduction of solids (10 studies)

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Gustafsson *et al.* 2004	Cohort	5/12 (+)	Baseline: 904 Follow-up at 18 months 638 (71%) completed questionnaire Follow-up at 4 years 613 (68%) completed questionnaire	Population group All children born between August 1991 and January 1992 and living in two municipalities in Sweden No exclusions at baseline. After 3 months – 87 were excluded (language problems, moved, died)	Information collected by questionnaire at 18 months on time of weaning, and introduction of cows' milk.	Information collected by questionnaire at 18 months on length of breastfeeding.	4 years	Atopic symptoms at 4 years (parental reports)	**Food allergy** **Parental reports of food allergy** No data provided, authors stated – 'The effect of duration of breast feeding and cows' milk introduction on the development of allergic symptoms was analysed but no relationships were observed'. Prevalence of reported food reactions 11.9% - authors say similar to other studies.
Notes	**Overall finding: Authors' report no associations between duration of breastfeeding and introductions of cows' milk and development of allergic symptoms; however actual results are not presented.** Assessment of food allergy is based upon parental reports. An assessment of the validity of parental reports on 186 children showed that about a third of children who parents reported symptoms had a positive IgE; where a positive IgE was found for 10% of children with no symptoms reported. A good response at the beginning of the study; however about one third of children were not followed-up up at 18 months or 4 years.								

Author year (study name)	Study type	Quality	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Kull *et al.* 2002 BAMSE	Cohort	8/12 (+)	Baseline: 4089 (75% of those eligible). An analysis of non-responders and those actively excluded showed that parental smoking was more prevalent in non-participating families compared with those taking part. Follow-up at 2 years 3791 completed all follow-up questionnaires (at 2 months, 1 year and 2 years) (93%). Included in analysis Exclusive breastfeeding – 3786 (93%) Partial breastfeeding – 3790 (93%)	Population group Infants born between Feb 1994 and Nov 1996 in Sweden. Inclusion criteria: Answered first questionnaire and collected samples of mattress dust in first year of life. Exclusion criteria: Families planning to move in the next year, insufficient knowledge of Swedish language, seriously ill child, sibling already included.	Exclusive breastfeeding < four months Partial breastfeeding < four months Questionnaire at 1 year and 2 year	Exclusive breastfeeding ≥ four months Partial breastfeeding ≥ four months	2 years	Parental reports from questionnaire. Reactions reported directly after consumption of food and/or doctor's diagnosis. Odds ratios for ≥ four months vs. < four months breastfeeding were adjusted for – gender, heredity, maternal age, smoking during pregnancy &/or first 3 months of life, year of construction of family home	**Food allergy** Parental reported adverse food reaction at 2 years **Exclusive breastfeeding** ≥ four months - 20% vs. < four months - 22% Odds ratio – 0.91(0.75, 1.11) NS **Partial breastfeeding** ≥ four months - 20% vs. < four months – 20% Odds ratio – 1.00 (0.85, 1.31) NS
Notes	**Overall finding: Exclusive breast feeding for 4 months or more was not associated with a reduced risk of parental reported food allergy.** There is no information on formulas or foods introduced after exclusive breast feeding is stopped. There was a reasonable initial response rate, although there was an indication that smokers were less likely to take part than non-smokers. The rate of follow-up was good. Assessment of food allergy relied on parental reports of either symptoms or doctor's diagnosis. There was no attempt to confirm the results. Results were not specific to particular food groups. Results were adjusted for other factors.								

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Kull *et al.* 2006A BAMSE	Cohort	7/13 (+)	Baseline: 4089 (75% of those eligible). An analysis of non-responders and those actively excluded showed that parental smoking was more prevalent in non-participating families compared with those taking part. Follow-up at 4 years 3670 completed all follow-up questionnaires (90%). Including in analysis: 2546 (62%)	Population group Infants born between Feb 1994 and Nov 1996 in Sweden. Inclusion criteria: Answered first questionnaire and collected samples of mattress dust in first year of life. Exclusion criteria: Families planning to move in the next year, insufficient knowledge of Swedish language, seriously ill child, sibling already included.	Consumed fish Once a month Two or three times a month Once a week > once a week Questionnaire administered at one year	Did not consume fish	4 years	IgE Food mix (cows' milk, hen's egg, cod fish, soy bean, peanut, wheat) (> 0.35 kU/l = +ve). Adjusted for parental allergic disease, maternal age, maternal smoking and breastfeeding	**Food sensitisation** **IgE (Food mix) at 4 years** % (n) with sensitisation by fish consumption in first year of life Never 26% (61) 1/month 19% (50) 2-3/month 17% (80) 1/week 14% (127) >1/week 13% (88) Adjusted odds ratios 1/month vs. never OR: 0.69 (0.45, 1.05) NS 2-3/month vs. never OR: 0.61 (0.41, 0.88) Sig 1/week vs. never OR: 0.48 (0.43, 0.68) Sig >1/week vs. never OR: 0.47 (0.33, 0.69) Sig P trend <0.001
Notes	**Overall finding: Consumption of fish in the first year of life was associated with a decreased risk of food sensitisation at age 4 years.** There was a dose response effect (regular consumption of fish was associated with more protection). There was a reasonable initial response and a good follow-up with the questionnaire data. However, only 62% could be included in the food sensitisation analyses. Results were adjusted for other factors. Due to the large sample size, the numbers of children with sensitisation resulted in a meaningful analysis. There is no information on maternal intake of fish or further details on the type and amount of fish consumed. It is not clear whether the questionnaire was validated.								

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Lack *et al.* 2003 ALSPAC	Cohort	7/13 (+)	Baseline 14541pregnant women invited and 13971 agreed to take part (96%) Follow-up: children up to age 38 months 12090 responded to at least one question on food avoidance and reactions to foods 86.5%). Plus children identified from questions regarding previous clinical history. Total number unclear. Included in analysis Breast feeding – 11179 (80%) Soy milk – 12324 (88%)	Population group Study enrolled pregnant women from Avon, UK with expected delivery date April 1 1991 and Dec 31 1992. Inclusion criteria: Mother resident in Avon when pregnant and on expected date of delivery. Exclusion criteria: Infant died before 1 year. Mother moved away from Avon before the 3rd trimester.	Infant not breastfed *OR* Used soy milk or formula in first two years of life Assessed by question-aire at 1, 6, 15 and 18 months and every 6 months thereafter	Infant breastfed *OR* No soy milk or formula used in first two years of life	Up to 38 months	Parental reports of peanut allergy Confirmed peanut allergy SPT Wheal ≥ 3mm = +ve followed by challenge (DBPCFC) Validity 49 parent reports of peanut allergy 36 (73%) went for further tests 29 +ve SPT Peanut allergy was confirmed in 23/49 (47%) by DBPCFC Adjusted for maternal atopy, rashes at 6 months and either breastfeeding or use of soy milk	**Food allergy** **Parental reports peanut allergy** -% (n) **Breastfed (Y vs. N) (unadjusted)** Yes – 0.5% (39) vs. No – 0.2% (6) Odds ratio 3.11 (0.73, 13.32) NS **Breastfeeding duration (months)(unadjusted)** 0 - 0.2% (6) <3 - 0.4% (13) 3-5- 0.5% (7) ≥6 - 0.6% (19) Odds ratio (≥6/12 vs. < 6/12) 2.60 (1.04, 6.53) P=0.03 Not statistically significant after adjustment **Soy milk or soy formula in first 2 years** Yes – 1.0% (12) vs. No – 0.3% (37) Odds ratio 3.6 (1.87, 6.92) P<0.001 unadjusted Odds ratio 2.61 (1.31, 5.20) P=0.006 adjusted **Peanut allergy +ve challenge % (n)** **Breastfed (Y vs. N) (unadjusted)** Yes – 0.2% (19) vs. No – <0.1% (2) Odds ratio 2.14 (0.91, 5.04) **Breastfeeding duration (unadjusted)** 0 - <0.1% (2) <3 - 0.2% (7) 3-5- 0.2% (3) ≥6 - 0.3% (9) Odds ratio(≥6/12 vs. <6/12) 3.67 (0.80, 16.94) NS Not statistically significant after adjustment **Soy milk or soy formula in first 2 years** Yes – 0.8% (8) vs. No – 0.1% (15) Odds ratio 5.9 (2.50, 13.96) P<0.001 unadjusted Odds ratio 3.15 (1.27, 7.80) P=0.01adjusted
Notes	**Overall finding: Exposure to soy protein in first 2 years of life was associated with an increased risk of peanut allergy. Duration of breastfeeding was not associated with development of peanut allergy.** No detailed information on peanut consumption in the children (allergic and non-allergic). In discussion authors report 'High levels of consumption of peanuts by infants did not appear to precede peanut allergy' and no subject was reported to have reactions to both peanut and soy. There was a good initial response and good follow-up. Cases of peanut allergy were confirmed by DBPCFC. % of children with confirmed peanut allergy was low 0.2%. Figures for all adjusted odds ratios were not provided in the paper.								

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Milner *et al.* 2004	Cohort	5/13 (+)	Baseline 1988 National Maternal and Infant Survey included ~ 9200 mothers who gave birth Follow-up Respondents followed up in 1991 – 90% (8285) Included in analysis 8073 – 88%	Population group of newborns. Blacks, individuals with low socioeconomic status and premature infants were intentionally overrepresented. Study carried out in USA. Includes 24% with <37 weeks gestation and 51% black.	Infant not breastfed Based on questionnaire data at 3 years	Infant breastfed	3 years	Parental report (verbal interview) of physician , or other health professional diagnosis of food allergy	**Food allergy** **Parental reports of food allergy** Breastfeeding (Y vs. N) (unadjusted) Odds ratio 1.39 (1.13, 1.71) P=0.002
Notes	**Overall finding**: **There was no association between whether infants were breastfed and parental reports of diagnosed food allergy at 3 years.** There is no information on initial response to the survey; however there was a good rate of follow-up. Food allergy was assessed by parental reports of diagnosed food allergy. There is no information on duration of breastfeeding or time of weaning. The result was not adjusted for other factors. The survey also included information on infant use of multivitamins. Use of multivitamins particularly in infants not breastfed was associated with an increased risk of food allergy. It is not clear whether the multivitamins included peanut oil.								

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Pesonen *et al.* 2006	Cohort	7/13 (+)	Baseline: 200 (90% of those asked to take part) Included in the analysis at 5 years Unadjusted - 160 (80%) Adjusted – 132 (66%) Included in the analysis at 11 years Unadjusted - 149 (75%) Adjusted – 126 (63%)	Population group Families and infants recruited from maternity hospital between June-Sept 1981 in Finland Inclusion criteria Healthy, full term with appropriate weight for gestational age, a 1 min Apgar score of at least 8, a healthy non-smoking mother with uncomplicated pregnancy and delivery and single birth	Exclusive breastfeeding <9 months Assessed at clinic appointments every two/three months+ families free to contact and visit the paediatrician between visits Mothers encouraged to breastfeed for as long as possible. No cows' milk formula was provided in hospital. If supplementary milk was required infants were given donated breast milk. Infants were weaned onto cows' milk formula. Solids introduced from 3 months.	Exclusive breastfeeding ≥9 months	11 years	Parental reports of allergic symptoms after ingestion of a specific food confirmed by personal interview. Adjusted for sex, maternal age, maternal educational level, smoking in the household during first year, day care attendance at the age of 1 year, sibship size 3 or more	**Food allergy** **Parental reports of food allergy** **Duration of exclusive breastfeeding (months) (unadjusted)** At 5 years >2 7% (2) 2 to < 6 6 %(2) 6 to < 9 11%(7) ≥ 9 26%(8) Odds ratio(≥9 vs. < 9) 3.2 (1.2, 9.0) P=0.02 At 11 years >2 0%(0) 2 to < 6 9%(3) 6 to < 9 10%(6) ≥ 9 23%(7) Odds ratio(≥9 vs. < 9) 3.6 (1.2, 10.5)P=0.01 **Exclusive breastfeeding ≥ 9 vs. < 9 months (adjusted)** At 5 years Odds ratio 2.5 (0.8, 7.6) NS *By family history of allergy* Positive OR 5.3 (1.2, 24.1) P=0.03 Negative OR 1.0 (0.1, 7.5) NS At age 11 years Odds ratio 1.9 (0.5, 7.0) NS *By family history of allergy* Positive OR 7.9 (1.4, 50.0) P=0.02 Negative OR 4.3 (0.1, 284) NS
Notes	**Overall finding: Prolonged exclusive breastfeeding of 9 months or more was associated with increased food hypersensitivity in children with a family history of allergy at 5 and 11 years of age. There was no association with children who did not have a family history of allergy.** Authors report that excluding children with atopy in first year did not change results and therefore reverse causation was not a factor. Food allergy was assessment by parental reports. An assessment of the validity of parental reports showed that at age 5 years of the 19 children with parental reports of allergy 12(63%) had a negative SPT whereas a positive SPT was observed in 10% of the 120 symptom-free children. At age 11 years of the 16 children with parental reports of allergy 8(50%) had a negative SPT whereas a positive SPT was observed in 20% of the 81 symptom-free children. A positive SPT was defined as a test reaction with a mean diameter equal to or greater than half of the diameter of the histamine wheal. Results of verified food allergy were not reported in the paper. There was a good initial response rate; however only two thirds of children were included in the adjusted analyses. Several important factors were adjusted for. Assessment of breastfeeding was assessed regularly.								

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Poole *et al.* 2006 DAISY	Cohort	7/13 (+)	Baseline 1819 - 55% of those eligible (HLA genotype) Follow-up at 4 years 1612 (88.6%) had at least one clinic visit and allergy and dietary data. 501 with a family history of diabetes and 1111 with HLA genotype	High risk Inclusion criteria 1) Newborn children with a sibling or parent with type 1 diabetes 2) Newborn screening for HLA genotype (high risk of diabetes and coeliac disease) Exclusion criteria Severe congenital abnormalities or extremely premature. From Denver, USA	Exposed to cereals before 6 months of age *OR* Shorter during of breastfeeding Telephone or face to face interviews. Breastfeeding initiation and termination and date of introduction of foods over last 3 months were recorded	Exposed to cereals after 6 months of age *OR* Longer duration of breastfeeding	4 years	Mothers reported presence of allergy to specific foods and whether diagnosed by physician at telephone or face to face interviews (children with positive screening for coeliac disease were excluded). Adjusted for cereal grain introduction, Rice introduction, breastfeeding duration, food allergy before 6 months, family history of allergy (as appropriate)	**Food allergy** **Parental reports of wheat allergy at 4 years of age** **Unadjusted odds ratios** **Cereal grain introduction** ≥ 7months vs. 0-6 months 4.77 (1.33, 17.09) Sig **Rice grain introduction** ≥ 7months vs. 0-6 months 2.7 (0.85, 8.37) NS **Breastfeeding duration** Mean duration 10.3 vs. 6.5 months for wheat allergy vs. no wheat allergy 1.11 (1.01, 1.11) Sig **Breastfed when first exposed to cereals** Yes vs. No 2.0 (0.71, 5.40) NS **Adjusted odd ratios** **Cereal grain introduction (wheat, barley, rye, oats)** ≥ 7months vs. 0-6 months 3.8 (1.18, 12.28) P=0.025 **Age exposed to rice cereal** ≥ 7months vs. 0-6 months 1.6 (0.46, 5.23) NS **Breastfeeding duration** Per 1-month increase 1.05 (1.00, 1.11) NS
Notes	**Overall finding: Delaying exposure of cereal grain introduction until after 6 months was associated with an increased risk of wheat allergy.** Food allergy was assessed by parental reports; 16 children were reported to have an allergy to wheat. Four of these had a physician diagnosis of which 3 tested positive for wheat specific IgE (>0.35KU/L). One of tested positive for wheat specific IgE. The 11(69%) remaining did not have either a doctor diagnosis of wheat allergy or a positive wheat specific IgE. Thus many of the parental reports could not be confirmed. The initial response rate was not high; however the rate of follow-up was good. Breastfeeding duration is expressed as an odds ratio per I month increase. It is not clear what the time point for the increase is (i.e. is it after 6 months).								

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Wetzig *et al.* 2000	Cohort	6/12 (+)	Baseline: 475 out of all 3540 newborns identified as high risk Follow-up at 1 year 323 (68%) examined Follow-up at 2 years 265 (56%)	All newborns were registered by level of cord blood IgE measured and family history of atopic disease in Leipzig, Germany High risk group: A)Healthy, appropriate for gestational age, Increased cord IgE (>0.9kU/L) OR B)double positive atopic family history (adults, siblings) independent of cord IgE	Exclusively breastfed < 5 months Information collected annually by questionnaire.	Exclusively breastfed ≥ 5 months	Two years	Specific IgE Egg RAST ≥ 1 = positive	**Food sensitisation** **Sensitisation to egg white** At one year **Odds ratio for ≥ 5 vs. <5 months of exclusive breastfeeding (unadjusted) by high risk group** *A) elevated cord blood IgE level* (N=48) Odds ratio 4.9 (1.2, 20.4) Sig *B) double positive atopic family history (*N=100) NS (*no result presented*) *C) elevated cord blood IgE level and double atopic family history (*N=101) NS (*no result presented*) At two years Authors report that no statistically significant association could be detected between length of breastfeeding and sensitisation to egg white.
Notes	**Overall finding: Infants with elevated cord blood IgE exclusively breastfed for 5 months or more had an increased risk of sensitivity to hen's egg at one year, but not at two years**. Identification of high risk group appears complete at baseline; however only two thirds were followed-up at 1 year and just over half at two years. There is no information on weaning or types of formula used. A RAST test result of 1 was considered positive. Results were not adjusted for other factors. It is unclear how the information on breastfeeding was ascertained from the questionnaire i.e. how the question(s) was/were phrased. Actual results at two years are not presented.								

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Zutaver n *et al.* 2006 LISA	Cohort	7/13 (+)	Baseline: 3097 newborns were enrolled with a 52-58% response rate depending on centre. Follow-up: At 2 years 2664 (86%) completed the questionnaire. Included in the analysis: 1. 2600 (84%) with parental reports of diagnosed food allergy. 2. 2094 (68%) with IgE at 2 years.	Population group Infants delivered between Nov 1997 and Jan 1999 in 4 cities in Germany Exclusion criteria: Preterm (<37 weeks gestation, low birth weight (<2500g), congenital malformation, antibiotic medication, in hospital or in intensive care during neonatal period. Non-German parents. Mothers had immune related diseases (autoimmune disorders, diabetes, hepatitis B)	Timing of introduction of foods ≤ 6 months Self-completed questionnaires filled in by parents. At 6 months asked about breastfeeding practices, and timing of introduction of 48 food items.	Timing of introduction of foods > 6 months	2 years	Allergy Parental reports of doctor diagnosed food allergy in first 2 years of life Sensitisation Specific IgE for egg, cows' milk, wheat, peanut, soybean, cod fish at 2 years RAST (+ve ≥ 0.35 kU/l) Adjusted for study centre, gender, parental education, parental atopy, birth weight, breastfeeding.	**Food allergy** **Parental reports of Dr diagnosed food allergy (unadjusted)** % (n) introduced milk or egg >6mo Yes - 87% (47) No - 76% (1884) Sig (P=0.05) **Food sensitisation** **Timing of introduction of solids and food sensitisation (adjusted odds ratios)** Any solids 5-6 vs. <5months:1.04 (0.71, 1.53) >6 vs. <5months:0.83 (0.49, 1.41) Solids diversity at 4months 1-2 vs. 0 groups: 1.04 (0.67, 1.61) 3-8 vs. 0 groups: 0.97 (0.58, 1.62) Solids diversity at 6months 1-2 vs. 0 groups: 1.52 (0.90, 2.54) 3-4 vs. 0 groups: 1.20 (0.74, 1.94) 5-8 vs. 0 groups : 1.06 (0.62, 1.81) No result was statistically significant
Notes	**Overall finding: There was no evidence of a protective effect of delayed introduction of solids past 6 months on doctor diagnosed food allergy or food sensitisation at 2 years.** The study aimed to carry out IgE tests on all children (not just those who reported symptoms); however not all parents agreed. The response rate at baseline was not good; there was a good follow-up for completing the questionnaire at 2 years; however only two thirds of children had IgE tests. There was a bias children with atopy, male gender and high parental education were all factors associated with having blood tests. Although a number of specific IgE tests were carried out the results are only presented as total food sensitisation. It is reported in the text that the timing of introduction of milk and egg was not associated with atopic sensitisation against the respective items. It is not clear whether the dietary questionnaire was validated. Results were adjusted for other factors. There was also no association in the number of different food groups introduced to the infant (vegetables, cereal, fruit, meat, dairy products, egg, fish, other).								

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Frank *et al.* 1999	Case-control	6/10 (+)	25 cases Cases with peanut sensitivity 18 controls Cases with milk or egg sensitivity No information on response rate	High risk group Children referred from hospital in South Africa with suspected food allergy aged between 0 and 3 years of age at time of diagnosis.	Earlier age of introduction of peanuts into the child's diet Earlier age of introduction of formula into child's diet Mother completed a standardized questionnaire. To avoid bias the questionnaire asked about intake of a variety of foods (not only peanuts)	Later age of introduction of peanuts into the child's diet Later age of introduction of formula into child's diet	Up to 3 years	Peanut specific IgE RAST (> 0.35 kU/l = +ve) No food challenge tests	**Food sensitisation** **Introduction of peanuts or peanut butter into child's diet** Mean age (SD) Cases – 12.5 (6.4) months Controls – 17.3 (5.5) months Sig (P=0.03) Mothers reported that 9 cases and 2 controls had not yet consumed peanuts or peanut butter Positive correlation between age of introduction of peanuts and peanut butter and age at clinical diagnosis was found (r=0.63 (0.19, 0.86) n=15). There was no significant correlation in control group (r=0.14) **Mean age of introduction of formula** Mean age Cases – 5.5 months Controls – 2.0 months NS Paper states that there was no significant different between cases and controls for age, weight, height, allergic disease in mother, grandparents or index child's siblings
Notes	**Overall finding: earlier introduction of peanuts into the infants' diet was associated with peanut sensitisation.** The sample size is small and there is no power calculation. The study did not account for inadvertent exposure to peanut in the child's diet by other caregivers or exposure outside the home. Cases were not confirmed by food challenges. As children were sensitised to other foods also symptoms at time of diagnosis may have been related to other foods the child was allergic to. Cases and control were not matched and the results were not adjusted for other factors.								

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Hourihane *et al.* 2007	Cross-section -al	6/11 (+)	1072 mother – child pairs were studied. 5072 were eligible, 1125 were recruited and 1072 (21%) had valid questionn aires Sample size calculation required 1000 children	Recruited through Primary Schools (114) in Manchester and Southampton Subjects were born between March 1999 and March 2000 and were assessed at 4-5 years of age. <u>General Population</u> Exclusion criteria: refused SPT, family not resident in UK at time of COT report or child born outside UK	At an arranged appointment a questionnaire was administered to mother (face to face interview). Mother was asked if they recalled the COT advice. Mother's consumption of peanut and peanut products during pregnancy and breastfeeding was assessed. Child's peanut consumption and current and resolved allergic conditions was assessed. Children had a SPT (positive result was indicated by a wheal at least 3mm in diameter). DBPCFC with peanut was used to confirm the diagnosis if parents consented and reaction had not occurred in last year and there was no specific IgE measurement suggesting peanut allergy			Children who were breast-fed were 3.8 times more likely to have peanut allergy than those bottle fed. This result was statistically significant (P<0.05); however when it was adjusted for the presence of eczema it was no longer statistically significant.	
Notes	**Overall finding: Breastfeeding was not associated with an increased risk of peanut allergy after adjusting for presence of eczema.** This is a cross-sectional study with a poor response rate.								

Research question 2 (Allergen exposure in childhood)
Multifaceted interventions (3 studies)

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Arshad *et al.* 2007, 2003 Isle of Wight prevention study	RCT	6/9 (+)	504 of 1116 pregnant women reported atopic symptoms in themselves, partners, or children. 301 (60%) agreed to take part. Baseline: 136 infants met inclusion criteria Intervention - 69 Control – 67 Follow-up: 8 years 120 Intervention: 58 (84%) Control: 62 (93%) Information on SPT at 8 years Intervention: 55 (80%) Control: 62 (93%)	Pregnant women were recruited at last ante-natal visit to hospital in UK Inclusion criteria: Not preterm High risk group: Two or more members of immediate family affected with an allergic disorder (asthma, atopic eczema or allergic rhinitis) or either parent or sibling affected with allergic disorder and cord serum IgE >0.5kU/L.	For first year Followed national guidelines at the time. Compliance: no change in exposure to HDM	For first year Reduced allergen exposure. Dairy products, eggs, wheat, nuts, fish, soya excluded from diet of infants and lactating mothers for first 9 months. EHP hypoallergenic formula to be used if required as a supplement to breastfeeding. Foods gradually to be introduced from 9 months. Also dust mite avoidance. Compliance: maternal diet as assessed by β lactoglobulin & casein was excellent. Infants – 3 had cows' milk & wheat between 24-32 weeks	8 years	**Sensitisation** SPT Wheal ≥ 3mm =+ve **Food allergy** Symptoms within 2 hours of ingestion of suspected food on 2 or more occasions Odds ratios (intervention vs. control) adjusted for age, sex, ; maternal, paternal and sibling allergy, asthma; high cord IgE, first born child; maternal education; separate bedroom; gas cooking; maternal smoking during pregnancy; maternal and paternal smoking at age 8 years; pet cat; and pet dog	**Food allergy - %(n)** **At any time in 8 years** **Food allergy diagnosed** Int 19% (11) Control 41.9% (26) P=0.005 Adjusted odds ratio 0.75 (0.27, 2.10) NS **Food allergy diagnosed and +ve SPT** Int 9.1% (5) Control 25.8% (16) P=0.02 Adjusted odds ratio 0.41 (0.11, 1.53) P=0.18 **Sensitisation** +ve SPT at 8 years-% (n) At age 8 years **Cows' milk** Int 0% (0) Control 6.5% (4) NS **Peanut** Int 0% (0) Control 1.6% (1) NS No child had +ve SPT to egg or fish **Food sensitisation at any time in 8 years** Int 25.5% (14) Control 59.7% (37) Adjusted odds ratio 0.15 (0.03, 0.80) Sig
Notes	**Overall finding: A strict dietary and dust mite regimes for first year of life compared with a control group following national guidelines was not associated with food allergy but was associated with a decreased risk of food sensitisation (all foods) at least once during the first 8 years of life.** Only 60% agreed to take part; however there was good compliance. Follow-up was good but slightly better for control group. Food allergy was confirmed by SPT but not food challenge. Results were adjusted for several important factors. Results for food allergy were presented for all foods than for specific foods.								

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Chang-Yeung *et al.* 2005	RCT	7/10 (+)	Of 1069 eligible pregnant women 545 (51%) agreed to take part. Baseline: 549 infants Intervention: 281 Control: 268 Follow-up 7 years: Intervention: 250 (89%) Control: 219 (82%) Included in analysis At 7 years Intervention: 194 (69%) Control: 173 (65%)	Pregnant women were recruited during 3rd trimester from community based hospitals and ante-natal clinics in Canada. High risk group: ≥ one first degree relative with asthma or 2 first degree relative with other IgE mediated allergic disease	Usual care from primary care physicians Compliance: 93% intervention and 92 % of control breast fed infant from birth. At 8 months 61% of intervention and 50% of controls were being breastfed. Solids introduced by 19.5% in intervention and 49.8% of control by 4 months	Mother's diet During last trimester of pregnancy and during lactation mothers to exclude peanuts, other nuts, fish, other seafish. Infant's diet for first year of life Breast feed for at least 4 months and for 1 year if possible. Partially hydrolysed formula used if supplementary feed required up to one year (if allergic given soy formula). To delay introduction of solids until 6 months and give according to agreed timetable. Exclude cows' milk, seafood, and peanuts from infants' diet for one year. HDM avoidance measures, no smoking, no pets	7 years	SPT Wheal ≥ 3mm = +ve	**Food sensitisation** % with +ve SPT at 7 years **Milk** Intervention: 0.5% Control: 1.0% **Egg** Intervention: 2.0% Control: 1.5% **Peanut** Intervention: 12.4% Control:6.9% (P=0.11) **Soy** Intervention: 7.5% Control: 5.0% **Wheat** Intervention: 1.0% Control: 1.0% No statistically significant differences
Notes	**Overall finding: A strict dietary and dust mite regimes for first year of life compared with a control group under care of primary care physicians was not associated with food sensitisation (milk, egg, peanut, soy, wheat) at 7 years.** Follow-up at 7 years was good; however not all children had SPT which resulted in only 2/3rds with follow-up data. Results were not adjusted for other factors. Both groups had a high uptake of breastfeeding and a significant % was still being breastfed at 8 months. There is no information on dietary habits after one year of age. It is not possible to separate the effects of mother's diet from infant's diet. Sensitisation to peanut was more common than for the other food allergens.								

Author year (study name)	Study type	Qua-lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Halmer-bauer *et al.* 2003	RCT	6/10 (+)	5601 screening questionnaire s were distributed, of which 4834 were returned (86%). Of these 1570 parents had a +ve screening and SPT performed on. 852 parents had +ve SPT 696 (82%) agreed to take part. Baseline: 696 Intervention: 349 Control: 347 Follow-up one year: Intervention: 337 (97%) Control: 333 (96%) Analysed at one year Intervention: 322 (92%) Control: 300 (86%)	Recruited at routine visit to obstetric wards during pregnancy or shortly after birth in children's dept of respiratory clinics in Austria, Germany, UK Inclusion criteria: Birth weight ≥ 2500g, no addition to neonatal IC for > 7days High risk group: One or both parents with allergic disease (allergic rhinitis, hay fever, bronchial asthma, atopic eczema) confirmed by SPT or IgE (5 aeroallergens)	Standard recommend ation for each country briefly reiterated: Exclusive breastfeedi ng for at least 3 months with delay in introduction of solid food until at least 6 months and cows' milk not until one year. Also avoidance of exposure to pets, cigarette smoking and keeping rooms ventilated	Exclusive breastfeeding for at least 3 months with delay in introduction of solid food and soy-milk formula until at least 6 months. If required supplementary feeding used hypoallergenic formula. Solids gradually introduced. Cows milk, egg fish not before one year, peanut or tree nuts not before 3 years. Measures to reduce HDM Also avoidance of exposure to pets, cigarette smoking Compliance: Questionnaire: 96.3% no egg in year 1, 100% no cows milk in year 1	One year	**Sensitisation** SPT or IgE SPT Wheal ≥ 2mm =+ve IgE +ve ≥1.43 kU/l **Food allergy** Parents reports of food intolerance Odds ratios for intervention vs. control. Adjusted for centre, gender and pets.	**Food allergy** **Parental reports of intolerance** Intervention 28.5% (99) Control 36.5 (125) *Assuming all lost did not have allergy* Odds ratio 0.67 (0.49, 0.92) P=0.014 *Assuming all lost did have allergy* Odds ratio 0.70 (0.50, 0.96) P=0.027 **Doctor diagnosed** Intervention 5.2% (18) Control 4.1% (14) NS **Food sensitisation** **% (n) +ve (SPT or IgE) at one year** **Egg** Intervention 4.67% (15) Control 5.35% (16) **Milk** Intervention 1.24% (4) Control 2.67% (8) *Assuming all lost were not sensitised* **Egg** Odds ratio 0.58 (0.39, 0.85) P=0.005 **Milk** Odds ratio 0.63 (0.41, 0.96) P=0.032 *Assuming all lost were sensitised* **Egg** Odds ratio 0.68 (0.40, 1.15) NS **Milk** Odds ratio 0.87 (0.43, 1.75) NS
Notes	**Overall finding: Assuming all those lost to follow-up did not have sensitisation/allergy strict dietary and dust mite regimes compared with following standard recommendations for first year of life was associated with reduced food sensitisation (milk, egg) and was not associated with reported doctor diagnosed food allergy.** No infant in intervention consumed cows' milk and only 3.7% consumed egg. Good rate of follow-up. Food allergy not confirmed by challenge. There is a difference in result if doctor diagnosed food allergy is used rather than parental reports. Results were not adjusted for all important factors.								

Research question 3 (Non-dietary exposure to peanuts in childhood) (2 studies)

Author year (study name)	Study type	Quality	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Kull *et al.* 2006B BAMSE	Cohort	7/13 (+)	Baseline: 4089 (75% of those eligible). An analysis of non-responders and those actively excluded showed that parental smoking was more prevalent in non-participating families compared with those taking part. Follow-up at 4 years 3670 completed all follow-up questionnaires (90%). Including in analysis: **Food allergy** – 3472 (85%) **IgE-** Peanut – 2447 (60%) Food mix – 2454 (60%) Milk – 2449 (60%) Egg white – 2450 (60%).	Population group Infants born between Feb 1994 and Nov 1996 in Sweden. Inclusion criteria: Answered first questionnaire and collected samples of mattress dust in first year of life. Exclusion criteria: Families planning to move in the next year, insufficient knowledge of Swedish language, seriously ill child, sibling already included.	Vitamins A and D in peanut oil Questionnaire administered at one year	Vitamins A and D in water	4 years	Allergy Parents report of symptoms covering the last two years (questionnaire at 4 years) Sensitisation IgE Food mix (cows' milk, hen's egg, cod fish, soy bean, peanut, wheat) and single allergens (peanut, milk, egg white). (> 0.35 kU/l = +ve). All results adjusted for parental allergic disease, maternal age, maternal smoking during pregnancy, at recruitment or both; fish consumption; and breastfeeding	**Food allergy** At 4 years **Parental reports of food hypersensitivity %(n)** Vitamins in oil 11% (351) Vitamins in water 20% (48) OR: 1.87 (1.32, 2.65) water vs. oil Sig. **Odds ratios by type of allergic disease (water vs. oil)** Transient: 1.05 (0.70, 1.56) NS Late onset: 0.64 (0.30, 1.40) NS Persistent: 2.99 (2.01, 4.42) Sig **Food sensitisation** **IgE** **Foodmix** Vitamins in oil – 15% (351) Vitamins in water –26% (41) OR: 1.75 (1.20, 2.56) water vs. oil Sig. **Single allergens** Odds ratios (water vs. oil) **Peanut** OR: 1.52 (0.84, 2.75) NS **Milk** OR: 1.54 (0.94, 2.51) NS **Egg white** OR: 2.27 (1.30, 3.59) Sig
Notes	**Overall finding: Supplementation of vitamin A and D in water soluble form in the first year of life increases the risk of food allergic disease up to 4years compared with vitamins given in peanut oil. Results for single allergens showed no association for peanut or milk, and an increased risk for sensitisation to egg white for vitamins in water vs. oil.** There was a reasonable initial response and a good follow-up with the questionnaire data. However, only 60% could be included in the food sensitisation analyses. Most children received vitamins in oil (90%) and the peanut oil used was highly refined. There is no information about vitamin supplementation after age 1 year.								

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Period of recall	Outcome measures	Effect size
Lack *et al.* 2003 ALSPAC	Case-control	7/11 (+)	Baseline 14541pregnant women invited and 13971 agreed to take part (96%) Follow-up: children up to age 38 months 12090 responded to at least one question on food avoidance and reactions to foods 86.5%). Plus children identified from questions regarding previous clinical history. Total number unclear. 23 cases +ve peanut challenge 70 atopic controls Random sample of children with eczema in first 6 months of life 140 normal controls Random sample of children with no peanut allergy	Population and high risk groups Study enrolled pregnant women from Avon, UK (ALSPAC study birth cohort) with expected delivery date between April 1 1991 and Dec 31 1992. Inclusion criteria: Resident in Avon when pregnant and on expected date of delivery. Exclusion criteria: Infant died before 1 year. If moved before the 3rd trimester.	Use of creams with peanut oil (maternal and infant) in first 6 months of life Interviewed by telephone	Did not use creams with peanut oil (maternal and infant) in the first 6 months of life	4-6 years	SPT Peanut (+ve 3mm) followed by DBPCFC 49 reports of reactions to peanuts 36 (73%)– went for further tests of which 29 had +ve SPT and 23 +ve DBPCFC	**Food allergy** **Peanut allergy** **Maternal use of breast creams with peanut oil** Peanut allergy cases – 35% Atopic controls – 47% Normal controls – 24% NS **Use of creams with peanut oil on infant's skin** Peanut allergy cases – 91% Atopic controls – 53% Normal controls – 59% Sig (P<0.001) No significant difference among the three groups in rate of use of infant creams not containing peanut oil (100%, 97% and 84% respectively). The association remained significant when results were adjusted for soy milk or formula, and rashes. The odds ratio was 8.34 (1.05, 66.1) for use of peanut oil preparation and positive peanut challenge. **Number of peanut oil preparations exposed to:** Cases – 1.91 Atopic controls – 0.93 Normal controls - 0.81 Sig (P<0.001)
Notes	**Overall finding: This study does not show an association between maternal use of breast creams and development of peanut allergy in the child. Use of creams with peanut oil applied to infants was associated with increased risk of peanut allergy.** Results were independent of presence of rashes or consumption of soy milk. Although the ALSPAC study is a birth cohort, this part of the study was analysed as case-control study. There was no matching between cases and controls. Key questions had not been included in the prospective interviews.								

Research question 4 – evaluation of 1998 COT advice – direct evidence (2 studies)

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Dean *et al.* 2007A Venter *et al.* 2006A	Cross-section -al	7/11 (+)	969 recruited (95% of target population (1064)). At age 2 years 88% were followed-up and 658 (76% of those followed up) consented by their parents to have a SPT. 62% of target population had SPT.	Birth cohort recruited through antenatal clinics and included all babies born on the Isle of Wight between 1 September 2001 and 31 August 2002. <u>General population</u> No exclusion criteria	Pregnant mothers completed a validated FFQ at 36 weeks gestation. However this information is reported separately in Venter 2006C. All children were followed up until 2 years of age and then if parents consented had SPT (positive result was indicated by a wheal at least 3mm in diameter). Questionnaire to assess compliance with COT advice administered to mothers at 2 year follow-up. Completed by 838 women (79% of target) Food challenges were not carried out as 85% of children had a family history of atopy and COT recommended that peanuts should not be introduced to children under the age of 3 years with atopic family history.			**<u>At 36 weeks gestation (Venter 2006A)</u>** Reliability study (2 administrations of FFQ at 30 and 36 weeks) on 91 women and validity study (FFQ vs. 4 x 7 day food diaries (weights of foods not recorded) in 57 women. <u>Validation study</u> % of women who reported never eating peanuts was 58% for diary and 54% for FFQ <u>Reliability study</u> % of women who reported never eating peanuts (FFQ) was 56% at 30 weeks and 54% at 36 weeks. **<u>At 2 year follow-up (Dean 2007A)</u>** 65% (62, 68) of mothers stated they avoided peanuts during pregnancy. No effect of maternal atopy (NS), nor family history of atopy (NS). 42% of mothers who responded recalled knowledge of COT report (not affected by maternal atopy P=0.63) or family history of atopy (NS). Mothers having their first child were almost twice as likely to change their diet – OR 1.97 (1.37, 2.84) adjusted for maternal and paternal atopy (P<0.001). Maternal and paternal atopy was not related. <u>Sensitisation to peanut</u> 2.0 (1.2, 3.4) % of 658 with SPT. If it is assumed that those who declined have negative SPT the estimated incidence falls to 1.5 (0.8, 2.6) %. Mothers of 77% (10/13) of the sensitised children stated they had avoided peanuts during pregnancy.	
Notes	**Overall finding: The findings demonstrate that the target population did not necessarily take up the advice. The COT advice appears to have been misunderstood as women not in the target group avoided peanuts**. This study is taken from a birth cohort; however the information presented in this paper is from the two year follow-up only and mother's were asked to recall dietary intakes rather than using the FFQ with information at 36 weeks. We have therefore reported this as a cross-sectional study as it has been analysed in this way and is comparable to the Hourihane 2007 study. Also the % reporting to avoid peanuts was higher in the 2 year recall than in the 36 week FFQ (54% vs. 65%).							

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Hourihane *et al.* 2007	Cross-section -al	6/11 (+)	1072 mother – child pairs were studied. 5072 were eligible, 1125 were recruited and 1072 (21%) had valid questionn aires Sample size calculation required 1000 children	Recruited through Primary Schools (114) in Manchester and Southampton Subjects were born between March 1999 and March 2000 and were assessed at 4-5 years of age. <u>General Population</u> Exclusion criteria: refused SPT, family not resident in UK at time of COT report or child born outside UK	At an arranged appointment a questionnaire was administered to mother (face to face interview). Mother was asked if they recalled the COT advice. Mother's consumption of peanut and peanut products during pregnancy and breastfeeding was assessed. Child's peanut consumption and current and resolved allergic conditions was assessed. Children had a SPT (positive result was indicated by a wheal at least 3mm in diameter). DBPCFC with peanut was used to confirm the diagnosis if parents consented and reaction had not occurred in last year and there was no specific IgE measurement suggesting peanut allergy			**<u>Recall of COT advice</u>** 111 mothers who never ate peanuts were excluded. 61% Recalled COT advice (33% did not and 6% missing). Maternal atopy had no effect on recall of COT advice. **<u>Likelihood of dietary change</u>** Of those who recalled COT advice 61% (357) reported a change in diet. 36 (10% of those who changed their diet, 6% who recalled advice, and 3.8% of whole group stopped eating peanuts whilst pregnant. A total of 4.6% of atopic mothers and 3.6% nonatopic mothers stopped eating peanuts (NS). Overall 328 (42%) of mother reported reduced peanut consumption. Mothers with more than one child were a third less likely to eliminate/reduce peanuts (OR 0.635 (0.543, 0.743) P<0.01). If father were atopic the chance of mother changing her diet was a third more likely (OR: 1.33 (1.03, 1.72) P<0.02) – both ORs adjusted for child sex, sibling atopy, marital status, parent country of birth, permanent residence in UK in 1998, parental smoking, level of peanut consumption before pregnancy, level of peanut consumption before first antenatal visit and level of peanut consumption during pregnancy and each other. Maternal atopy was not statistically significant. 688 mothers had consumed peanuts regularly before becoming pregnant and breastfed their child. 46% of these changed their diet (5% eliminated peanuts). 41% who breastfed thought they had eaten peanuts while breastfeeding. **<u>Peanut sensitisation of children</u>** 65% of children were reported to have consumed peanuts. The mean age of introduction was 36 months. Prevalence of peanut sensitisation was 2.8% (1.8-3.8) (+ve SPT or high >100KUa/L peanut specific IgE). **<u>Peanut allergy</u>** 9/30 declined DBPCFC. 15 challenges were +ve. 20 were considered to have peanut allergy (challenge or strong history + skin and blood test results). Prevalence of peanut allergy was 1.8% (1.1, 2.7).	

						Peanut consumption (maternal) and peanut sensitisation Of 20 children with peanut allergy, 9 mothers were atopic. Mothers of 8 recalled changing their diet when pregnant (1 eliminated peanuts). Of those who changed 5 were atopic mothers. Authors reported that no difference was found in the rate of change of peanut consumption between mothers whose children became sensitised and those whose children were not sensitised to peanut (no actual data reported in the paper, it is unclear whether the maternal intake related to intake during breastfeeding or lactation or both). **Peanut consumption (child) and peanut sensitisation** Peanut was introduced at mean age of 32 months for peanut sensitised and 29 months for those not sensitised (NS).
Notes	**Overall finding: Government advice seems not to have had a significant impact on mothers' diets and seems to have been assimilated by the general population, rather than acted upon by the target group who would develop allergies.** Peanuts have been introduced at a later stage 36 months compared with 1989 Isle of Wight birth cohort (12.6 months, prevalence 0.5%). Limitation of the study – mothers were asked to recall diet between 5 and 6 years ago, the response rate was low. Possible over-estimate of prevalence as further cases were not identified through checking clinic records and prospectively seeking eligible children coming to clinic.					

Research question 4 – evaluation of 1998 COT advice – indirect evidence (2 studies)

Author year (study name)	Study type	Qua-lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Venter *et al.* 2006 B	Prevalence	6/7 (++)	1440 were eligible based on school attendance 798 (55.4%) participated	All Primary Schools (52)in the Isle of Wight consented to take part Subjects were born between 1 September 1997 and 31 August 1998 and were assessed at 6 years of age. <u>General Population</u> No exclusion criteria	1. Questionnaire completed by parents asked "Does your child currently have a problem with milk, egg, peanut, tree nut, wheat, fish, sesame or other?" If yes they were asked to give further details 2. SPT was offered to all children (positive result was indicated by a wheal at least 3mm in diameter). 700 agreed (87.8% of responding sample and 49% of eligible sample). 3. Questionnaires were screened and children with a history of food reactions or a +ve SPT were invited for an open food challenge. 4. Children with a positive open challenge were invited for a DBPCFC unless the open challenge resulted in a severe reaction or there was a history of anaphylaxis.				**Peanut allergy** 1.9% (15/798) of children had parental reports of reactions to peanut. After questionnaire screening 10 children with reported peanut reactions were invited for open challenge and 6 accepted of which 2 were +ve. The 4 who declined had known allergies (3 peanut). No child had a DBPCFC. 0.6% (5/798) had either known peanut allergy or a +ve open challenge. **Peanut sensitisation** 2.6% (18/700) of children had a +ve SPT
Notes	**Overall finding: Prevalence of peanut allergy was 0.6% and the prevalence of peanut sensitisation was 2.6% in 2003-4 in 6 year old children on the Isle of Wight.** The main weakness is the 55% response rate; however some information was collected on non-responders such as sex, area of residence, type of school and no significant differences were found. DBPCFC was not used to determine peanut allergy.								

Author year (study name)	Study type	Qua -lity	Number of subjects	Subject characteristics	Exposure to food allergen	Avoidance or reduced exposure to food allergen	Length of follow-up	Outcome measures	Effect size
Venter *et al.* 2006C **Dean *et al.* 2007B**	Preval-ence	5/7 (+)	969 recruited (95% of target population (1064)). At age 1 year children were reviewed and approached for a SPT 900 follow-up questionnaires were completed and 763 children had SPT (72% of target population) 807 of children were seen at 1, 2 and 3 years of age. 543 (56%) agreed to have a SPT on each occasion.	Birth cohort recruited through antenatal clinics and included all babies born on the Isle of Wight between 1 September 2001 and 31 August 2002. <u>General population</u> No exclusion criteria	At 3, 6, 9 months reported symptoms of atopy were obtained. The questionnaires were screened and children who reported an adverse reaction were contacted and invited to Allergy Centre for a more detailed history and SPT. [Note challenges were carried out for most food allergens but none were undertaken for peanut allergy as children were aged under 3 years]. All infants were approached for a SPT (positive result was indicated by a wheal at least 3mm in diameter).				**Peanut sensitisation** **<u>Sensitisation rates at one year</u>** 0.4 % (3/763) were sensitised to peanut. **Prevalence of sensitisation to peanut in 543 children who had SPT at 1, 2 and 3 years** One year - 0.6%(3) Two years – 2.0% (11) Three years – 1.3% (7)
Notes	**Overall finding: Prevalence of peanut sensitisation was 0.4% in 2000-1 in 1 year old children on the Isle of Wight in the whole sample. In the sample of children with SPT at 1, 2 and 3 years the prevalence of sensitisation to peanut was 0.6% at one year, 2.0% at two years and 1.3% at three years.** Sensitisation rate at one year is very low. It was not possible to work out the incidence of peanut allergy from the paper. The most common food allergens in this age group were egg and milk. The % of children undergoing a SPT was high (72%) and included all children whether or not their parents reported symptoms								