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Does maternal diet during pregnancy and lactation affect outcomes in offspring? A systematic review of food-based approaches

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DOES MATERNAL DIET DURING PREGNANCY AND LACTATION AFFECT ALLERGY OUTCOMES IN THEIR OFFSPRING? A SYSTEMATIC REVIEW OF FOOD BASED APPROACHES.

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Abstract:

Objectives: To investigate the relationship between maternal diet during pregnancy and lactation and development of atopic disorders in childhood.

Methods: We included studies published up to August 2011 which either assessed food-based maternal dietary interventions or examined associations between maternal dietary intake during pregnancy and/or lactation and allergic outcomes (eczema, asthma, hay fever and sensitization) in their children.

Results: We included 43 studies (over 40 000 children): 11 intervention studies (including seven RCTs), 27 prospective cohort studies, four retrospective cohort studies and one case-control study. In the RCTs, no significant difference was noted overall in the prevalence of eczema and asthma in the offspring of women on diets free from common food allergens during pregnancy. The prospective cohorts investigated a large number of potential associations, but reported few significant associations between maternal dietary intake and development of allergy. Maternal diets rich in fruits and vegetables, fish and foods containing vitamin D and 'Mediterranean' dietary patterns were among the few consistent associations with lower risk of allergic disease in their children. Foods associated with higher risk included vegetable oils and margarine, nuts and fast food.

Conclusion: This review did not find widespread or consistent links between mother's dietary intake and atopic outcomes in their children. However, maternal consumption of 'Mediterranean' dietary patterns, diets rich in fruits and vegetables, fish and vitamin D containing foods were suggestive of benefit, requiring further evaluation.

Key words: diet, pregnancy, lactation, atopy, allergy, sensitization, eczema, asthma.

INTRODUCTION

The prevalence of allergic diseases in most industrialised countries has increased over the last 20 years and is now estimated to affect one in five individuals[1-3]. Common manifestations of allergic disease include allergic rhinitis or hay fever, asthma, eczema or atopic dermatitis, and food allergies. The risk of allergic disease is increased to about 1 in 3 if one first degree relative (parent or sibling) is atopic and to 70% if both parents are atopic [4]. The pattern of allergy expression differs with age, with the greatest incidence of food allergy and atopic eczema peaking by 1 year of age while asthma and allergic rhinitis continue to rise until around 15 years of age [5]. Many childhood allergies persist with about 50% of childhood asthma sufferers and 80% of hay fever sufferers continuing to have symptoms into adulthood [6, 7]. The cost to the health care system and the burden for the family are high [8, 9] and it is estimated that asthma alone costs Europe €25 billion per year [10].

The increase in allergic disease has occurred too rapidly (within one to two generations) to be a result of population genetic changes, so is likely to be related to environmental changes. Across the industrialised world, there is strong evidence that environmental factors accompanying higher socioeconomic conditions and hygiene standards have contributed to the increased prevalence of allergic disease. Societies with fewer respiratory infections, greater use of antibiotics early in life, fewer older siblings in the household, less contact with farm animals and general lack of early microbial exposure are repeatedly associated with the greatest burden of allergic disease [11]. The atopic predisposition is believed to arise where the infant has an innate tendency to produce IgE antibodies (sensitization), which in some individuals progresses to allergic disease. The allergens causing sensitization are nearly always proteins originating from the environment including pollens, house dust mite or food. Why children are becoming increasingly sensitized to environmental allergens is a matter of debate. Several factors may be involved, including whether the child is breastfed from birth [12], the anti-oxidant status of the individual [13], the balance of n-6 to n-3

polyunsaturated fatty acids (PUFA) in the diet [14] and environmental influences such as microbial exposure, cigarette smoke and other pollutants [15].

Since many infants develop allergic symptoms early in infancy, and exposure to allergens may be important in the development of food allergies, there is great interest in maternal dietary strategies during pregnancy and lactation that may prevent childhood allergies, and thus reduce the burden of disease. This systematic review evaluates the effect of food-based approaches in the maternal diet for the prevention of childhood allergies.

METHODS

INCLUSION CRITERIA

We included studies of any design which either compared a food-based maternal dietary intervention during pregnancy and/or lactation with another intervention or no intervention. We also included studies that examined associations between maternal dietary intake during pregnancy and/or lactation and allergic outcomes in their children from that pregnancy (cohort and case-control studies). Studies with co-interventions, such as timing of introduction of solid foods into the child's diet, use of hydrolysed formula and non-food based interventions such as dust mite control were eligible for inclusion.

We pre-specified primary outcomes as child eczema, asthma, hay fever and food allergy and secondary outcomes as allergy symptoms, atopy or atopic disorder, dyspnoea, hay fever (allergic rhinitis or allergic rhinoconjunctivitis), wheeze (and recurrent wheeze), cough, food hypersensitivity (IgE mediated food allergy or food intolerance) and sensitization (e.g. milk, egg, nut, food, inhalant).

We excluded studies assessing infantile colic, as this was not considered an allergic outcome.

As maternal intake needed to be food based, intervention studies designed to assess the effect of dietary supplements were not eligible for inclusion, nor were those where dietary intakes were expressed only in terms of nutrients.

We excluded studies which only investigated maternal nut (including peanut) consumption during pregnancy and/or lactation since nut allergy (particularly peanut) warrants a separate examination and assessment.

SEARCHING

We searched MEDLINE, EMBASE and the Cochrane Library (last searched end of August 2011) and scanned reference lists of systematic reviews and other relevant retrieved papers for additional studies.

Search terms included prenatal, antenatal, maternal, mother, pregnan*, lactat*, breastf*, intake, consumption, food, diet, wheez*, dermatitis, eczema, atop*, asthma, allerg*, food allergy hypersensitivity. The full search strategy is documented in Appendix 1.

STUDY SELECTION AND DATA EXTRACTION

Two authors independently assessed search results against study eligibility criteria. Two authors also independently conducted data extraction for each included study.

DATA SYNTHESIS

Where possible, the results of randomized controlled trials (RCTs) were pooled using the meta-analysis program RevMan [16]. We used risk ratios with 95% confidence intervals to express dichotomous outcomes. Where statistical heterogeneity was substantial ($I^2 > 40\%$) we used a random effects model. Differences between subgroups were assessed using interaction tests [17].

The results of non-randomized intervention studies were narratively reported.

The results from cohort and case-control were tabulated and narratively summarised. Where available, we reported the adjusted outcomes for these study designs. Results were presented by age of the children, with the youngest age first.

RISK OF BIAS

For RCTS, we assessed the risk of bias using the methods outlined in the Cochrane Handbook for Reviews of Interventions [17]. For other study designs we took account of the risk of selection bias, attrition bias and reporting bias.

RESULTS

This systematic review included 43 studies. See Table 1 – Characteristics of Included Studies. Twelve were intervention studies (seven RCTs, one participant preference trial and four non-randomized comparisons). These studies examined the effect of eliminating or restricting common allergens from the maternal diet during pregnancy and lactation. Some included co-interventions such as manipulation of the infant's diet, or environmental measures.

The remaining 32 studies were 27 prospective cohorts, four retrospective cohorts and one case-control study. These studies looked at the association of different dietary patterns or the frequency of consumption of different foods with atopic outcomes.

One intervention and seven other studies were excluded [18-25]. The intervention study reported the outcomes of an intervention based on a supplement rather than food; seven cohort studies reported dietary intakes in terms of nutrients rather than foods.

Results are reported by the major clinical outcomes (eczema, asthma and wheeze, hay fever, sensitization and food allergy) and study design (intervention or observational).

RISK OF BIAS ASSESSMENT SUMMARY

The risk of bias assessments are described in Table 1 (Association studies) and in Table 2 (Intervention studies). Overall the 11 intervention studies had at least moderate risk of bias. None of the RCTs fully described the methods they used to conceal allocations at the time of randomisation, only one study was able to devise a way to blind the intervention and most studies had moderate losses of participants.

The 32 association studies were of reasonable quality – 12 had low risk of bias; two were of low-moderate risk and 17 were of moderate risk of bias.

1. MATERNAL DIET AND ECZEMA IN CHILDREN

1.1 INTERVENTION STUDIES

Five randomized trials and two non-randomized comparisons assessed the effects of maternal dietary restriction on eczema in their children (Table 1). The five RCTs examined the effect of avoiding one of more common allergens in the maternal diet during pregnancy and lactation. Falth-Magnusson et al [27] randomized 212 women to a diet free of cow's milk and egg during pregnancy and lactation or a normal diet, and tracked the development of eczema, allergic rhinoconjunctivitis, asthma and food allergy in the offspring up to 5 years of age. Zeiger [34] restricted cow's milk, egg and peanut and limited intake of soy and wheat during pregnancy and lactation in the intervention group. Children were followed up until 7 years of age and reported any atopic disorder (asthma; food allergy; allergic rhinitis; eczema and aeroallergen sensitization). In the Isle of Wight Study [36], the 58 women in the intervention group followed a diet without cow's milk, egg, nut and fish during lactation. This study delayed introduction of allergenic foods in the offspring, and introduced house dust mite control. Lovegrove et al [39] randomized women to a diet without cow's milk during pregnancy and lactation, and Lilja et al [32] implemented a diet

with a strictly reduced cow's milk and egg intake during late pregnancy. Both trials followed the offspring until 18 months of age. Lovegrove et al reported the development of eczema, and Lilja et al reported cord blood IgE, eczema and asthma. In a non-randomized comparison, Hattevig et al [29, 30] compared the children of 65 women who adhered to a diet free of cow's milk, egg and fish while breastfeeding with 50 women who maintained a normal diet. Solid foods were delayed and the children were followed for eczema and food allergy until 10 years of age. Herman et al [41] enrolled 150 pregnant women into a patient preference trial of avoiding cow's milk and egg during pregnancy and lactation. They followed children until 1 year of age for eczema and sensitization.

In the five RCTs [27, 32, 34, 36, 39], there was no significant difference overall in the prevalence of childhood eczema (RR 0.76 95% CI 0.50 to 1.16, total of 682 children, random effects). These trials showed statistical (I^2 = 44%) and clinical heterogeneity with different dietary restrictions and eczema assessed at different ages. The only RCT showing a significant reduction in childhood eczema included house dust mite control as well as dietary restrictions [36]. Due to the heterogeneity, a pooled result for the five RCTs was not presented - see Figure 1.

Two non-randomized comparative studies also showed no evidence for an effect of dietary restriction. In one non-randomized preference trial, 30 women chose to completely avoid milk and eggs in the last trimester of pregnancy and while breastfeeding exclusively; 33 women also avoided all milk and eggs, but only while breastfeeding; and 41 women chose no dietary restrictions [41]. In this study, six children of mothers in each of the avoidance groups had eczema in the first year of life compared with 5 children in the group where mothers did not follow dietary restrictions.

In a non-randomized concurrent comparison, where mothers had a diet free from eggs, cow's milk or fish in the first three months of their baby's life, the infants were significantly less likely to develop eczema up to six months compared with those whose mothers had no dietary restriction. This effect was not sustained after six months of age or at follow-up when the children were 10 years old [29, 30].

1.2 OBSERVATIONAL STUDIES

Sixteen prospective cohort studies reported eczema in children as an outcome (Table 1). All used adjusted analyses, unless otherwise stated. A detailed summary of each study may be found in E-Table 1.

- **3 months to one year**

Four prospective cohort studies examined the relationship between maternal diet and eczema in children up to one year of age. Doctor-diagnosed eczema in 3-4 month old Japanese children was not associated with their mothers' intake of dairy products, eggs or fish during pregnancy. However, in this population, a significantly increased risk of eczema was noted with higher levels of meat consumption (> 64 grams per day) [71]. For children up to one year of age, daily consumption of about 30 g of fish by their mothers during pregnancy (Jedrychowski et al [72]) and increased consumption (daily vs less frequently) in Romieu et al [53] showed protective effects against eczema. However neither of these studies adjusted their results for potential confounders. In another unadjusted study [47], increased vitamin C concentration in atopic mothers' breast milk (attributed to dietary intake of vitamin C from fruit and vegetables during lactation) was associated with significantly reduced rates of eczema in their children.

In Jedrychowski et al [72], daily maternal fish consumption of about 30 g weakened the otherwise borderline deleterious association between high maternal exposure to pollutants (fine particulate matter measured by environmental air monitors worn by the women and exposure to environmental tobacco smoke) and infant eczema.

- **2 to < 3 years**

Six prospective cohort studies and one retrospective cohort study examined the relationship between maternal diet and eczema in children from two to less than three years of age. Four of the

six prospective studies included the same cohort of women and their children, with each study reporting on different maternal dietary exposures.

Two studies compared maternal dietary patterns (healthy, western, traditional or processed) [62, 75] and two compared consumption of total and individual dairy products [54, 68] with childhood eczema at two to three years of age, and found no significant association. This was also the case for maternal intake of fruit and vegetables in both studies, except that green and yellow vegetables and citrus fruit showed protective associations against eczema in Miyake et al [69]. Spinach, celery, cabbage, salad and citrus fruits did not show significant associations in Sausenthaler et al [54]. Sausenthaler et al also looked for associations between childhood eczema and foods rich in fats, finding high maternal consumption of margarine and vegetable oils significantly associated with an increased risk of eczema, but there were no significant associations with eggs, butter, seeds, deep-frying vegetable fat and nuts.

High maternal fish intake (once or twice a week during pregnancy) was associated with significantly lower rates of children's eczema in one study [54]. Another retrospective study with unadjusted analyses [67] failed to find an association between maternal consumption of fish at least once a week during pregnancy and childhood eczema, as did Miyake et al [61], where mothers in the highest quartile consumed over 70 g of fish a day.

Miyake et al [61] also failed to find an association between maternal meat intake during pregnancy and childhood eczema.

- **3 years**

Lange et al [66] compared four maternal dietary patterns during pregnancy – a Mediterranean diet, a 'Healthy' diet, a 'Prudent' diet and a Western dietary pattern. None of these dietary patterns consumed by mothers while pregnant showed significant associations with development of eczema in their children at three years of age.

- **5 years**

At least one serve a fish a week by mothers during pregnancy was protective for eczema in their children at five years of age in one study, while none of the other foods tested (including fruit and vegetables, grains and fats) showed any consistent associations [58]. One study [60] also found no association between vitamin D from food consumed during pregnancy and development of eczema in children at five years of age.

Grandjean et al [65] measured children's polychlorinated biphenyl (PCB) and mercury levels as a marker of maternal dietary intake of fish likely to be contaminated with marine pollutants, and compared the incidence of atopic eczema in the offspring. At 5 years of age the children with atopic eczema had lower prenatal PCB levels, indicating lower maternal fish intake, compared with those children without eczema.

- **7 years**

Shaheen 2009 [62] found no significant associations between childhood eczema at seven years of age and maternal dietary patterns during pregnancy.

Grandjean et al [65] reported lower prenatal PCB levels in children with atopic eczema than those without eczema, at 7 years of age, as they also reported at 5 years of age.

1.3 INTERVENTION STUDIES RELATED TO MANAGEMENT OF CHILDHOOD ECZEMA

Three papers [43-45] considered manipulating the maternal diet to manage existing eczema in breast-fed children, as opposed to the effects of the maternal diet on preventing eczema.

In a cross-over RCT, Cant et al [43] studied the effect of maternal exclusion of cow's milk, egg, chocolate, wheat, nuts, fish, beef, chicken, citrus fruits, artificial food colourings and preservatives during lactation compared with periods of inclusion of cow's milk and eggs on eczema scores in

children with eczema aged 6 weeks to 6 months. At each time point, there were no significant differences in eczema scores.

Palmer et al [44] studied eczema and sensitization to egg (on skin prick testing) in 32 exclusively breast-fed babies. All mothers had an egg free diet, followed by a randomised double blind crossover challenge with egg. There was an improvement in the eczema score (SCORAD) with time for both the intervention and control groups, but no statistical difference between the groups related to the egg challenge.

Uenishi et al [45] described the effect of a non-randomized elimination diet and rechallenge with 92 exclusively breast-fed children with eczema. Maternal exclusion of chocolate, coffee and fermented foods (cheese, yoghurt, soy sauce, miso soup and fermented soy beans) for eight weeks during lactation was associated with improved eczema scores in their babies in 67/92 cases. Reintroduction of the foods, predominantly chocolate, yoghurt, soy sauce and miso soup, into the maternal diet was associated with deterioration in the eczema score.

2. MATERNAL DIET AND ASTHMA OR WHEEZE IN CHILDREN

2.1 INTERVENTION STUDIES

Four RCTs assessed the effects of maternal dietary restriction on asthma in children (Falth Magnusson et al [27], Zeiger et al [34], Arshad et al [36] and Lilja [32] (Table 1). As described in section 1.1, one intervention required avoiding cow's milk and egg during pregnancy [32]and two trials continued this restriction while the mother was breast feeding [27, 34]. Zeiger et al also restricted peanut and limited soy and wheat intake during pregnancy and lactation. Arshad et al [36] started their intervention post-partum, and in addition to avoiding cow's milk, egg, nuts and fish, also included household dust mite control measures. Pooling of the four RCTs found no

significant differences between maternal restricted and unrestricted diets (RR 0.95 95% CI 0.70 to 1.30; 619 children) on development of asthma in children. See Fig 2.

No RCTs reported wheeze as an outcome.

2.2 OBSERVATIONAL STUDIES

Eighteen prospective cohort studies reported wheeze or asthma in children as an outcome. All used adjusted analyses, unless otherwise stated. Detailed reports of the study results are available in E-Table 2.

- **Up to 2 years**

A retrospective study with unadjusted analyses [67] failed to find an association between maternal consumption of fish at least once a week during pregnancy and childhood asthma.

Castro-Rodriguez et al [64] reported that antenatal use of olive oil was significantly inversely associated with wheezing in the first year of a child's life.

Miyake et al [75] found an inverse relationship between a maternal 'western' dietary pattern and childhood wheeze at 16-24 months which was no longer apparent when adjusted for maternal α-linolenic acid and vitamin E intake during pregnancy. Neither of the other two dietary patterns in this study ('healthy' and 'Japanese') showed any significant associations with childhood wheeze at 16-24 months.

Miyake and co-workers also measured mercury content of maternal hair samples as an indirect estimate of fish intake during pregnancy and found no significant difference between lower and higher mercury content and childhood wheeze at 29-33 months [74].

- **3 years**

In a retrospective cohort [52], no significant associations were seen between asthma in three-year children and an extensive range of fruits and vegetables eaten by their mothers during pregnancy.

Lange et al [66] failed to find any significant associations between the dietary pattern consumed by their mothers during pregnancy (Mediterranean, Alternate Healthy Eating Index modified for pregnancy (AHEI-P), western or prudent pattern) and the development of asthma in three-year old children. However this study found fewer cases of recurrent wheeze in 3 year old children of women who had a higher Mediterranean diet score compared with those with lower scores. No significant difference in numbers of children with recurrent wheeze at three years was observed between the highest and the lowest AHEI-P quartile.

In a UK cohort study [62], wheeze in children at 3.5 years (and at six months) was not generally associated with various dietary patterns such as 'health conscious', 'traditional', 'processed', 'vegetarian' or 'confectionery'.

Carmago et al [50] reported that a moderate to high intake of vitamin D fortified cow's milk during pregnancy was associated with a lower incidence of wheeze.

- **5 years**

Lumia et al [73] noted no significant associations between consumption of milk and milk products, oils, margarines, butter, other fats, fish and meat consumed by mothers during pregnancy and occurrence of asthma in their five-year old children.

Willers et al [58] found no consistent associations between mothers' intake of total fruit, citrus, kiwi fruit, total vegetables, green leafy vegetables, fruit juice, whole grain products, fat from dairy products or butter versus margarine/low fat spread use during pregnancy and the incidence of asthma in their 5 year old children. However this study reported that high maternal consumption of apples (more than four a week) appeared to have a protective effect for asthma in children, when

assessed as doctor-diagnosed asthma or 'ever had' asthma (but not if assessed as asthma and wheeze in the last 12 months).

In a nested case-control study [48], high maternal intake of oily fish during pregnancy was found to be protective against early persistent asthma in five year old children, but results for any asthma, early transient asthma or late-onset asthma were not significant. The protective association of oily fish consumption seemed to be more effective when mothers themselves already had asthma, compared with those without asthma. In contrast, this study found maternal consumption (at least monthly during pregnancy) of fish fingers (which contained trans fats) was significantly associated with an increased risk of any asthma in the children.

- **At 6 to 8 years of age**

Shaheen et al [62] found no significant associations between mothers' dietary patterns while pregnant and development of asthma in their children at 7.5 years of age. The retrospective study of De Batlle et al [57] also failed to show differences for wheeze in the children.

Chatzi et al [56] found no difference between the cereal content of mothers' diets and persistent or atopic wheeze in their 6.5 year old children.

Willers et al [58] looked at maternal diet during pregnancy and reported no significant associations between the frequency of consumption of many foods (vegetables, fish, nuts, egg, milk or milk products) and any wheeze from 1 to 8 years of age in the children. Only daily, versus rare, maternal consumption of nut products such as peanut butter was associated with an increased risk of wheeze in the children.

Grandjean et al [65] reported that children with asthma at 7 years of age had slightly higher PCB exposures than non-allergic children, although this could be attributed to chance. There was no association with mercury levels.

3. MATERNAL DIET AND HAY FEVER OR RHINITIS IN CHILDREN

3.1 INTERVENTION STUDIES

Two studies examined maternal elimination of allergens from the diet and included allergic rhinitis or hay fever as outcomes.

Zeiger et al [34, 35] report the results of maternal avoidance of cow's milk, egg and peanut during the last trimester of pregnancy and breast feeding, with delayed and staged introduction of solid foods, compared with 'standard dietary advice' during pregnancy and solids introduced from 4-6 months of age. There were no significant differences in the rates of allergic rhinitis between dietary avoidance and control groups at 4, 12 and 24 months of age and this was maintained at follow-up at 4 and 7 years of age.

Likewise, Falth-Magnusson et al [28] reported the 5 year follow up of a cohort of 212 children in which 104 mothers (randomized) eliminated cow's milk and egg from their diet from 28 weeks gestation to birth (and partially during early lactation) versus 108 (randomized) to follow their usual diet (typically 0.5 L milk/day and 3-5 eggs/week). The elimination group had extra calcium and casein hydrolysate provided. The incidence of allergic rhinitis did not differ between groups.

No meta-analysis was performed as the studies were unsuitable for pooling.

3.2 OBSERVATIONAL STUDIES

Four cohort studies examined dietary associations that included allergic rhinitis in their outcomes. All studies were prospective cohorts with adjusted analyses, unless otherwise stated.

3.2.1 Dietary associations – diet types

De Batlle et al [57] compared Mediterranean diet scores for mothers during pregnancy and reported more sneezing at 6-7 years of age in offspring of mothers with lower Mediterranean diet scores.

Shaheen et al [62] also assessed the intake of processed foods (meat pies, sausages, burgers, fried foods, pizza, chips, crisps, white bread, eggs, baked beans) in the maternal diet during pregnancy and described more hay fever at 7.5 years of age in children whose mothers had a more highly processed diet, although the difference was lost when the results were adjusted for confounding factors.

3.2.2 Dietary associations – multiple food groups or multiple individual foods

- **At 5 to 7 years**

Erkkola et al (DIPP Study, Finland)[60] compared vitamin D from food in the maternal diet during the eighth month of pregnancy. The lowest quartiles of maternal intake of vitamin D were positively associated with allergic rhinitis in the child at 5 years of age. This association remained significant after adjustment for confounding variables. These results were also corrected for vitamin D supplementation.

In a study of pregnant Scottish women, Willers et al [58] reported that the mothers who consumed oily fish more than once a week during the second trimester of pregnancy (N=161 (0.37 (0.14 to 0.98)) were less likely to have children with hay fever at five years of age. No association was found between maternal cereal intake and hay fever.

4. MATERNAL DIET AND SENSITIZATION IN CHILDREN

4.1 INTERVENTION STUDIES

The results of three RCTs investigating maternal dietary restriction and sensitization in the offspring are shown in Figure 3. Differing interventions and timings outcome assessment precluded pooling,

although each of the multiple restriction studies showed lower sensitization rates for the intervention compared with controls [34-36] – see Fig 3. Falth-Magnusson et al [26] randomly allocated women to a normal diet (n=108) or one without cow's milk and egg (n=104) from 28 weeks gestation to birth and early lactation. No significant difference in sensitization was noted in the offspring up to 5 years of age, although the women on the milk and egg-free diet gained significantly less weight during their pregnancy compared with the normal diet group. In 58 women with a family history of atopy Arshad et al [36] used a restricted diet during lactation, delayed introduction of allergenic solid foods (cow's milk, soy, egg, wheat, nut and fish) and controlled dust mite. At eight years of age, 37 (59.7%) children had been sensitized to one or more allergens at any time in the control group compared with 14 (25.2%) in the prophylactic group (RR 0.40 95% CI 0.25 to 0.67) [38]. Zeiger [34, 35] reported a significantly reduced rate of definite or probable food allergy in children whose mothers were in the restricted diet group compared with those from the unrestricted group (RR 0.37 95% CI 0.17 to 0.80) at 2 years, but not at 4 or 8 year follow up.

Three other intervention studies also reported the effects of maternal dietary restriction on sensitization [29, 41, 42, 57]. In one [42], no time point showed significant differences between groups for sensitization to any type of food, except for a significantly higher rate of sensitization to egg at two years of age in the intervention group compared to the control group (RR 1.91 95% CI 1.03 to 3.53).The other studies [29, 41] reported no significant difference in the rates of sensitization between their intervention groups and control groups at any of the time points measured.

The timing of the maternal dietary intervention varied, with Appelt, Zeiger and Herman intervening in the last trimester of pregnancy and continuing this into lactation. Herman and Hattevig only changed the maternal diet during breast feeding. The type and extent of maternal dietary modifications also varied (see e-table 5 for the details).

If the babies were not breast fed, five studies [26, 29, 34, 41, 42] used partly or extensively hydrolysed formula rather than standard infant formula. The timing of introduction to solid foods and the types of solid foods that were offered also varied. In Zeiger et al and Hattevig et al's studies, solid foods were not offered until 6 months of age, and introduction of allergenic solid foods was delayed in Zeiger et al's group.

4.2 OBSERVATIONAL STUDIES

Eight cohort studies reported the relationship between maternal food intake and sensitization to foods or aeroallergens in children as an outcome. All studies were prospective cohorts with adjusted analyses, unless otherwise stated.

Dietary associations – diet types, multiple food groups or multiple individual foods

No studies assessed the relationship between maternal dietary types or patterns and sensitization or allergy outcomes in children younger than 5 years of age.

- **At 5 to 7 years**

Two studies compared the type of maternal diet or patterns and sensitization or development of allergy in the offspring at 5 to 7 years.

Chatzi et al [56] reported that a lower Mediterranean dietary score in pregnant women was associated with more atopy at 6.5 years of age (defined as sensitization or positive skin prick testing to aeroallergens). Chatzi et al scored the diet of 482 pregnant women by assigning positive scores to beneficial components (vegetables, legumes, fruits, nuts, cereal, fish and dairy products) if maternal intake was above the median; a detrimental component (meat) was scored positively if intake was below the median. This association remained significant after the child's own diet was

adjusted for adherence to a Mediterranean dietary pattern. No sub analysis was reported for the mother's atopic status although adjustment was made for it.

However, different results were reported by Shaheen et al [62] in the UK ALSPAC study which compared dietary patterns during pregnancy and two measures of atopy at 7 years of age – log total serum IgE and positive skin prick testing to dust mite, cat and grass. No association was found between the maternal dietary pattern and childhood atopy, but the health conscious and vegetarian dietary patterns were associated with increased total serum IgE compared with a traditional dietary pattern**.**

Dietary associations – individual foods

- **At 1 year**

Judging by occurrence of atopic eczema and positive skin prick testing, Hoppu [47] described a decreased risk of atopy at 1 year of age, with increasing vitamin C in breast milk – which reflected maternal intake of fruits and vegetables.

In the Isle of Wight, Venter [63], reported frequency of maternal intake of common allergens during pregnancy and lactation and food hypersensitivity in the offspring at 1 and 3 years of age. However the numbers were too small to detect any differences.

Erkkola [60] compared a low and high intake of cow's milk and dairy foods during pregnancy and lactation. However the data from this study could not be used for this review as it reported IgA levels and had no clinical data relating to sensitization in the offspring.

- **At 2 years**

The German LISA birth cohort looked at diet during pregnancy and allergic sensitization in 2641 children - defined as specific serum IgE ≥ 0.34kU/L to egg, cow's milk, wheat, peanut, soy, codfish, house dust, cat dander, mixed mould, seasonal pollen allergens [54]. Several associations were found, but it should be noted that the confidence intervals are wide. Increasing maternal intake of

celery (1.61 (1.07 to 2.41) p<0.05), raw sweet pepper (1.45 (1.03 to 2.06) p<0.05) and citrus fruit (1.82 (1.29 to 2.56) p<0.05) were associated with increased childhood sensitization to any allergen. Increased maternal intake of deep frying vegetable fat (OR 1.61 (1.02 to 2.54), p<0.05) and citrus (1.72 (1.02 to 2.92) p<0.05) were also associated with increased sensitization to aero allergens. Intake of celery and citrus were associated with increased sensitization to food allergens (1.85 (1.18 to 2.89) p<0.05) and 1.73 (1.18 to 2.53) p<0.05) respectively).

- **At 4 years**

Romieu et al [53] found no association with maternal fish intake during pregnancy and specific IgE levels or sensitization to house dust mite in the offspring at 4 years of age.

- **At 5 years**

Several studies have reported atopy and sensitization in children at 5 years of age.

Nwaru et al [70] reported more sensitization to inhalant allergens in offspring of mothers who had consumed greater fruit and vegetable intake, particularly citrus fruit during pregnancy and the first three months of lactation. This remained significant after adjustment. No association was found with food allergen sensitization.

As part of the DIPP Nutrition Study in Finland, Nwaru et al [76] also assessed the associations between maternal intake during lactation in 652 mothers and atopy in the child (measured as serum IgE sensitization to birch, cat, timothy grass, cow's milk, egg and wheat). After adjustment, none of the dietary variables was significantly associated with sensitization to milk, egg or timothy grass allergens.

With foods, maternal consumption of butter and butter spreads was associated with increased risk, while margarine and low-fat spreads were associated with decreased risk of sensitization for wheat allergen in the children. Maternal consumption of potatoes, milks, margarine and low-fat spreads

was associated with a decreased risk of sensitization to birch. For sensitization to cat allergen, the risk was decreased by maternal consumption of potatoes and increased by consumption of eggs.

In models in which all significant uncorrelated dietary variables were studied together (foods studied separately from the nutrients), butters (increased risk), margarine (decreased risk), total and n-3 PUFAs and saturated fatty acids (increased risk) were the most strongly related to wheat allergen. Potatoes (decreased risk), eggs and vitamin C (both increased risk) remained the most significantly related to cat allergen, while potatoes, milks and margarine and low fat spreads (all decreased risk) were the most strongly related to birch allergic sensitization. Further adjustment for number of siblings at the time of child's birth, maternal age, maternal education and pets in the house by 1 year of child's age did not change any of these results.

Calvani et al [49] investigated associations between the type of fat in the maternal diet during pregnancy and allergic sensitization in five year old children born to allergic and non-allergic mothers. They reported less sensitization to common food allergens at 5 years of age with more frequent intake of fish during pregnancy in non-atopic mothers but not in the offspring of atopic mothers. Calvani et al also reported less sensitization to inhalant allergens in 5 year olds born to atopic mothers who consumed butter once a week (0.27 (0.10 to 0.73)), however this association not maintained for more frequent intakes (1.59 (0.51 to 4.79)). In non-atopic mothers, intake of butter once a week, but not for greater intakes, was associated with more inhalant sensitization in the offspring ((1.73(1.00 to 2.99) and 0.81(0.38 to 1.70)).

- **At 6 and 7 years**

Chatzi et al [56] studied the diet during pregnancy in 482 atopic and non-atopic mothers in the Spanish island of Menorca. Skin prick testing indicated that 70 of the offspring were sensitized to aeroallergens. A low intake of vegetables (≤ 8 compared with > 8 serves a week) was associated with a greater rate of sensitization to aeroallergens.

SUMMARY OF RESULTS

Eleven intervention studies were included in this review. The RCTs noted no significant difference overall in the prevalence of eczema and asthma in the offspring of women whose diets were free of common food allergens during pregnancy and lactation. One study [36], which had multiple interventions, including restriction of allergens in the maternal diet during lactation, delayed introduction of allergens into the child's diet, and dust mite control reported a lower rate of sensitization in the intervention group at all ages followed up. All of the RCTs testing the relationship between maternal diet and atopy outcomes were judged to be of moderate to high risk of bias, as well as low numbers of participants affecting their statistical power.

A summary of the results from the cohort studies examining the effect of maternal diet during pregnancy and lactation and atopic outcomes in their offspring is presented in Table 3. The results from 27 prospective cohort studies, four retrospective cohort studies and one case-control study were included, involving approximately 40 000 children.

Compared to the RCTs, the prospective cohort studies looked at significantly more investigations into relationships between foods and atopic outcomes. Most studies showed no association between maternal food intake and allergy outcomes in their offspring. Maternal dietary patterns associated with less risk of allergic disease in offspring included 'Mediterranean' dietary patterns, diets rich in fruits and vegetables, fish and vitamin D containing foods. Food patterns associated with higher risk of atopy included vegetable oils and margarine, nuts and fast food.

DISCUSSION

The lack of widespread and consistent influences of maternal diet on children's allergies is perhaps not surprising. Although the development of a predisposition towards allergy may be programmed early in fetal life, possibly in the first or second trimester [78], influences early in the neonatal period such as the mode of birth, feeding type, early infections, introduction to solid foods and

exposure to allergens also influence the developing immune system. Parental atopy, epigenetic factors, gut microbiota, dietary and other environmental influences (such as pollution, tobacco smoke, alcohol consumption) all have potential to affect this programming. There is interplay between allergen exposure and other dietary components that may have the potential to influence the tendency towards atopy. This systematic review considered foods in a holistic manner rather than individual nutrients alone, aligning with messages from dietary guidelines to emphasise whole foods and dietary patterns. However, it is also useful to reflect how food based dietary patterns relate to the investigations of individual nutrients and findings regarding allergy outcomes, in particular related to long chain polyunsaturated fatty acids, antioxidants, vitamin D and allergen avoidance.

1. Balance of n-3 and n-6 Long Chain Polyunsaturated Fatty Acids

The types and amounts of long chain polyunsaturated fatty acids present in the diet have known immunomodulatory effects [79]. Diets high in n-6 fatty acids such as vegetable oils rich in linoleic acid (18:2n-6) can enhance the synthesis of T helper cell type 2 cytokines promoting atopic responses [80]. On the other hand, diets rich in n-3 polyunsaturated fatty acids may alter the T helper cell balance, inhibiting T helper cell type 2 differentiation, thus moving away from development of allergy [81].

In this review, several cohort studies captured responses that may have reflected effects of differing fatty acid profiles in the diet. These included studies considering margarine and vegetable oil intake, fish intake and studies focussing on dietary patterns (see table 3). Four of the 10 studies investigating links between maternal fish intake (high n-3) and eczema showed a decreased risk of associated childhood eczema; and a decreased risk of childhood asthma was seen in one out of six studies. Two of the dietary profiles associated with increased total serum IgE at 7 years of age in the study by Shaheen et al [62] (health conscious dietary and vegetarian diet patterns) were likely

to be rich in n-6 fatty acids, particularly linoleic acid, although the diets are not described to this level of detail in the studies**.**

A number of clinical trials of fish oil intervention during pregnancy have reported modulation of the neonatal immune response towards a less allergenic phenotype and lower rates of eczema and sensitization in the first year of life [80, 82-84]. The similarity between the cohort studies and the individual nutrient RCTs highlights the possibility that alterations in fatty acids in the food supply may be an important factor in reducing the rates of allergic disease.

2. Antioxidants

Foods (particularly fruits and vegetables) contain many antioxidants, including, but not limited to, vitamins C, A and E, zinc and selenium. Two opposing theories relate to antioxidant intake and the potential for development of atopy. The first is that dietary antioxidants are protective against oxidant damage and inflammation of airways. Decreased dietary antioxidants have been suggested as one cause of the increased prevalence of atopy in the Western world [69, 85]. The opposing theory suggests that increased or excessive antioxidant intake suppresses T helper cell type 1 differentiation and because of immune regulatory mechanisms, promotes the development of a T helper cell type 2 profile (towards atopy)[85].

Several cohort studies focussing on the mother's intake of foods rich in antioxidants showed protective effects against development of eczema and sensitization in their children. However, some cohort studies reported an increased risk of sensitization and others reported null findings (see table 3). None of the cohort studies found any association with maternal intake of breads and cereals (as sources of zinc) and subsequent intake of childhood atopy.

The associations between immune development and maternal fruit and vegetable intake may be partly related to their antioxidant content, although we were unable to find any RCTs using antioxidant vitamin supplements during pregnancy and lactation specifically reporting atopic

outcomes in the offspring. Note, however that as well as vitamins and minerals with antioxidant potential, fruits and vegetables also contain a range of phytonutrients with the potential to interact with the immune system [86].

3. Vitamin D

Vitamin D is a hormone with multiple biological roles, including immunoregulation. There is increasing interest in the link between low vitamin D status as a risk factor for the development of atopy, including food allergy [87]. Vitamin D status is derived from exposure to sunlight, natural food sources, vitamin D fortified foods and dietary supplements. This review includes two studies assessing vitamin D from foods [51, 60]. Some studies also showed associations between intake of cow's milk and reduced atopy. As some countries fortify cow's milk with vitamin D such associations may indirectly reflect vitamin D intake.

One RCT evaluating the effect of vitamin D supplementation in 180 women during late pregnancy reported no difference between offspring in the supplemented or unsupplemented groups for wheeze, allergic disease, lung function or allergic inflammation in the first three years [88]. The outcomes of other vitamin D supplementation intervention trials that are in progress will provide information for future evidence-based dietary guidelines related to vitamin D in the diet and development of atopy.

4. Allergens in the Maternal Diet

Several small RCTs tested the effect of maternal avoidance of common dietary allergens during pregnancy and lactation in families with a history of atopic disease and the subsequent development of atopy in their offspring. No RCTs found any difference in asthma, hay fever and rhinitis in offspring of women who followed restricted diets. Pooling of these RCTs found no difference in asthma and eczema in offspring of women who followed restricted diets. The only RCT to show any difference in maternal restriction of food allergens and the development of

eczema in the offspring also reduced exposure to house dust mite [36]. Arshad et al also showed a difference in overall rates of sensitization in the offspring of the allergy avoidance group in their first eight years. Zeiger et al [34] reported a significantly reduced rate of food allergy at two years of age, but not at other ages studied.

Some of the cohort studies compared high and low maternal intakes of common allergens and atopic outcomes in their children. For example comparing high versus low intakes of common allergens and atopic outcomes (eczema and sensitization to food or aeroallergens) in children at one and two years of age, Sausenthaler et al [54] noted no difference between groups for cow's milk, eggs and nuts but did find less eczema in the children at one year of age whose mothers had a high intake of fish. The sensitization rates reported for these groups showed no differences. Romieu et al [53] described a similar finding with maternal fish intake and eczema in children. Other association studies investigating intake of common allergens failed to show any relationship [71]. Overall, there were no clear patterns, but emerging trends suggest that higher intakes of fish [53, 54] and nuts [58] during pregnancy may reduce allergy risk in some populations.

Differences in outcomes between allergy avoidance intervention studies and observational studies may be related to differing study designs (as well as selected population groups vs general population studies, and co-interventions), and low numbers leading to lack of statistical power. More work is needed to strengthen recommendations regarding the inclusion of common allergens in the maternal diet during pregnancy and lactation as this continues to cause confusion for health professionals and families. Feeding guidelines for prevention of food allergy have moved to an emphasis on promotion of induction of tolerance by inclusion of allergens early into the child's diet rather than avoidance of allergens [89, 90]. Inclusion rather than exclusion of allergens in the maternal diet may also play a role in early immune programming.

Maternal Diet During Lactation as a Treatment for Allergies Presenting in Breast Fed Babies

Four trials investigating the use of maternal diet during lactation to manage known food allergy in the breast-fed infant were also captured in this review. Although this is a separate issue to the aetiology of allergy, allergens have been isolated in breast milk and maternal diet adjustment is commonly used to manage food allergies in a breast-fed infant. The studies reviewed tested breastfeeding infants with atopic eczema for sensitization to allergens, which were then removed from the maternal diet. Maternal dietary restriction of known allergens during lactation was associated with reduction in the infant's eczema scores. Our search did not locate any trials that evaluated maternal dietary restriction for non-IgE mediated allergies in infancy, or for colitis, although this is common practice and an area requiring more research.

Limitations of this Review

This is a difficult area to synthesise and so with data from many different sources, there were several limitations. In addition the 'atopic march' means that children develop different symptoms as they grow older (eczema and food allergies when young, and then asthma and hay fever as they age). For the cohort studies, the methodology used to gather data on maternal dietary intake varied. Many studies relied on retrospective dietary recall questionnaires which are less accurate than dietary data collected prospectively. The studies were heterogeneous in terms of the atopic potential of the participants. The atopic history of the parents was often not stated, or was adjusted out in the final analysis, making comparisons difficult and possibly masking associations specific to those who have an atopic tendency.

Many studies were subsets of larger cohort studies where atopy was not always a primary consideration (for example the DIPP study investigating diabetes). Most of the cohort studies followed children from the same country and differences in local eating patterns may restrict the generalizability of the outcome data, for example one Japanese study compared low vs higher dairy food intake, but their highest quartile only consumed 280g of dairy product per day [68]. The

scoring systems used to rate 'Mediterranean dietary patterns' varied [57, 66] making direct comparisons difficult.

The primary allergic outcomes in the offspring were not standardised in terms of diagnostic criteria and age at follow-up or diagnosis. Some studies reported medically-diagnosed outcomes using standardised criteria, often the ISAAC criteria [2], thus enabling more accurate comparisons between studies. Others reported results of parental questionnaires as the primary outcomes. Many of the cohort studies did not follow children beyond 12 months of age. As the natural progression of atopic disease is that different manifestations are expressed at different ages – eczema, food hypersensitivity, asthma and then hay fever, studies should plan and fund for long-term follow-up, even though it is expensive and participant dropout rates can be high. When sensitization was used as an outcome, the methods of diagnosis varied, with studies reporting outcomes of serum specific IgE measures or skin prick test results to common allergens. Where sensitization to food allergens is reported as an outcome, it is difficult to draw clear conclusions, as positive tests may not be accompanied by allergic signs when the food is ingested. The gold standard for diagnosis of food hypersensitivity is the clinical outcome on oral challenge to the food. For large studies, this is difficult and costly.

Areas for Future Research

The results of this systematic review support current policy documents recommending that no specific restrictions in the maternal diet during pregnancy are indicated to prevent the development of atopic disorders in the newborn at this time [89-91].

The influence of maternal diet on childhood allergy continues to be a question addressed by researchers, particularly in the form of large cohort studies such as the Danish National Birth Cohort. We have judged that results from relevant studies published after our search cut-off date would not have substantially changed our findings and conclusions. However some notable

examples are possible attenuation of a link between high maternal fish consumption and reduced eczema risk [92]; alongside a potentially stronger association between high fish intake and decreased risk of asthma [93]. Two subsequent studies have reported links between maternal shellfish intake and increased risk of eczema [92], and also food allergy in children [94]. Associations with maternal intake of dairy products remain unclear, exemplified by one study which reported both risks and protective effects on asthma [95]. A new finding of a link between maternal consumption of artificially sweetened (but not sugar sweetened) soft drink and increased risk of asthma was reported by Maslova et al [96].

A well-balanced diet rich in fruits and vegetables, fish and with vitamin D containing foods may be beneficial and should be investigated in further studies. Nutrient interactions with the immune system are complex, multifactorial and may be related to genetic susceptibility, interactions with gut microbiota and other dietary and environmental factors. As a single simple answer or solution is unlikely, a combination of study designs investigating individual nutrients, foods and dietary patterns may be most useful in understanding the effect of maternal diet on allergy outcomes in the offspring. The links beginning to appear between maternal fish consumption and n-3 long chain polyunsaturated fatty acids deserve further investigation in populations at high and normal risk of allergic disease.

The regular inclusion of fresh fruits and vegetables and dietary sources of vitamin D in the maternal diet also warrant further investigation. As food composition varies, data about a combination of foods, nutrients and dietary patterns may provide the most useful information.

In addition, any further studies should report parental atopic status, particularly the existence of maternal allergy, as well as relevant environmental variables.

Conclusion

The development of atopic disease is complex and multifactorial, depending on genetic potential along with many environmental influences. This review found no consistent link between maternal dietary intake and atopic outcomes in their offspring despite considering 11 RCTs and 32 cohort studies including over 40 000 children. Dietary patterns more likely to be associated with less risk of allergic disease include 'Mediterranean' dietary patterns, diets rich in fruits and vegetables, fish and vitamin D containing foods. Food patterns associated with higher risk of atopy included vegetables oils and margarine, nuts and fast food. These findings require further evaluation.

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Conflict of Interest

MN serves on a scientific advisory board for Nutricia. MM serves on scientific advisory boards for Nestle, Fonterra and Nutricia. Associated honoraria are paid to the institution to support conference travel and continuing education for post-graduate students and early career researchers. No other disclosures were reported.

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Legends to figures

Figure 1: Forest plot representing the meta-analysis of randomized controlled trials assessing the effect of maternal dietary restriction on childhood eczema.

Figure 2: Forest plot representing the meta-analysis of randomized controlled trials assessing the effect of maternal dietary restriction on childhood asthma.

Figure 3: Forest plot representing the meta-analysis of randomized controlled trials assessing the effect of maternal dietary restriction on childhood sensitization.

APPENDIX 1

ALLERGY SEARCH STRATEGIES

MEDLINE (and as adapted for EMBASE) - From inception to end of August 2011

1. prenatal or antenatal or lactat* or breastf* or maternal or mother or pregnan*
2. intake or consumption or food or diet or wheez* or dermatitis or eczema or atop* or asthma or allerg* or food allergy sensitivity or IgE
3. 1 and 2

COCHRANE LIBRARY (last searched August 2011)

(prenatal) or (antenatal)

(lactat*) or (breastf*) or (maternal) or (mother) or (pregnan*)

(wheez*) or (dermatitis) or (eczema) or (atop*) or (asthma)

(allerg*)

(#1 OR #2)

(#3 OR #4)

(#5 AND #6)