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Maternal prenatal and/or postnatal n-3 long chain polyunsaturated fatty acids (LCPUFA) supplementation for preventing allergies in early childhood (Review)

Gunaratne AW, Makrides M, Collins CT

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Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD010085.

DOI: [10.1002/14651858.CD010085.pub2](https://doi.org/10.1002/14651858.CD010085.pub2).

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[Intervention Review]

Maternal prenatal and/or postnatal n-3 long chain polyunsaturated fatty acids (LCPUFA) supplementation for preventing allergies in early childhood

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Editorial group: Cochrane Pregnancy and Childbirth Group.

Publication status and date: New, published in Issue 7, 2015.

Citation: Gunaratne AW, Makrides M, Collins CT. Maternal prenatal and/or postnatal n-3 long chain polyunsaturated fatty acids (LCPUFA) supplementation for preventing allergies in early childhood. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No.: CD010085. DOI: [10.1002/14651858.CD010085.pub2](https://doi.org/10.1002/14651858.CD010085.pub2).

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ABSTRACT

Background

Allergies have become more prevalent globally over the last 20 years. Dietary consumption of n-3 (or omega 3) long chain polyunsaturated fatty acids (LCPUFA) has declined over the same period of time. This, together with the known role of n-3 LCPUFA in inhibiting inflammation, has resulted in speculation that n-3 LCPUFA may prevent allergy development. Dietary n-3 fatty acids supplements may change the developing immune system of the newborn before allergic responses are established, particularly for those with a genetic predisposition to the production of the immunoglobulin E (IgE) antibody. Individuals with IgE-mediated allergies have both the signs and symptoms of the allergic disease and a positive skin prick test (SPT) to the allergen.

Objectives

To assess the effect of n-3 LCPUFA supplementation in pregnant and/or breastfeeding women on allergy outcomes (food allergy, atopic dermatitis (eczema), allergic rhinitis (hay fever) and asthma/wheeze) in their children.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (6 August 2014), PubMed (1966 to 01 August 2014), CINAHL via EBSCOhost (1984 to 01 August 2014), Scopus (1995 to 01 August 2014), Web of Knowledge (1864 to 01 August 2014) and ClinicalTrials.gov (01 August 2014) and reference lists of retrieved studies.

Selection criteria

We included randomised controlled trials (RCTs) evaluating the effect of n-3 LCPUFA supplementation of pregnant and/or lactating women (compared with placebo or no treatment) on allergy outcomes of the infants or children. Trials using a cross-over design and trials examining biochemical outcomes only were not eligible for inclusion.

Data collection and analysis

Two review authors independently assessed eligibility and trial quality and performed data extraction. Where the review authors were also investigators on trials selected, an independent reviewer assessed trial quality and performed data extraction.

Main results

Eight trials involving 3366 women and their 3175 children were included in the review. In these trials, women were supplemented with n-3 LCPUFA during pregnancy (five trials), lactation (two trials) or both pregnancy and lactation (one trial). All trials randomly allocated women to either a n-3 LCPUFA supplement or a control group. The risk of bias varied across the eight included trials in this review with only two trials with a low risk of selection, performance and attrition bias.

N-3 LCPUFA supplementation showed a clear reduction in the primary outcome of any allergy (medically diagnosed IgE mediated) in children aged 12 to 36 months (risk ratio (RR) 0.66, 95% confidence interval (CI) 0.44 to 0.98; two RCTs; 823 children), but not beyond 36 months (RR 0.86, 95% CI 0.61 to 1.20; one RCT, 706 children). For any allergy (medically diagnosed IgE mediated and/or parental report), no clear differences were seen in children either at 12 to 36 months (RR 0.89, 95% CI 0.71 to 1.11; two RCTs, 823 children) or beyond 36 months of age (RR 0.96, 95% CI 0.84 to 1.09; three RCTs, 1765 children).

For the secondary outcomes of specific allergies there were no clear differences for food allergies at 12 to 36 months and beyond 36 months, but a clear reduction was seen for children in their first 12 months with n-3 LCPUFA (both for medically diagnosed IgE mediated and medically diagnosed IgE mediated and/or parental report). There was a clear reduction in medically diagnosed IgE-mediated eczema with n-3 LCPUFA for children 12 to 36 months of age, but not at any other time point for both medically diagnosed IgE mediated and medically diagnosed IgE mediated and/or parental report. No clear differences for allergic rhinitis or asthma/wheeze were seen at any time point for both medically diagnosed IgE mediated, and medically diagnosed IgE mediated and/or parental report.

There was a clear reduction in children's sensitisation to egg and sensitisation to any allergen between 12 to 36 months of age when mothers were supplemented with n-3 LCPUFA.

In terms of safety for the mother and child, n-3 LCPUFA supplementation during pregnancy did not show increased risk of postpartum haemorrhage or early childhood infections.

Authors' conclusions

Overall, there is limited evidence to support maternal n-3 LCPUFA supplementation during pregnancy and/or lactation for reducing allergic disease in children. Few differences in childhood allergic disease were seen between women who were supplemented with n-3 LCPUFA and those who were not.

PLAIN LANGUAGE SUMMARY

Fish oil (n-3 or omega-3) for pregnant mothers or breastfeeding mothers to prevent allergies in their young children

Fish and fish oil are the major sources of omega-3 long chain fatty acids. Dietary marine omega-3 fatty acid supplements during pregnancy may change the immune system of the newborn before allergic responses are established, particularly for those with a genetic predisposition to the production of the immunoglobulin E (IgE) antibody. Individuals with IgE-mediated allergies have both the signs and symptoms of the allergic disease and a positive skin prick test (SPT) to the allergen.

Allergy is an important public health problem that places a burden on individuals, society and healthcare costs. Allergic diseases include food allergies, eczema (atopic dermatitis), asthma or wheeze and hay fever (allergic rhinitis). Many childhood allergies continue into adulthood.

Pregnant women, especially those from Western countries, are not eating as much fish and allergic diseases have been increasing over the time that pregnant women have been eating less fish. The unborn baby gets nutrition from his or her mother and so the mother's diet is important. Supplementing women with omega-3 fatty acids from marine origin may be important in preventing their children from developing allergies.

In this review of randomised controlled studies, we evaluated the effects of adding marine omega-3 fatty acids to women's diets during pregnancy or lactation on allergic diseases in their children. We analysed eight trials that involved 3366 women and 3175 children. The women were randomly assigned to receive a marine omega-3 supplement (as fish oil capsules, or added to foods) or no treatment during pregnancy (five trials), during breast feeding (two trials) or both pregnancy and breast feeding (one trial). Overall, the methodological quality of the trials varied, with only two trials being at low risk of bias.

Overall, the results showed little effect of maternal marine omega-3 supplementation during pregnancy and/or breast feeding for the reduction of allergic disease in the children. However there were reductions in some outcomes such as food allergy during the baby's first year and eczema with marine omega-3 supplementation in women with a baby at high risk of allergy. Currently, there is not enough evidence to say that omega-3 supplements from marine origin during pregnancy and/or breast feeding for mothers will reduce allergies in their children.

In terms of safety for the mother and child, omega-3 fatty acids supplementation from marine origin during pregnancy did not show increased risk of excessive bleeding after the baby was born (postpartum haemorrhage) or early childhood infections.

BACKGROUND

Description of the condition

Over the past 20 years the prevalence of allergies in industrialised countries has increased fivefold, from approximately 4% to an estimated 20% (Asher 2006; Pawanker 2011). Allergic diseases include food allergies, atopic dermatitis (eczema), asthma and allergic rhinitis (hay fever) (Arkwright 2008). The pattern of allergy expression differs with age (Spiegel 2003). Food allergies and eczema are common in children under three years of age, while asthma and allergic rhinitis are more common between the ages of three and 15 years (Saarinen 1995). Regardless of these changing patterns of allergic disease in childhood, many childhood allergies persist, with 50% of childhood asthma sufferers and 80% of allergic rhinitis sufferers continuing to experience allergic symptoms into adulthood (Asher 2006; Barbee 1998; Greisner 1998; Spiegel 2010).

Atopy is defined as a genetic predisposition to the production of specific immunoglobulin E (IgE) antibodies to allergens and atopic people are more liable to have immune reactions that lead to allergies (Sears 1996). One of the principal methods of determining specific IgE sensitisation to an allergen is the skin prick test (SPT). To perform a SPT, a drop of allergen extract is placed on the skin and a small prick is made through the drop. This allows a small amount of allergen to enter the skin. If allergic to the tested allergen, a small lump (wheal) will appear at the site of testing within 15 to 20 minutes. A test is positive if there is a mean wheal diameter of 3 mm or greater (Bousquet 2012). A positive SPT to an allergen, along with clinical allergy symptoms, forms the basis for IgE-mediated allergy diagnosis (Johansson 2001; Johansson 2004).

The risk of allergy is 30% greater if one first degree relative (parent or sibling) is atopic, but if both parents are atopic then the allergy risk increases to 70% (Sears 1996). Allergic responses are reactions to an extrinsic substance (allergen) that is mediated by an immunological response (Arkwright 2008). This immunological response may cause mild to severe reactions in different individuals and can be life threatening (Arkwright 2008). Thus allergy is an important public health problem which places a burden on individuals, society and the healthcare system (Gupta 2004).

Environmental factors seem to have had an important influence on the increasing incidence of allergies. Possible contributing factors include lack of breastfeeding, higher socio-economic conditions with higher standards of hygiene, fewer respiratory infections, greater use of antibiotics early in life, fewer older siblings in the household, less contact with farm animals, general lack of microbial exposure and changes in dietary patterns (Gupta 2004; Strong 2005).

Among the changes in dietary patterns, it has been hypothesised that the balance of long chain polyunsaturated fatty acids (LCPUFA), specifically the n-3 (omega 3) to n-6 (omega 6) ratio, may be a factor in the increased incidence of childhood allergies (Calder 2000; Calder 2010b; Prescott 2004). Furthermore, maternal fish consumption during pregnancy has also reduced due to precautionary public health advice regarding the consumption of specific fish which may contain methyl mercury (Oken 2003).

Description of the intervention

Fish and fish oil are the major sources of n-3 LCPUFA, while vegetable oils are the major source of n-6 LCPUFA. Recent data

suggest that dietary consumption of n-3 LCPUFA has declined in Western diets to favour the intake of n-6 fatty acids (Meyer 2003). Epidemiological data suggest that a higher fish intake during pregnancy is associated with fewer symptoms of allergic diseases in the offspring in early childhood (Calvani 2006; Romieu 2007; Sausenthaler 2007; Willers 2007). Thus, supplementing maternal diets with n-3 LCPUFA may be an important factor in reducing the incidence of allergic diseases.

How the intervention might work

Dietary n-3 LCPUFA supplementation during pregnancy and lactation has been suggested to modulate the immune system of the fetus, neonate or infant before allergic responses are established (Denburg 2005). The early programming of fetal immune responses to allergens possibly begins in the epithelial tissue where antigen (allergen) proteins first encounter antigen-presenting cells (Prescott 2007). The pattern of cytokine production by antigen-presenting cells determines the pattern of T-helper (Th) cells differentiation (Prescott 2007). T cells producing Type 1 T cells (Th1), develop under the influence of interleukin (IL)-12 and IL-2, whereas T cells producing Type 2 T cells (Th2), develop in the relative absence of pro-Th2 factors such as IL-4 (Snijdwint 1993). The differences in T cell phenotypes also determine the pattern of B-cell antibody production with Th2 cytokines (IL-4, IL-5, and IL-13), prompting IgE production and allergic inflammation, whereas Th1 cytokines (IFN- γ) largely inhibit this in favour of low level IgG production (Calder 2006; Calder 2010a). Th2 cytokines are also important in determining whether these immune responses result in clinically relevant diseases such as asthma, allergic rhinitis or allergic dermatitis (Calder 2003; Georas 2005; Prescott 2007). A well regulated placental balance between the Th1 and Th2 responses is important for developing a robust immune system during pregnancy (Wilczynski 2005).

Maternal n-3 LCPUFA intervention studies support this immune programming hypothesis (Krauss-Etschmann 2007; Lauritzen 2005; Lee 2013; Romero 2013). Two studies investigated Th1/Th2 related molecules in cord blood (Krauss-Etschmann 2008; Romero 2013), and the other investigated cytokine production in children at two and a half years of age (Lauritzen 2005). These studies showed that allergy-related immune parameters were lower in the offspring of women who had n-3 LCPUFA supplementation during pregnancy or lactation (Krauss-Etschmann 2008; Lauritzen 2005; Romero 2013). The other study also showed that maternal n-3 LCPUFA supplementation during pregnancy was associated with balancing Th1/Th2 and modulating IFN γ and IL13 in infants (Lee 2013).

Supporting evidence from mechanistic (Denburg 2005; Prescott 2007) and small scale intervention studies show that allergy markers and allergy mechanisms are influenced by n-3 LCPUFA (Dunstan 2003; Prescott 2007a). Also there were studies in which maternal or postnatal consumption of n-3 LCPUFA through oily fish or fish oil had an effect on allergy outcomes in children (Hodge 1996; Romieu 2007), as well as a transient effect on allergy outcomes (Mihrrshahi 2004; Oddy 2004).

Why it is important to do this review

Allergy is an important public health problem that places a burden on individuals, society and healthcare costs (Gupta 2004; Kemp 1999; Pawanker 2011). Consequently, allergy prevention is a major global challenge (Strong 2005) and the World

Allergy Organization (WAO) recommends that allergy preventative strategies are urgently needed (Asher 2004). It is uncertain if n-3 LCPUFA supplementation during pregnancy or lactation reduces allergic disease in children. For these reasons, we need clear evidence from intervention studies. Therefore, in this systematic review we aim to evaluate the effects of maternal n-3 LCPUFA supplementation during pregnancy and/or lactation on allergy outcomes in children. The safety aspects of n-3 LCPUFA also need to be considered; it is postulated that high doses of n-3 LCPUFA may have antithrombotic antiplatelet properties which may lead to bleeding (Simopoulos 1991), as well as immune cell alterations which may have an effect on infections (Calder 2007).

OBJECTIVES

To assess the effect of maternal n-3 LCPUFA supplementation during pregnancy and/or lactation on the allergy outcomes of their children.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) focusing on n-3 LCPUFA supplementation of pregnant and/or lactating women (compared with placebo or no treatment) and assessed allergy outcomes of the infants or children. Quasi-RCTs and RCTs using a cluster-randomised design were eligible for inclusion but none were identified. Trials published in abstract form only were not identified for inclusion. In future updates we will only consider abstracts for inclusion if unpublished data can be obtained from the trials. Trials using a cross-over design and trials examining biochemical outcomes only were not eligible for inclusion.

Types of participants

Women and their children, with either a normal or high risk of developing allergic disease, were included. A fetus or a child with a first degree relative with medically diagnosed allergies, or a positive a SPT, or a positive radioallergosorbent test (RAST) was defined as being at high risk of allergies. Infants were also considered at high risk of allergies if their cord blood IgE level was above 0.70 IU/mL.

Types of interventions

We considered all randomised comparisons of n-3 LCPUFA supplementation given to pregnant or lactating women (either with or without arachidonic acid), with placebo or no supplementation as a control, regardless of dose regimens and duration of intervention. Trials in which fish was the intervention were included if appropriately controlled, for example, if the diet was appropriately adjusted to match the protein contribution of fish.

Types of outcome measures

Primary outcome measures included children with allergy, including food allergy, atopic dermatitis (eczema), asthma/wheeze, allergic rhinitis (hay fever) or any allergies (children with one or more of the allergy types). Outcomes were assessed as short term (occurring at less than 12 months of age), medium term (occurring from 12 to less than 36 months of age) and long term (36 months of age and older). Outcomes were also assessed by combining short-

term, medium-term and long-term results to assess the cumulative incidence.

Primary outcomes

1. Medically diagnosed any allergy with sensitisation, i.e. IgE-mediated allergies where both the signs and symptoms of the allergic disease and a positive SPT and/or RAST test are present.
2. Medical diagnosis or parental report (using validated questionnaire) of any allergy, +/- IgE sensitisation.

Secondary outcomes

Secondary outcome measures included children with specific forms of allergy, including food allergy, atopic dermatitis (eczema), asthma/wheeze, allergic rhinitis (hay fever) with IgE sensitisation and +/- IgE sensitisation, SPT results, and parent-reported allergies using non-validated questionnaires. Secondary safety outcomes included infant safety (e.g. infections) and maternal safety (e.g. postpartum haemorrhage or infection) due to the theoretical risk associated with higher doses of n-3 LCPUFA.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (6 August 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we searched PubMed (1966 to 01 August 2014) (Appendix 1), CINAHL via EBSCOhost (1984 to 01 August 2014) (Appendix 2), Scopus (1995 to 01 August 2014) (Appendix 3), Web of Knowledge (1864 to 01 August 2014) (Appendix 4) and [ClinicalTrials.gov](#) (01 August 2014) (Appendix 5).

Searching other resources

We searched reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

Selection of studies

Two review authors Anoja W Gunaratne (AWG) and Carmel T Collins (CTC) independently assessed the eligibility of trials identified by the search. Disagreements were resolved through discussion or, if required, by consultation with the third review author Maria Makrides (MM).

Data extraction and management

Two review authors (AWG, CTC) independently extracted the data from eligible trials using the agreed form. Discrepancies were resolved through discussion or through consultation with the third author (MM) if required. When information was unclear or incomplete, we attempted to contact authors of the original reports to provide further details. We entered data into Review Manager software 5.3 ([RevMan 2014](#)) and checked them for accuracy.

Assessment of risk of bias in included studies

Two review authors (AWG, CTC) independently assessed the risk of bias for each trial using the criteria outlined in *the Cochrane Handbook for Systematic Reviews of Interventions (Handbook)* ([Higgins 2011](#)). We resolved any disagreement by discussion or by involving a third assessor (MM). MM and CTC are Investigators on two trials, [Makrides 2009](#) and [Makrides 2010](#) included in the review. These trials were independently assessed for risk of bias and data extracted by AWG and an independent researcher third party Karen Best (KB).

(1) Random sequence generation (checking for possible selection bias)

For each included trial, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it would produce comparable groups.

We assessed the method as:

low risk of bias (any truly random process, e.g. random number table, computer random number generator); high risk of bias (any non-random process, e.g. odd or even date of birth, hospital or clinic record number); unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

For each included trial, we described the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen before recruitment, during recruitment or changed after assignment.

We assessed the methods as:

low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described the methods used, if any, to blind trial participants and personnel from knowledge of which intervention a participant received for each trial. We considered that trials were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

low, high or unclear risk of bias for participants; low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received for each included trial. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods used to blind outcome assessment as:

low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described the completeness of data, including attrition and exclusions from the analysis, for each included trial and for each outcome or class of outcomes. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants). We also outlined the reasons for attrition or exclusion, where reported, and whether missing data were balanced across groups or related to outcomes. We included missing data in the analyses where sufficient information was reported or could be supplied by the trial authors.

We assessed methods as:

low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups); high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation); unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described our investigation of possible selective outcome reporting bias and our results for each included trial.

We assessed the methods as having a:

low risk of bias – where it is clear that all of the trial's pre-specified outcomes and all expected outcomes of interest to the review were reported; high risk of bias – where not all the trial's pre-specified outcomes had been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; or trial failed to include results of a key outcome that would have been expected to have been reported; unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described any important concerns we had about other possible sources of bias for each included trial.

We assessed whether each trial was free of other problems that could put it at risk of bias, as low, high or unclear risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether trials were at high risk of bias according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses – see [Sensitivity analysis](#).

Measures of treatment effect

Dichotomous data

Results are presented as summary risk ratio with 95% confidence intervals.

Continuous data

We planned to present the results of continuous data as the mean difference, if outcomes were measured in the same way between trials. We would have used the standardised mean difference to combine trials that measured the same outcome but used different methods.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials for inclusion in this review. If we identify cluster-randomised trials in future updates of this review, we will include them in the analyses along with individually-randomised trials. We will adjust their sample size using the methods described in the *Handbook* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a trial of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we will synthesis the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the trial designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials are not an appropriate design for this review.

Other unit of analysis issues

Trials with more than two treatment groups

Trials using one or more treatment groups (multi-arm trials) were combined to create a single pair-wise comparison where

appropriate. We used the methods described in the *Handbook* (Higgins 2011) to ensure that we did not double count participants.

Dealing with missing data

We noted levels of attrition within the included trials. We used sensitivity analyses to explore the impact of including trials with high levels of missing data on the overall assessment of treatment effect. For all outcomes, we carried out analyses (as far as possible) on an intention-to-treat basis. This meant that we attempted to include all participants randomised to each group in the analyses with all participants analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator used for each outcome was the number randomised minus the number with missing outcomes. In studies where there were missing data, we imputed results, if the imputed results differed little from the raw data.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2 , I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the T^2 was greater than zero or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In future updates, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analyses using the Review Manager software 5.2 (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that trials were estimating the same underlying treatment effect: that is, where trials were examining the same intervention and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. We did not combine trials if the average treatment effect was not clinically meaningful.

Where we used random-effects analyses, the results are presented as the average treatment effect with 95% confidence intervals and estimates of T^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

Substantial heterogeneity was investigated using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful, and if it was, used random-effects analyses.

We planned to carry out the following subgroup analyses.

1. Timing of supplementation
 - a. n-3 LCPUFA supplementation during pregnancy versus placebo or no supplementation during pregnancy
 - b. n-3 LCPUFA supplementation during lactation versus placebo or no supplementation during lactation
 - c. n-3 LCPUFA supplementation during pregnancy and lactation versus placebo or no supplementation during pregnancy and lactation
2. Allergy risk
 - a. Maternal n-3 LCPUFA supplementation in women whose infants were at high risk of allergic disease versus placebo or no supplementation
 - b. Maternal n-3 LCPUFA supplementation in women whose infants were not considered as at high risk of allergic disease versus placebo or no supplementation
3. Infant maturity
 - a. Maternal n-3 LCPUFA supplementation in term born infants versus placebo or no supplementation
 - b. Maternal n-3 LCPUFA supplementation in preterm born infants versus placebo or no supplementation

We restricted subgroup analyses to the primary outcomes.

Sensitivity analysis

We planned to carry out sensitivity analyses for the review's primary outcomes to investigate the effect of trial quality by

removing those trials rated as 'high' or 'unclear' risk of selection, performance or attrition bias to establish whether it was likely to impact on the findings.

RESULTS

Description of studies

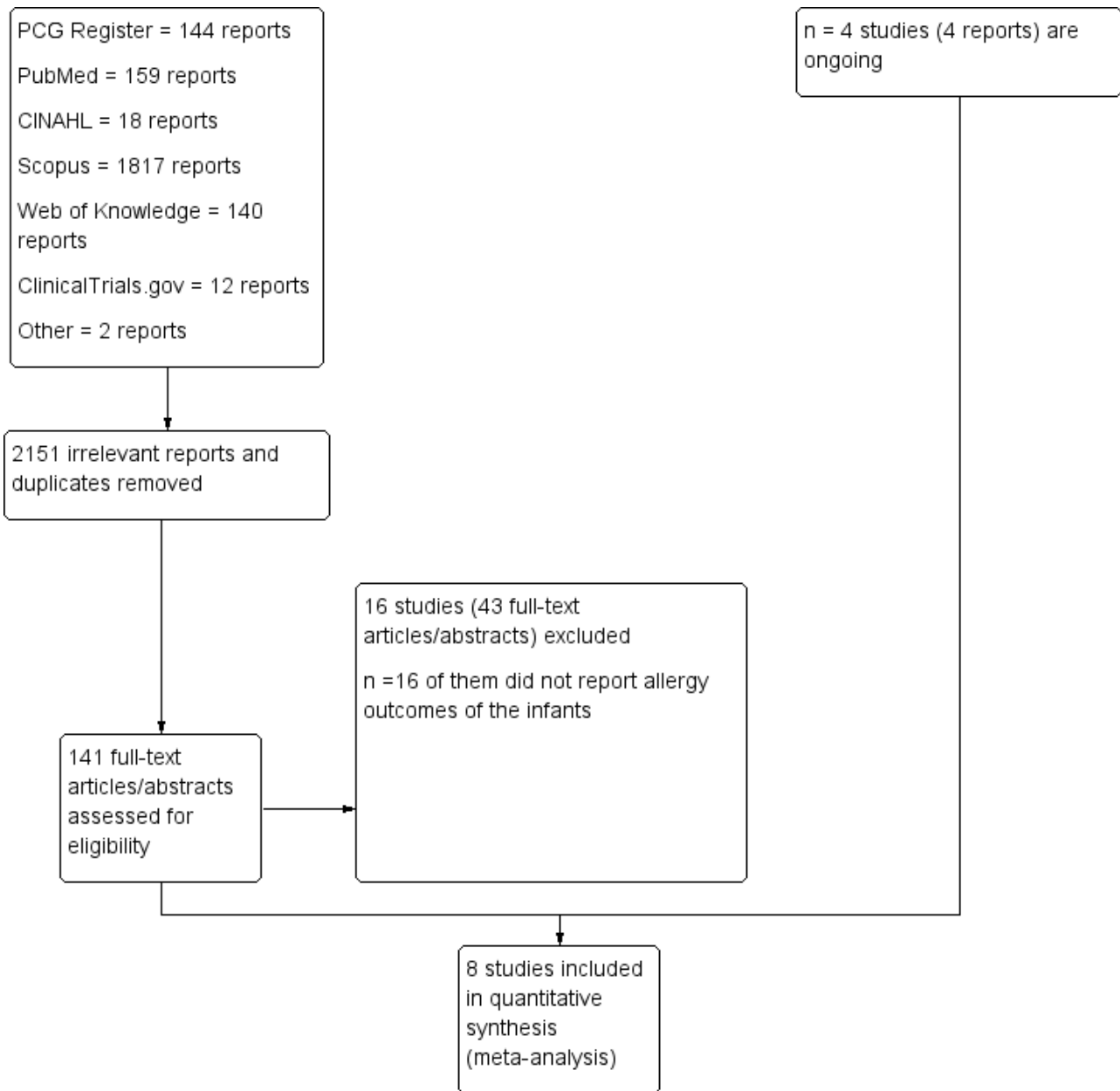
See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

Electronic searches yielded 2290 records. The Cochrane Pregnancy and Childbirth Trials Register search (06 August 2014), retrieved 144 reports. Other electronic databases, PubMed (1966 to 01 August 2014), CINAHL via EBSCOhost (1984 to 01 August 2014), Scopus (1995 to 01 August 2014), Web of Knowledge (1864 to 01 August 2014) and [ClinicalTrials.gov](#) (01 August 2014) retrieved 159, 18,1817, 140 and 12 reports respectively. Two additional reports included the doctoral thesis (submitted) of AWG and an unpublished honours dissertation supervised by MM and CTC.

Of the 2292 records, we removed duplicates and irrelevant reports and identified 141 titles and abstracts by considering the inclusion criteria. Sixteen trials (with 43 reports) were excluded, leaving eight trials (with 94 reports) for inclusion in this review. Four trials (with four reports) are ongoing ([Bisgaard 2012](#); [Duchen 2012](#); [Laitinen 2013](#); [Liu 2013](#).) See [Figure 1](#).

Figure 1. Study flow diagram.



Included studies

See: [Characteristics of included studies](#).

We identified eight randomised controlled trials with 3366 women (3175 children) who were supplemented with oily fish, or n-3 LCPUFA supplements during pregnancy and/or during lactation and assessed allergic outcomes in their children.

Study design

All eight trials were parallel randomised controlled trials published in English. Six trials had two parallel groups (Dunstan 2003; Furuhejm 2009; Makrides 2009; Noakes 2012; Makrides 2010; Ramakrishnan 2010), one trial included two parallel groups and a high fish intake non-randomised reference group (Lauritzen 2005),

and one trial had three parallel groups including intervention, placebo and no oil group (Olsen 1992).

Full details of the included trials are provided in the [Characteristics of included studies](#) table.

Participants

Of the 3366 women included in the review, 667 were supplemented during the postnatal period only (Lauritzen 2005; Makrides 2009), 145 received supplementation in both the prenatal and postnatal period (Furuhejm 2009) and the remaining 2554 women were only supplemented in the prenatal period (Dunstan 2003; Noakes 2012; Olsen 1992; Makrides 2010; Ramakrishnan 2010). Women with a fetus at high risk of allergies (n = 1072) were included in four trials (Dunstan 2003; Furuhejm 2009; Noakes 2012; Makrides 2010)

while the remainder included women with a fetus at both high and normal risk of allergies (Lauritzen 2005; Makrides 2009; Olsen 1992; Ramakrishnan 2010), see 'types of participants for definition of high risk'. In one trial, only preterm infants were included (Makrides 2009).

Sample sizes

The sample sizes of the included trials ranged from 98 (Dunstan 2003) to 1094 (Ramakrishnan 2010). Four trials had approximately 100 to 150 mothers (Dunstan 2003; Furuholm 2009; Lauritzen 2005; Noakes 2012) and four trials had > 500 participants (Makrides 2009; Makrides 2010; Olsen 1992; Ramakrishnan 2010).

Study location

Three trials (Dunstan 2003; Makrides 2009; Makrides 2010) were undertaken in Australia, two (Lauritzen 2005; Olsen 1992) in Denmark, one (Furuholm 2009) in Sweden, one (Ramakrishnan 2010) in Mexico, and one (Noakes 2012) in the UK. Most of the trials were conducted in high-income, well-developed industrialised countries except one trial (Ramakrishnan 2010) which was conducted in a upper-middle income country.

Intervention

Six trials used n-3 LCPUFA capsules (Dunstan 2003; Furuholm 2009; Makrides 2009; Makrides 2010; Olsen 1992; Ramakrishnan 2010), one used muesli bars containing microencapsulated fish oil as a source of n-3 LCPUFA (Lauritzen 2005), and the remaining trial used oily fish (Noakes 2012). The daily dosage of n-3 LCPUFA varied between 400 mg and 4500 mg; providing between 331 mg and 2070 mg of docosahexaenoic acid (DHA) and 100 mg and 1600 mg of eicosapentaenoic acid (EPA). Control groups received olive oil in three trials (Dunstan 2003; Lauritzen 2005; Olsen 1992), soy oil in two trials (Furuholm 2009; Makrides 2009), a blend of vegetable oils (rapeseed, sunflower, and palm in equal proportions) in one trial, (Makrides 2010), or a blend of corn and soy oil in one trial (Ramakrishnan 2010). Olsen 1992 included a third randomised group who did not receive any supplementation and the control group in Noakes 2012 also received no supplementation.

The prenatal supplementation trials commenced supplementation between 18 to 20 weeks (Ramakrishnan 2010), at 20 (Dunstan 2003; Makrides 2010; Noakes 2012) and 30 (Olsen 1992) weeks of gestation and continued until delivery. One trial supplemented in both the prenatal and postnatal period, commencing from 25 weeks' gestation and continuing until the infant reached four months of age (Furuholm 2009). In the two postnatal supplementation trials, supplementation commenced within one week after delivery (Lauritzen 2005; Makrides 2009). The duration of supplementation was four months in Lauritzen 2005 while in Makrides 2009 trial in preterm infants, supplementation continued until the infant reached 40 weeks postmenstrual age (a median duration of 9.4 weeks supplementation).

Outcome measures

The allergy outcomes were determined by parental reports of doctor diagnosed allergy in one trial (Lauritzen 2005), parental reports of allergy symptoms in one trial (Ramakrishnan 2010) and parental reports of allergy symptoms and parental reports of doctor diagnosed allergy in one trial (Makrides 2009). Allergy was medically diagnosed in the remaining trials (Dunstan 2003; Furuholm 2009; Noakes 2012; Olsen 1992; Makrides 2010). In Olsen

1992, the medical diagnosis of allergy was obtained from the Danish Medical registries. Parent reports of allergy outcome data were collected using a non-validated questionnaire and validated International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire in Makrides 2009 trial. Parent reports of allergy outcome data were collected using a non-validated questionnaire in Ramakrishnan 2010 trial. Additionally, Makrides 2010 trial also had parent reports of allergy outcome data using a non-validated questionnaire. The data that were collected using non-validated questionnaires were only included in the secondary outcomes.

The age of assessments differed in the trials. Assessments were conducted at one month and three months (Ramakrishnan 2010), six months (Furuholm 2009; Noakes 2012; Makrides 2010; Ramakrishnan 2010), 12 months (Dunstan 2003; Furuholm 2009; Makrides 2009; Makrides 2010), 18 months corrected age (Makrides 2009; Ramakrishnan 2010), 24 months (Furuholm 2009), 30 months (Lauritzen 2005), three to five years corrected age (Makrides 2009) (subgroup), 36 months (Makrides 2010), seven years of age (Makrides 2009), and 16 years of age (Olsen 1992). Of the five trials that used medical diagnosis of allergies (Dunstan 2003; Furuholm 2009; Noakes 2012; Olsen 1992; Makrides 2010), four performed skin prick tests (SPT) (Dunstan 2003; Furuholm 2009; Noakes 2012; Makrides 2010) and included children at high risk of allergy. Two trials (Furuholm 2009; Noakes 2012) reported SPT results for children under 12 months of age, three trials (Dunstan 2003; Furuholm 2009; Makrides 2010), reported SPT between 12 to 36 months of age, and one trial (Makrides 2010) reported SPT in children at 36 months of age.

IgE-mediated allergies were reported in Furuholm 2009 and Makrides 2010. Two trials (Furuholm 2009; Noakes 2012) used blood samples for IgE detection in infants and one trial (Noakes 2012) reported the results at birth and six months of age while the other trial (Furuholm 2009) analysed the serum IgE levels at three and 12 months of age, but results were not reported.

The type of allergies reported in the trials differed. Five trials (Dunstan 2003; Furuholm 2009; Lauritzen 2005; Makrides 2009; Makrides 2010) reported food allergy. Six trials (Dunstan 2003; Furuholm 2009; Lauritzen 2005; Makrides 2009; Noakes 2012; Makrides 2010) reported eczema. All trials (Dunstan 2003; Furuholm 2009; Lauritzen 2005; Makrides 2009; Noakes 2012; Olsen 1992; Makrides 2010; Ramakrishnan 2010) reported asthma or wheeze. Three trials (Furuholm 2009; Makrides 2009; Makrides 2010) reported allergic rhinitis and four trials (Furuholm 2009; Makrides 2009; Olsen 1992; Makrides 2010) reported any allergy.

Two trials (Olsen 1992; Makrides 2010) reported postpartum haemorrhage. Makrides 2010 (n = 2399) was the primary trial from which the Palmer 2012 participants were recruited (see table of included studies); the incidence of postpartum haemorrhage is reported for the primary trial. Four trials (Noakes 2012; Makrides 2009; Makrides 2010; Ramakrishnan 2010) reported early childhood infections. Infection outcomes (in-hospital proven late onset sepsis) for Makrides 2009 are reported for the whole sample (n = 657). Ramakrishnan 2010 also reported fever in infants.

Excluded studies

See: [Characteristics of excluded studies.](#)

We excluded 16 randomised controlled trials where the intervention was n-3 LCPUFA supplementation but allergy outcomes of the infants and/or children were not reported (Bergmann 2008; Campos-Martinez 2012; Carlson 2013; Colombo 2004; Courville 2011; Granot 2011; Hauner 2009; Helland 2001; Innis 2007; Judge 2007; Karlsson 2010; Knudsen 2006; Krauss-Etschmann 2007; Martin-Alvarez 2012; Pena-Quintana 2011; Ribeiro 2012). Many of these trials are included in the Cochrane Systematic Review currently being updated (Makrides 2006).

Characteristics of ongoing studies

See: [Characteristics of ongoing studies](#).

There are four ongoing trials (Bisgaard 2012; Duchon 2012; Laitinen 2013; Liu 2013).

Risk of bias in included studies

Overall, the eight included studies had various levels of risk of bias for methodological quality. See [Figure 2](#) and [Figure 3](#) for details.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

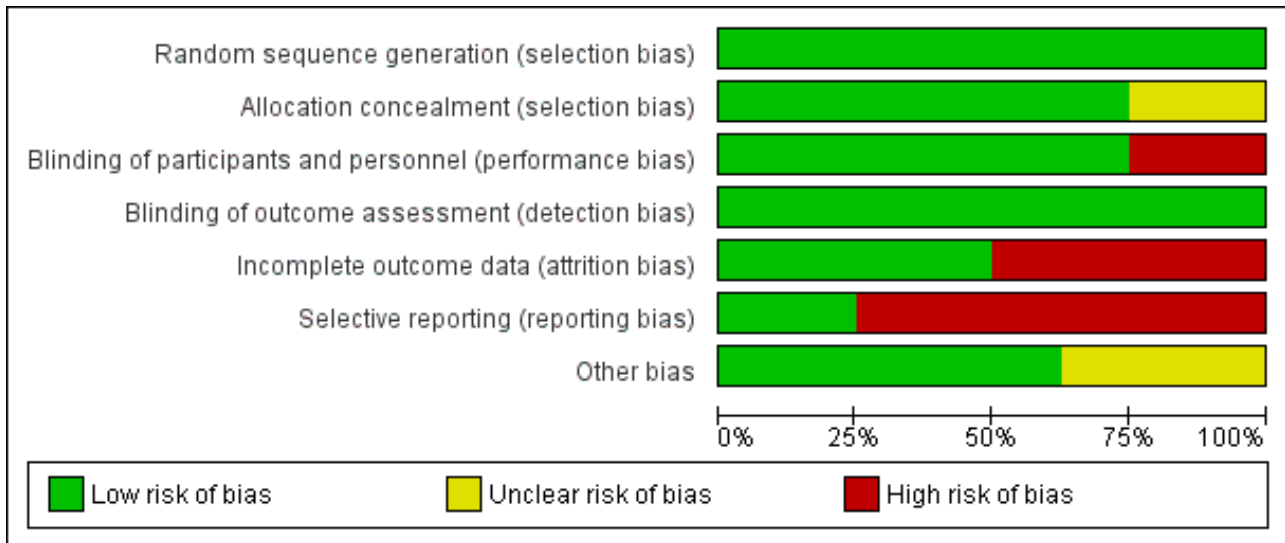


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dunstan 2003	+	+	+	+	-	-	?
Furuhjelm 2009	+	+	+	+	-	+	+
Lauritzen 2005	+	+	+	+	-	-	+
Makrides 2009	+	+	+	+	+	-	?
Makrides 2010	+	+	+	+	+	+	?
Noakes 2012	+	?	-	+	-	-	+
Olsen 1992	+	+	-	+	+	-	+
Ramakrishnan 2010	+	?	+	+	+	-	+

Allocation

All of the eight trials were at low risk of bias for sequence generation.

Six trials reported adequate allocation concealment methods (Dunstan 2003; Furuhjelm 2009; Lauritzen 2005; Makrides 2009; Makrides 2010; Olsen 1992) and two trials (Noakes 2012; Ramakrishnan 2010) had an unclear risk of bias as the method of allocation concealment was not described.

Blinding

Women, care providers and research personnel were blinded in six trials (Dunstan 2003; Furuhejm 2009; Lauritzen 2005; Makrides 2009; Makrides 2010; Ramakrishnan 2010). In two trials (Noakes 2012; Olsen 1992), women who were randomised to the 'no supplement' group could not be blinded.

Outcome assessments were performed by assessors who were blinded to the trial supplementations in all eight trials (Dunstan 2003; Furuhejm 2009; Lauritzen 2005; Makrides 2009; Makrides 2010; Noakes 2012; Olsen 1992; Ramakrishnan 2010).

Incomplete outcome data

All trials reported withdrawals and dropouts. We assessed four trials (Makrides 2009; Makrides 2010; Olsen 1992; Ramakrishnan 2010) as having a low risk of attrition bias. Makrides 2009 reported 6% of participant losses to follow-up at 18 months, 8% at three to five years of age and 10.5% at seven years of age. Olsen 1992 reported 1% of participant losses to follow-up at 16 years of age. Makrides 2010 reported participant follow-up losses of 3.5% and 9.6% at one and three years of age respectively. Ramakrishnan 2010 reported 25% participants losses to follow-up at six months, but balanced between group, and reasons for withdrawals were reported (intervention (23%) and control (24%)). Dunstan 2003, Furuhejm 2009, Lauritzen 2005 and Noakes 2012 were assessed as having a high risk of attrition bias. Dunstan 2003 reported a loss of 15% to follow-up and participant exclusion after randomisation, which differed between intervention (n = 12, 23%) and control (n = 3, 6.5%). More women in the intervention group discontinued treatment because of nausea (n = 7, 13.5%) than in the control (n = 1, 2%). Furuhejm 2009 reported a 19% loss of participants to follow-up (n = 16), with 23% in the treatment group (n = 9) and 12% in the placebo group excluded from the analysis because they did not complete the 15-week intervention. Lauritzen 2005 had large follow-up losses of more than 47%, with no reasons reported for the withdrawals (treatment n = 25, 40%; control n = 32, 53%). Noakes 2012 also had large follow-up losses (30%) at six months with no reasons reported (treatment n = 16, 23%; control n = 23, 37%).

Selective reporting

All trials (Dunstan 2003; Lauritzen 2005; Makrides 2009; Noakes 2012; Olsen 1992; Ramakrishnan 2010) except two (Furuhejm 2009; Makrides 2010) were assessed as having a high risk of reporting bias, as expected outcomes of interest to this review were not reported or were not reported completely.

Other potential sources of bias

There were no obvious other potential sources of bias identified in four trials (Furuhejm 2009; Lauritzen 2005; Noakes 2012; Ramakrishnan 2010). There was an unclear risk of bias in the two trials that included subgroups of their original trials (Makrides 2009; Makrides 2010). In Olsen 1992 the placebo group and no oil group were combined in this review. We conducted analyses with the n-3 LCPUFA supplementation group compared to olive oil control group separately to n-3 LCPUFA supplementation group compared to no supplement control group, and found that although the direction of effect differed it made little difference to the meta-analysis therefore for this review the control groups were combined. Dunstan 2003 was rated as having an unclear risk of bias

because preterm infants were excluded from their analysis after randomisation.

Effects of interventions

N-3 LCPUFA supplementation versus placebo or no supplementation

Primary outcomes - any allergy

See: Table 1; Table 2.

We considered any allergy that included children with one or more allergy types including food allergy, atopic dermatitis (eczema), asthma/wheeze, allergic rhinitis (hay fever) as primary outcomes of the review. Allergic disease was considered in two ways. Firstly, the effect of n-3 LCPUFA supplementation on IgE-mediated allergic disease, then the effect of supplementation on all allergic disease (+/- IgE sensitivity) was analysed, for each of the allergic diseases under study. The effect of supplementation was analysed at various points in the child's life - short term (up to 12 months of age), medium term (12 to 36 months), and long term (36 months and beyond). We were unable to report cumulative incidences due to variation in reporting between studies.

Any allergies (Analysis 1.1; Analysis 1.2)

N-3 LCPUFA supplementation showed a clear reduction in IgE-mediated allergies in 12 to 36 months of age children when compared with the control group (Analysis 1.1; Furuhejm 2009; Makrides 2010, 823 children, risk ratio (RR) 0.66, 95% confidence interval (CI) 0.44 to 0.98). No clear differences were found in IgE-mediated allergies between treatments in 36 months of age or older children (Makrides 2010, 706 children, RR 0.86, 95% CI 0.0.61 to 1.20). No included trials reported on combined IgE-mediated allergies in infants under 12 months of age.

When all allergies (+/- IgE sensitivity) were considered, n-3 LCPUFA supplementation did not show clear differences in allergies in children at 12 to 36 months (Furuhejm 2009, Makrides 2010, RR 0.89, 95% CI 0.71 to 1.11, 823 children) or 36 months and beyond (Makrides 2009, Makrides 2010, Olsen 1992, RR 0.96, 95% CI 0.84 to 1.09, 1765 children) (Analysis 1.2). No included trials reported on combined +/- IgE-mediated allergies in infants under 12 months of age.

Secondary outcomes

See: Table 1; Table 2.

As secondary outcomes, we considered specific forms of allergy including food allergy, atopic dermatitis (eczema), asthma/wheeze and allergic rhinitis (hay fever) (IgE-mediated and +/- IgE sensitivity).

Food allergy (Analysis 2.1; Analysis 2.2)

N-3 LCPUFA supplementation reduced the incidence of IgE-mediated food allergies in children up to 12 months of age (Furuhejm 2009, 117 infants, RR 0.13, 95% 0.02 to 0.95; Analysis 2.1), but there were no clear differences found between the intervention and control groups at any other age (12 to 36 months Furuhejm 2009; Makrides 2010, 825 children, average RR 0.58, 95% CI 0.18 to 1.88; > 36 months of age Makrides 2010, 706 children, RR 1.43, 95% CI 0.63 to 3.26). A random-effects analysis was used as substantial heterogeneity was noted at the 12- to 36-month

time point ($\text{Tau}^2 = 0.39$; $P = 0.15$; $I^2 = 51\%$) (Analysis 2.1). The heterogeneity may be due to the duration of the intervention, the dose used and the difference in assessment ages.

When food allergies +/- IgE sensitivity were considered (Analysis 2.2), results showed few differences from those for IgE-mediated allergies (Analysis 2.1) with no differences in the direction of findings from those for IgE-mediated allergies (up to 12 months of age, Furuhejm 2009, 117 infants, RR 0.13, 95% CI 0.02 to 0.95; between 12 to 36 months, Dunstan 2003; Furuhejm 2009; Lauritzen 2005; Makrides 2010, 973 children, RR 0.72, 95% CI 0.40 to 1.30; > 36 months of age Makrides 2010, 706 children, RR 1.43, 95% CI 0.63 to 3.26).

Eczema (Analysis 2.3; Analysis 2.4)

N-3 LCPUFA supplementation reduced the incidence of IgE-mediated eczema in children at 12 to 36 months of age (Furuhejm 2009; Makrides 2010; 823 children, RR 0.61, 95% CI 0.39 to 0.95, Analysis 2.3). There were no clear differences between groups at the other time points (< 12 months Furuhejm 2009; 117 children, RR 0.38, 95% CI 0.13 to 1.11 or > 36 months of age Makrides 2010, 706 children, RR 0.84, 95% CI 0.57 to 1.23)

When eczema outcomes +/- IgE sensitivity were considered (Analysis 2.4), results showed few differences from those for IgE-mediated eczema (Analysis 2.3), however the direction of effect was reversed for the 12- to 36-month age group (up to 12 months of age (Furuhejm 2009; Noakes 2012, 203 infants, average RR 0.76, 95% CI 0.22 to 2.62; between 12 to 36 months, Dunstan 2003; Furuhejm 2009; Lauritzen 2005; Makrides 2010, 973 children, average RR 0.96, 95% CI 0.69 to 1.33; > 36 months of age, Makrides 2009; Makrides 2010, 1237 children, average RR 0.88, 95% CI 0.68 to 1.13). A random-effects analysis was used all time points as substantial heterogeneity was noted at the 12-month time point ($\text{Tau}^2 = 0.57$; $P = 0.06$; $I^2 = 71\%$) (Analysis 2.4).

Allergic rhinitis (Analysis 2.5; Analysis 2.6)

No clear difference was seen between n-3 LCPUFA and control groups in either IgE-mediated allergic rhinitis (Analysis 2.5: 12 to 36 months, Furuhejm 2009; Makrides 2010, 825 children, RR 0.47, 95% CI 0.07 to 3.06; > 36 months of age, Makrides 2010, 706 children, RR 0.83, 95% CI 0.44 to 1.54 or allergic rhinitis +/- IgE sensitivity (Analysis 2.6: 12 to 36 months, Furuhejm 2009, Makrides 2010, 805 children, RR 0.53, 95% CI 0.25 to 1.12; > 36 months of age, Makrides 2009, Makrides 2010, 1169 children, RR 1.03, 95% CI 0.81 to 1.30) across any age group. No included trials reported allergic rhinitis outcomes in infants under 12 months of age.

Asthma (Analysis 2.7; Analysis 2.8)

No clear differences were found between n-3 LCPUFA and control groups in children with either IgE-mediated asthma (Analysis 2.7; 12 to 36 months, Furuhejm 2009; Makrides 2010, 824 children, RR 0.86, 95% CI 0.21 to 3.49; > 36 months of age, Makrides 2010, 706 children, RR 1.10, 95% CI 0.34 to 3.58), or asthma +/- IgE sensitivity (Analysis 2.8; < 12 months, Noakes 2012, 83 infants, RR 1.26, 95% CI 0.54 to 2.94; 12 to 36 months, Dunstan 2003, Furuhejm 2009, Lauritzen 2005, Makrides 2010, 955 children, RR 0.93, 95% CI 0.73 to 1.18; > 36 months of age, Makrides 2009, Makrides 2010, Olsen 1992, 1697 children, RR 0.94, 95% CI 0.78 to 1.13) across any age group. No included trials reported IgE-mediated asthma outcomes in infants under 12 months of age.

Maternal safety (Analysis 3.1)

There was no clear difference in postpartum haemorrhage (defined as > 500 mL of blood loss post delivery) in women supplemented with n-3 LCPUFA compared with those in the control group (Analysis 3.1; Makrides 2010; Olsen 1992, n = 2932, average RR 0.73, 95% CI 0.49 to 1.10). Given the substantial heterogeneity between trials, a random-effects model was used ($\text{Tau}^2 = 0.05$, $P = 0.11$; $I^2 = 60\%$; Analysis 3.1). Postpartum infection was not reported in any of the included trials.

Infant safety (Analysis 3.2)

Infant safety was assessed using early childhood infections. Four trials reported this outcome (Makrides 2009; Makrides 2010; Noakes 2012; Ramakrishnan 2010, 2280 infants) with no clear difference between the n-3 LCPUFA and control group (RR 0.99; 95% CI 0.87 to 1.12). Ramakrishnan 2010 reported fever in 834 infants and found no differences between groups (RR 0.99; 95% CI 0.74 to 1.31; Analysis 3.2).

Sensitisation to allergens (Analysis 4.1 to Analysis 4.9)

See: Table 3.

Sensitisation is the strongest predictor of IgE-mediated allergy and was defined by a positive skin prick test to an allergen (de Jong 2011). Sensitisation to egg (Analysis 4.1) was reduced in the n-3 LCPUFA group compared with the control in 12- to 36 month-old children (Dunstan 2003; Furuhejm 2009; Makrides 2010, 893 children, RR 0.55; 95% CI 0.39 to 0.77). No clear differences between groups were seen in egg sensitisation in children up to 12 months of age (Furuhejm 2009; Noakes 2012) or in children 36 months or older (Makrides 2010).

Sensitisation to cows' milk was not different between the treatment groups at any age of assessment (Analysis 4.2), although no trials contained data for children aged 36 months or older. Given the substantial heterogeneity at 12 to 36 months, a random-effects model was used ($\text{Tau}^2 = 0.48$; $P = 0.19$; $I^2 = 40\%$).

There were no clear differences between groups in peanut sensitisation at any time point (Analysis 4.3; no trials in infants under 12 months of age),

The effect of n-3 LCPUFA supplementation on wheat sensitisation was not different from the control group at any age (Analysis 4.4) and similar results were seen with sensitisation to fish (Analysis 4.5; no trials up to 12 months of age), inhalant allergens (pollens) (Analysis 4.6; no trials up to 12 months of age), dust mites (Analysis 4.7; no trials up to 12 months of age) and cats (Analysis 4.8).

When all allergens were considered (Analysis 4.9), no clear differences were found between treatments for infants up to 12 months and beyond 36 months. However, n-3 LCPUFA showed a clear reduction in sensitisation in 12 to 36 months of age children (Dunstan 2003; Furuhejm 2009; Makrides 2010, 892 children, RR 0.70; 95% CI 0.53 to 0.94).

Parent's report of allergies from non-validated questionnaires (Analysis 5.1 to Analysis 5.5)

Three trials (Makrides 2009; Makrides 2010; Ramakrishnan 2010), included parents' reports of allergy collected using non-validated questionnaires. No clear differences were found between n-3 LCPUFA supplementation and control at any age in the incidence

of parental reports of food allergies ([Analysis 5.1](#)), eczema ([Analysis 5.2](#)), allergic rhinitis ([Analysis 5.3](#)), asthma/wheeze ([Analysis 5.4](#)), or any allergies ([Analysis 5.5](#)).

Subgroup analysis

Data were reported at last time point only in the subgroup analysis comparisons.

Timing of supplementation (Analysis 6.1 to Analysis 6.2)

Five trials included in the review confined supplementation with n-3 LCPUFA to the prenatal period only ([Dunstan 2003](#); [Noakes 2012](#); [Olsen 1992](#); [Makrides 2010](#); [Ramakrishnan 2010](#)). [Ramakrishnan 2010](#) collected allergy outcome data using a non-validated questionnaire, therefore these data did not meet the inclusion criteria for the primary outcome. Two of the included trials supplemented women with n-3 LCPUFA in the postnatal period only ([Lauritzen 2005](#); [Makrides 2009](#)), and only one trial ([Furuhjelm 2009](#)) supplemented women with n-3 LCPUFA through both prenatal and postnatal periods.

There were no significant subgroup differences for any of the outcomes ([Analysis 6.1](#); [Analysis 6.2](#)).

Allergy risk of the offspring (Analysis 5.1 to Analysis 5.5)

Four trials ([Dunstan 2003](#); [Furuhjelm 2009](#); [Noakes 2012](#); [Makrides 2010](#)) provided n-3 LCPUFA supplements to women whose fetuses were at high risk of allergy development with two reporting only IgE-mediated allergies ([Furuhjelm 2009](#); [Makrides 2010](#)). Three trials studied the effect of n-3 LCPUFA supplementation on allergy in women with fetuses or women with infants who were not selected on the basis of allergy risk ([Lauritzen 2005](#); [Makrides 2009](#); [Olsen 1992](#)). There were no significant subgroup differences for any outcome ([Analysis 7.1](#)).

Infant maturity

Subgroup analyses based on infant maturity were not able to be conducted. Although data from preterm children were available for [Makrides 2009](#), it was not possible to separate out children according to their gestational age in the remaining included trials ([Furuhjelm 2009](#); [Lauritzen 2005](#); [Noakes 2012](#); [Olsen 1992](#); [Makrides 2010](#)). [Dunstan 2003](#) excluded preterm infants after randomisation.

Sensitivity analysis

Sensitivity analyses were conducted for the primary outcome removing trials with high or unclear risk of selection, performance or attrition bias; [Makrides 2009](#) and [Makrides 2010](#) were the only trials with low risk of bias across these parameters. Removing trials with high or unclear risk of bias changed the direction for IgE-mediated any allergy at 12 to 36 months time point, but not beyond the 36 months time point, or for medically diagnosed IgE mediated and/or parental report any allergy outcome at any time points ([Analysis 8.1](#); [Analysis 8.2](#)).

DISCUSSION

Summary of main results

Eight trials involving 3366 women with 3175 children were included in this review. Supplementation occurred during pregnancy, lactation or both pregnancy and lactation.

Overall, the available evidence shows that maternal n-3 LCPUFA (long chain polyunsaturated fatty acid) supplementation showed little benefit in the reduction of childhood allergic disease. There was no clear overall effect of maternal n-3 LCPUFA supplementation on the incidence of medically diagnosed or parental reports of allergy (+/- IgE sensitisation) including food allergy, eczema, allergic rhinitis, asthma/wheeze or any allergy. No reduction was observed with maternal n-3 LCPUFA supplementation on IgE-mediated allergic rhinitis or IgE-mediated asthma.

However, there were reductions in some outcomes such as IgE-mediated food allergy up to 12 months of age, IgE-mediated eczema between one and three years of age and the risk of developing any IgE-mediated allergic disease between one and three years of age. However, this needs to be interpreted with caution as IgE-mediated allergies were reported in only two trials, which only focused on high-risk populations of allergy.

There was also a reduction in the incidence of sensitisation to egg and any allergen in children in the n-3 LCPUFA group.

Overall completeness and applicability of evidence

The majority of the evidence came from children of women supplemented with n-3 LCPUFA during pregnancy and/or lactation and from women with a fetus at high risk of allergy (who were supplemented during pregnancy). Most of the trials included in this review were conducted in high-income industrialised countries and the findings are therefore applicable to the most affluent societies where the burden of allergy is known to be high.

IgE-mediated allergies, where both the signs and symptoms of the allergic disease and a positive skin prick test (SPT) and/or radioallergosorbent test (RAST) were present, were reported in two trials ([Furuhjelm 2009](#); [Makrides 2010](#)) and all trials except three ([Lauritzen 2005](#); [Makrides 2009](#); [Ramakrishnan 2010](#)), used medical diagnosis of allergy for the analyses (with IgE status not tested or unknown).

Most allergic responses are mediated by IgE antibodies, specific to the trigger allergen ([Johansson 2001](#); [Sicherer 2012](#)). However, although the presence of IgE antibodies indicates a sensitised state, the most reliable diagnosis of allergic disease should take into account clinical history as well ([Sicherer 2012](#)). Thus, diagnoses involving laboratory tests (RAST), SPT and assessment of clinical symptoms are more reliable than clinical presentation or parental reports (using validated questionnaires), or laboratory reports alone.

As asthma is difficult to diagnose in young children, authors often report 'wheeze' ([Lauritzen 2005](#); [Makrides 2010](#); [Noakes 2012](#); [Ramakrishnan 2010](#)); we therefore included reports of wheeze in asthma outcomes.

The selection of women differed with respect to fish intake, with three trials targeting women with a low fish intake ([Dunstan 2003](#); [Lauritzen 2005](#); [Noakes 2012](#)), while fish intake was not related to inclusion criteria in other trials ([Furuhjelm 2009](#); [Makrides 2009](#); [Makrides 2010](#); [Olsen 1992](#); [Ramakrishnan 2010](#)). One of the reasons for some of the mixed results in this review may be due to the mothers baseline intake of n-3 LCPUFA not being considered in some studies.

In the two trials where there was not an assigned control and women continued their 'usual diet' (Noakes 2012; Olsen 1992), the women in these groups may have had a high intake of dietary n-3 LCPUFA as the benefits of dietary n-3 LCPUFA in pregnancy was promoted in the countries in which these two trials were conducted.

In relation to diet and supplementation, some studies excluded women who were known to be allergic to fish (Dunstan 2003; Olsen 1992), as a safety precaution in case they may have reacted to fish oil capsules. Consequently, not many studies looked at fish allergy and hence data in this area may be limited (Dunstan 2003; Olsen 1992).

The evidence is incomplete for subgroup comparisons on the timing of supplementation, allergy risk of infants and maturity of infants. The trial in which n-3 LCPUFA supplementation started during pregnancy and continued through to lactation was limited by small sample size and high risk of attrition bias (Furuhjelm 2009).

Quality of the evidence

The majority of the comparisons in this review were based on data from two trials (Furuhjelm 2009; Makrides 2010). The quality of the evidence for each of the comparisons greatly depends on the quality of these two trials. However, other primary outcome data regardless of IgE mediation were based on all included trials except Ramakrishnan 2010. The risk of bias varied across the eight included trials with only two trials (Makrides 2009; Makrides 2010) with a low risk of selection, performance and attrition bias.

Women's adherence to the supplementation may also impact on the outcomes. Blood analysis was used to check adherence to the supplementation in most trials (Dunstan 2003; Furuhjelm 2009; Lauritzen 2005; Noakes 2012; Olsen 1992; Makrides 2010), and all reported a significant n-3 LCPUFA increase in the intervention group. The use of fish, rather than fish oil as a supplement also needs consideration as it may contribute to the energy and protein content in the maternal diet and influence outcomes in a different way. In this review we included one trial (Noakes 2012) which supplemented with fish, however this trial had been designed to overcome any additional effect of the diet by using it as a replacement for white fish, chicken and some red meat; thus minimising any additional energy and protein contributions (personal communication Noakes 2012).

Potential biases in the review process

Our search strategy was comprehensive and was not limited by language or publication status. We searched the major international and local bibliographic databases, handsearched major journals and the proceedings of major conferences in the field and set weekly current awareness alerts for a further 44 journals as well as monthly BioMed Central email alerts. We used a clear inclusion criteria and thorough quality assessment methodology to appraise each trial. Two review authors (AWG, CTC) independently screened and appraised the trials, and used pre-designed data extraction forms to extract data. Therefore, biases in the review process are unlikely. Review authors MM and CTC were investigators on two trials (Makrides 2009; Makrides 2010) included in the review. These trials were independently assessed for inclusion, risk of bias and data extracted by AWG and an independent researcher Karen Best (KB).

Agreements and disagreements with other studies or reviews

Two systematic reviews (Klemens 2011; Kremmyda 2011), have been recently published on this topic. Kremmyda 2011 aimed to determine the effect of n-3 LCPUFA supplementation during the perinatal period on allergies (irrespective of IgE status) in children, but did not conduct a meta-analysis. Klemens 2011 conducted a meta-analysis and reported that n-3 LCPUFA supplementation during pregnancy reduced the incidence of childhood asthma but had no effect on atopic dermatitis. Their analysis did not include the most recent trials (Makrides 2009; Makrides 2010; Noakes 2012; Ramakrishnan 2010). Neither of the Klemens 2011 or Kremmyda 2011 reviews separated IgE-mediated allergies from allergies with or without IgE mediation.

AUTHORS' CONCLUSIONS

Implications for practice

Overall, there is limited evidence to support maternal n-3 LCPUFA supplementation during pregnancy and/or lactation for the reduction of allergic disease in the children with few differences seen in allergic disease in children between women who were supplemented with n-3 LCPUFA and those who were not. However, at some time points there were reductions in some outcomes such as IgE-mediated food allergy, IgE-mediated eczema and IgE-mediated any allergy, with n-3 LCPUFA supplementation in women with a fetus at high risk of allergy; therefore, further research is warranted.

Implications for research

As the studies included in this review used differing doses, docosahexaenoic acid (DHA) to eicosapentaenoic acid (EPA) ratios and duration of n-3 LCPUFA supplementation, and did not take into account the baseline n-3 long chain polyunsaturated fatty acid (LCPUFA) status of the women, further research is needed to investigate the influence of these factors on childhood allergic outcomes. Trials should clearly differentiate between children at high risk of allergy and children at low risk of allergy given the suggestion of benefit to children who were at high risk of allergy. Trials should report both IgE-mediated allergy and allergy +/- IgE mediation and should include follow-up into the school years. Studies should also be conducted in other than high-income countries to determine the generalisability of findings.

ACKNOWLEDGEMENTS

To Michael Draper, research librarian University of Adelaide, who developed extra search strategies.

To Karen Best for assessing and data extracting the Makrides 2009; and Makrides 2010 trials.

As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and referee who is external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed

therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]
Dunstan 2003

Methods	Randomised controlled trial. Dunstan 2003 was the main trial with 12 publications at different times with different outcomes. All 12 publications are included in the references to included studies.
Participants	Setting: Australia. 98 pregnant atopic women whose fetus was considered to be at high risk of allergic disease. All women had a history of physician-diagnosed allergic rhinitis and/or asthma and 1 or more positive SPT to common allergens. Exclusions: women who smoked, had other medical problems, complicated pregnancies, seafood allergy or if normal dietary intake exceeded 2 meals of fish per week.
Interventions	Intervention: 4 (1 g) n-3 LCPUFA capsules per day comprising a total of 3.7 g of n-3 LCPUFAs with 56.0% as DHA and 27.7% as EPA to give 2.07 g of DHA and 1.03 g of EPA (n = 52). Control: 4 (1 g) capsules of olive oil per day containing 66.6% n-9 oleic acid and < 1% n-3 LCPUFAs (n = 46). Duration of intervention: 20th week of gestation until delivery.
Outcomes	Dunstan 2003 reported. Primary outcomes: allergen-specific T-cell responses in cord blood.

Dunstan 2003 (Continued)

Secondary outcomes: medically-diagnosed allergies including incidence of asthma, atopic eczema, and food allergy at 1 year of age. The diagnosis of asthma was made in children with recurrent wheezing; i.e. 3 or more episodes with at least 1 episode confirmed by a paediatrician or general practitioner. Atopic eczema diagnosis was made in infants exhibiting typical skin lesions or physician-diagnosed eczema response to topical steroids. The severity was scored according to the modified assessment clinical tool called SCORing Atopic Dermatitis (SCORAD).

The SPT was performed using a standardised technique and allergen extracts (egg, milk, peanut, house dust mite, cat), the positive control was histamine and negative control glycerin, a wheel diameter of ≥ 2 mm was considered positive.

Notes Contacted authors to determine if they diagnosed IgE-mediated allergies - no response received to date.

Supported by grants from the National Health and Medical Research Council and Raine Medical Research Foundation, Australia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The groups were block-randomised according to parity, prepregnancy BMI, age and maternal allergy".
Allocation concealment (selection bias)	Low risk	Quote: "Randomization and allocation of capsules occurred at a different centre separate from the recruitment of participants. Capsules were administered to the participants by someone separate from those doing the allocation".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The capsules in the 2 groups were image matched, and the participants, research scientists, and paediatrician remained blinded to the groups for the duration of the trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, research scientists, and paediatrician remained blinded to the groups for the duration of the trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomised n = 98 (52 intervention, 46 control). At birth 15 (15%) excluded (12 treatment, 3 control): 8 discontinued intervention due to nausea (7 treatment, 1 control), 1 cord blood not collected (control), 4 gestation < 36 weeks (3 treatment, 1 control), 2 unrelated infant disease (treatment), (85% follow-up rate; intervention 77%, control 94%). Outcomes were reported on n = 83 (85%) at 1 year of age (fish oil group n = 40, 77% and control group n = 43, 94%). Of the 83, telephone interviewed n = 11, clinic visit and SPT n = 72.
Selective reporting (reporting bias)	High risk	Trial registered at anzctr.org.au Identifier: ACTRN12611000041954. Prespecified outcomes were reported in this trial according to their protocol. Unable to determine IgE-mediated allergy from results reported although both medically diagnosed allergy and SPT results reported separately (authors contacted for information).
Other bias	Unclear risk	Preterm infants were excluded from their analysis after randomisation.

Furuhjelm 2009

Methods	<p>Randomised controlled trial.</p> <p>Furuhjelm 2009 was the main trial with 6 reports. All 6 publications are included in the references to included studies.</p>
Participants	<p>Setting: Sweden.</p> <p>145 pregnant women who were at high risk of having a baby with atopy were recruited through antenatal care clinics during a 2-year period in 2003–2005. Women were considered at high risk if they, or their husband or an older child had current or previous allergic symptoms, i.e. bronchial asthma diagnosed by a doctor, atopic eczema, allergic food reactions, itching and running eyes and nose on exposure to pollen, pets or other known allergens.</p>
Interventions	<p>Intervention: Women took 9 500 mg capsules a day containing 35% EPA, and 25% DHA, to provide 1.6 g of EPA and 1.1 g of DHA, n = 70.</p> <p>Control: 9 soy oil capsules a day, containing 58% LA to provide 2.5 g LA/day and 6% ALA to provide 0.28 g ALA/day, (n.=.75).</p> <p>Duration of intervention: 25th week of gestation to delivery, encouraged to continue during lactation (average 3 to 4 months).</p>
Outcomes	<p>1. Furuhjelm 2009 reported</p> <p>Medically diagnosed allergy outcomes at 3, 6 and 12 months of age including: IgE antibody analysis, food allergy and eczema.</p> <p>Food allergy was defined as gastrointestinal symptoms, hives, aggravated eczema or wheeze following ingestion of egg or milk in the presence of detectable IgE antibodies or a positive SPT towards the particular food. Recovery from symptoms after elimination of the particular food from the diet and reoccurrence after ingestion of the food was required for the diagnosis. IgE-associated eczema was characterised as reoccurring and itching eczematous, lichenified or nummular dermatitis according to the criteria modified by Oranje 1995 in the presence of detectable IgE antibodies or positive SPT towards egg, milk or wheat.</p> <p>2. Furuhjelm 2011 reported</p> <p>Medically diagnosed allergy outcomes at 2 years of age including: food allergy, eczema, allergic rhinitis, asthma and any allergies with or without IgE associated.</p>
Notes	<p>The trial was supported financially by the Medical Research Council of Southeast Sweden (FORSS), The Östergötland County Council, The Ekhaga Foundation, Swedish Asthma and Allergy Association, The Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning (FORMAS), The Swedish Society of Medicine and Glaxo Smith Kline, Sweden.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The mothers were randomly allocated to dietary supplementation either with ω -3 fatty acids or placebo".
Allocation concealment (selection bias)	Low risk	Quote: "Producer performed the block randomisation". We interpreted this as central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Active and placebo capsules could not be distinguished from each other".

Furuhjelm 2009 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The research nurses, the paediatricians and the person performing the laboratory analyses were blinded during the intervention and follow-up".
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomised n = 145 (70 intervention, 75 control). 25 did not complete the requested 15 week intervention period (16, 23% treatment and 9, 12% placebo) and were excluded from the analysis, 1 withdrew post delivery, 2 not followed as moved before 6/12 follow up (group not stated). Total 28 (19%) not included in analysis, 117 included (81%). SPT 117 (81%) at 6 months, 115 (79%) at 12 months. Medically diagnosed allergy outcomes were reported on n = 117 (81%) (fish oil group n = 52 (74%) and control group n = 65 (87%), at 6 months and at 1 year of age. Medically diagnosed allergy outcomes were reported on n = 119 (82%) (fish oil group n = 54 (77%) and control group n = 65 (87%), at 2 years of age.
Selective reporting (reporting bias)	Low risk	Trial registered at ClinicalTrials.gov identifier: NCT00892684. Prespecified outcomes were reported in this trial according to their protocol. Outcomes of interest to the review are reported.
Other bias	Low risk	No obvious risk of other bias.

Lauritzen 2005

Methods	Randomised controlled trial. Lauritzen 2004 was the main trial with 9 publications at different times with different outcomes. All 9 publications are included in the references to included studies.
Participants	Setting: Denmark. Recruited from among pregnant women recruited for the Danish National Birth Cohort study based on their intake of n-3 LCPUFA. Inclusion criteria included: an uncomplicated pregnancy, pre-pregnancy BMI < 30 kg/m ² , no metabolic disorders, and the intention to breastfeed for at least 4 months. Infants had to be healthy, term and singleton with normal weight for gestation and Apgar score > 7, women with a fish intake below the population median (< 0.4 g n-3 LCPUFA/day) were recruited for the randomised intervention trial (n = 122) and women with a fish intake in the upper quartile (> 0.8 g n-3 LC-PUFA/day) as a high-fish-intake reference group.
Interventions	Intervention: microencapsulated fish oil given in muesli bars. The fish oil supplement provided 1.5 g/day of n-3 LCPUFA (equivalent to 4.5 g/day of fish oil) with 22.8% as DHA and 10% as EPA to provide 0.342 g per day of DHA and 0.15 g per day of EPA. As an alternative, the supplements were offered in homemade cookies or oil capsules (n = 62) Control: microencapsulated olive oil given in muesli bars . As an alternative, the olive oil supplements were offered in homemade cookies or oil capsules (n = 60). Referance group: 64 women with high fish intake (> 0.8 g n-3 LC-PUFA/day). Duration of intervention: 4 months postpartum.
Outcomes	1. Lauritzen 2004 reported

Lauritzen 2005 (Continued)

Primary outcomes - DHA content of breast milk and infant red blood cell membranes at 2 and 4 months of age, and infant visual acuity at 2 and 4 months of age.

2. Lauritzen 2005 reported

Primary outcome - immune function assessed by interferon gamma and interleukin 10 production and plasma immunoglobulin E (IgE).

Secondary outcomes - parent report of doctor diagnosed allergy: food allergy, wheeze, eczema at 2.5 years of age.

Notes

The high fish intake reference group participants were not included in our meta-analysis as this group was not randomised.

The trial was funded by FOTEK-The Danish Research and Development program for Food Technology and BASF Aktiengesellschaft.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After birth, the women with fish intakes below the 50th percentile were randomly assigned to a supplementation group by a randomisation schedule prepared by a person uninvolved in the study".
Allocation concealment (selection bias)	Low risk	Quote: "Owing to the non-identical appearance of the capsules for the two groups, a person who was not otherwise involved in the project handled the capsules in order to avoid breaking the blinding of the investigators".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators and families were blinded to the randomisation".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A person not otherwise involved in the study handled the capsules in order to avoid breaking the blinding of the investigators".
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomised: trial entry n = 122 (intervention 62, control 60). At 2.5 years of age: n = 65 (53%) (fish oil group n = 37 (60%) and control group n = 28 (47%)). Large losses to follow-up, all noted as 'withdrawals' or no reason given.
Selective reporting (reporting bias)	High risk	Trial registered at ClinicalTrials.gov identifier: NCT00266305. Most of the prespecified review outcomes were not reported in this trial.
Other bias	Low risk	No obvious risk of other bias.

Makrides 2009

Methods

Randomised controlled trial - the DINO trial.

Unpublished data reporting outcomes for subgroup of infants whose mothers were providing breast milk at trial entry from [Makrides 2009](#) are included in this systematic review. There are 11 publications,

Makrides 2009 (Continued)

1 thesis and 1 dissertation from this trial. All publications, the thesis and dissertation details are included in the references to included studies.

Participants

Setting: 5 Australian perinatal centres.

Infants born before 33 weeks' gestation and within 5 days of any enteral feeds were eligible to participate (included n = 657 infants and 545 women).

Excluded were infants 1) with major congenital or chromosomal abnormalities, 2) from a multiple birth in which not all live-born infants were eligible, or 3) were in other trials of fatty acid supplementation. Lactating women in whom tuna oil was contraindicated (for example, because of bleeding disorders or therapy with anticoagulants) were also excluded.

To meet the inclusion criteria for this systematic review only infants whose mothers were supplying breast milk at trial entry were included (n = 603 infants; 92% of the 657 randomised to the trial; 297/322, 92% high-DHA and 306/335, 91%, control). A follow-up of the first 143 infants who participated in the pilot phase was conducted at 3 to 5 years corrected age (Simmonds 2007), again only infants whose mothers were providing breast milk at trial entry are included in this systematic review (n = 125).

A follow-up of was conducted at 7 years corrected age and n = 569 children completed ISAAC questionnaires, again only infants whose mothers were providing breast milk at trial entry are included in this systematic review (n = 531).

Interventions

Intervention: lactating women whose infants were randomly assigned to the high-DHA group consumed 6 x 500 mg DHA-rich tuna oil capsules per day which provided 900 mg DHA and 195 mg EPA. The intent was to achieve a breast milk DHA concentration that was ~1% of total fatty acids without altering the naturally occurring concentration of AA in breast milk. If supplementary formula was required, infants were given a high-DHA preterm formula (1% DHA and 0.6% AA).

Control: lactating women with infants allocated to the standard-DHA group consumed 6 500 mg placebo soy oil capsules with no n-3 LCPUFA. If supplementary formula was required in this group, a standard preterm infant formula was used (0.35% DHA and 0.6% AA).

Duration of the intervention: within 5 days from the infant receiving any enteral feeds until infants reached their expected date of delivery.

Outcomes

1. Makrides 2009 reported

Primary outcome: neurodevelopment at 18 months corrected age.

Secondary outcomes: infection outcomes (in-hospital proven late onset sepsis).

2. Manley 2011 reported

Secondary outcomes: parental reported food allergy, eczema, asthma and allergic rhinitis at 18 months corrected age.

3. Simmonds 2007 reported

ISAAC questionnaire was used to collect parent report of allergy diagnosis and parent report of doctor diagnosis eczema, allergic rhinitis and asthma at 3 to 5 years corrected age. (The ISAAC questionnaire is not validated for this age group).

4. Gunaratne 2014 reported

ISAAC questionnaire was used to collect parent report of allergy outcomes at 7 years of corrected age and parent report of allergy outcomes from birth to 7 years of corrected age for eczema, allergic rhinitis and asthma. (The ISAAC questionnaire is validated for this age group.)

Notes

This study was supported by a grant from the Australian National Health and Medical Research Council (grant 250322) and by the Channel 7 Children's Research Foundation of South Australia Inc. Treatment and placebo capsules were donated by Clover Corp and infant formula was donated by Mead Johnson Nutritionals and Nutricia Australasia.

Risk of bias
Bias
Authors' judgement
Support for judgement

Makrides 2009 (Continued)

Random sequence generation (selection bias)	Low risk	Quote "Mother-infant pairs were randomly assigned a unique study number through a computer-driven telephone randomisation service according to an independently generated randomisation schedule. Stratification was by centre, birth weight (1250 grams vs 1250 grams), and infant sex. Multiple births were considered a single randomisation unit and randomisation of twins or triplets was according to the sex and birth weight of the first born infant".
Allocation concealment (selection bias)	Low risk	Central allocation by a computer-driven telephone randomisation service.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote "Parents, clinicians, and all research personnel were blinded to participant study group".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "Parents, clinicians, and all research personnel were blinded to participant study group".
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>A total of 603 infants whose mothers were providing breast milk at trial entry were enrolled in the trial (297 were randomised to the high DHA group and 306 to the control).</p> <p>18 months corrected age: 565 (94%) completed the allergy follow up (274, 92% in the intervention and 291, 95% in the control)</p> <p>3 to 5 years corrected age: 120 infants whose mothers in the pilot phase of the study were providing breast milk at trial entry (55 in intervention and 65 in control), at 3 to 5 years corrected age 110 (92%) completed the allergy follow-up (49, 89% in the intervention and 61, 94% in the control).</p> <p>7 years corrected age: 531 (88%) completed ISAAC questionnaire (260, 87.5% in the intervention and 271, 88.6% in the control)</p>
Selective reporting (reporting bias)	High risk	<p>Trial registered at anzctr.org.au Identifier: ACTRN12606000327583.</p> <p>Most of the prespecified review outcomes were not reported in this trial.</p>
Other bias	Unclear risk	The children included in this review were a subgroup of the primary DINO trial and included children of mothers who were providing breast milk at trial entry, 92% of the infants randomised to the primary trial met this criteria.

Makrides 2010

Methods	<p>Randomised controlled trial.</p> <p>Makrides 2010 was the main trial with 10 publications. All 10 publications and 1 thesis are included in the references to included studies.</p>
Participants	<p>Setting: Australian maternity hospitals.</p> <p>Recruitment to primary 'DOMInO' trial (Makrides 2010): women with singleton pregnancies at less than 21 weeks' gestation.</p> <p>Excluded were women already taking a prenatal supplement with DHA, with a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, fetus had a known major abnor-</p>

Makrides 2010 (Continued)

mality, or were unable to give written informed consent or if English was not the main language spoken at home (n = 2399).

Pregnant women were approached to enter the allergy follow-up ([Palmer 2012](#)) after randomisation into the DOMInO trial. Only Adelaide-based women were eligible for the allergy follow-up. Women were eligible if the unborn baby had a mother, father, or sibling with a history of any medically diagnosed allergic disease (asthma, allergic rhinitis, eczema) (n = 706).

Interventions	<p>Intervention: 3 x 500 mg capsules daily of DHA rich fish oil concentrate, providing 800 mg of DHA and 100 mg of EPA per day.</p> <p>Control: 3 500 mg vegetable oil capsules daily without DHA.</p>
Outcomes	<p>1. Makrides 2010 reported</p> <p>Primary outcome - maternal postnatal depression at 6 weeks and 6 months; child neurodevelopment at 18 months of age.</p> <p>Secondary outcomes included a range of clinical outcomes including postpartum haemorrhage.</p> <p>2. Palmer 2012 reported</p> <p>Primary outcome: At 1 year of age</p> <p>1) IgE-associated allergic diseases including: food allergy, eczema, asthma, allergic rhinitis and any allergy with sensitisation .</p> <p>2) Medically diagnosed allergic diseases with or without IgE-mediated allergic diseases including: food allergy, eczema, asthma/wheeze, allergic rhinitis and any allergy with or without sensitisation based on medically diagnosed allergy at the age of 1 year.</p> <p>Secondary outcomes included IgE sensitisation - SPT at 1 year of age. Infants with respiratory tract infections between birth and 1 year.</p> <p>3. Palmer 2013 reported</p> <p>the 3-year follow-up of the same children in Palmer 2012 to evaluate medically diagnosed allergy.</p> <p>Reported IgE-associated allergic diseases including food allergy, eczema, asthma, allergic rhinitis and any allergy with sensitisation at 3 years of age.</p> <p>Obtained medically diagnosed allergic diseases with or without IgE-mediated allergic diseases including: food allergy, eczema, asthma/wheeze, allergic rhinitis and any allergies with or without sensitisation at the age of 3 years.</p> <p>4. Gunaratne 2014 reported</p> <p>parental reports of doctor diagnosed allergy outcomes including food allergy, eczema, asthma, allergic rhinitis and any allergy below 36 months of age. Modified ISAAC questions were used to collect parent report of doctor diagnosed eczema, allergic rhinitis and asthma from birth to 3 years of age. (The ISAAC questions are not validated for this age group.)</p>

Notes Supported by grants from the Australian National Health and Medical Research council and Australian Egg Corporation Limited. Treatment and placebo capsules were donated by Efamol, UK.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote " Women were randomly allocated to a unique number that corresponded to treatment or control through a computer driven telephone ran-

Makrides 2010 (Continued)

		domisation service according to an independently generated randomisation schedule, with balanced variable sized blocks. Stratification was by centre and parity".
Allocation concealment (selection bias)	Low risk	Computer-driven telephone randomisation service.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To maintain the blind, both active and placebo capsules were identical in appearance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neither the parents nor the research staff were aware of the treatment allocated. Described as "double-blind".
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>681/706 (96.5%) infants (intervention: 357/368, 97%, placebo: 324/338, 96%) attended their 1-year medical review and 666/706 (94.3%) infants had SPT results. Missing data were imputed for all IgE-mediated allergy outcomes and medically diagnosed food allergy, eczema and any allergy but not imputed for medically diagnosed asthma (wheeze) and allergic rhinitis. In secondary outcomes missing data were imputed for egg, cow's milk, peanut and any SPT sensitisation but not for wheat, fish, pollen, house dust mite and cat allergens.</p> <p>638/706 (90.4%) infants (intervention: 333/368, 90.5% placebo: 305/338, 90.2%) attended their 3-year medical review and 587/706 (83.1%) infants had SPT results; missing data were imputed for all IgE-mediated allergy outcomes and medically diagnosed food allergy, eczema and any allergy but not imputed for medically diagnosed asthma (wheeze) and allergic rhinitis. In secondary outcomes missing data were imputed for egg, wheat, peanut, fish, cat and any allergens but not for pollens and house dust mite allergens. Parent reported allergy: below 12 months of age - 695/706 (98.4%) (intervention: 362/368, 98.4%, placebo: 335/338, 99%), between 12- 36 months of age - 698/706 (99%), (intervention: 365/368, 99%, placebo: 333/338, 98.5%) and at 36 months of age - 638/706 (90%) (intervention: 333/368, 90.5%, placebo: 305/338, 90%) were available. Missing data were not imputed for any parent reported allergy outcomes.</p> <p>Results using imputed data were reported to differ little from raw data (Palmer 2012; Palmer 2013).</p>
Selective reporting (reporting bias)	Low risk	<p>Trial registered at anzctr.org.au Identifier: ACTRN12605000569606</p> <p>Prespecified outcomes were reported in this trial according to their protocol. Most of the outcomes of interest to the review are reported.</p>
Other bias	Unclear risk	Of the original DOMInO trial (n = 2399), a subgroup of mothers whose unborn child had a family history of allergies were included.

Noakes 2012

Methods	Randomised controlled trial.
	Miles 2011 was the main trial with 13 reports. All 13 publications are included in the references to included studies.
Participants	Setting: United Kingdom.

Noakes 2012 (Continued)

Women aged 18 to 40 years who were at 19 weeks' gestation with a healthy uncomplicated pregnancy who reported low habitual consumption of oily fish (2 portions/month excluding canned tuna and no use of fish oil supplements in previous 3 months) and had a family history of atopy (1 or more first-degree relatives of the infant affected by atopy, asthma, or allergy) were recruited to the trial (n = 123). Excluded were those participating in another research study, known diabetes, autoimmune disease, learning disability, terminal illness or mental health problems.

Interventions

Intervention: women in the salmon group (n = 62) were asked to incorporate 2 portions of salmon (300 g) which contained 7.12 g total n-3 LCPUFAs (1.14 g EPA/week and 2.32 g DHA/week) into their diet from week 20 (trial entry) until they gave birth. Women and their partners were provided with 2 portions of salmon per week to incorporate into their diet. They also received a cookbook that provided recipes for preparing and cooking salmon. Each portion of salmon was to replace a serve of protein (e.g. white fish, chicken or red meat).

Control: women in the control group were asked to continue their habitual diets; these women received the information sheet that described the possible health benefits of consuming oily fish during pregnancy and the government recommendation that pregnant women consume 1 or 2 oily fish meals/week. They also received a cookbook providing recipes for healthy eating during pregnancy.

Outcomes

1. [Miles 2011](#) reported

Primary outcome - determine the effect on maternal and umbilical cord plasma n-3 LCPUFA content.

2. [Noakes 2012](#) reported

Effect on neonatal immune responses and diagnosis, by research nurse, of eczema and wheeze at 6 months of age.

Chest infections and SPT at 6 months of age.

Notes

Supported by the European Commission under Framework 6: Sustainable aqua feeds to maximize the health benefits of farmed fish for consumers (Aquamax; FOOD-CT-2006-16249). 2 researches were supported by the Southampton NIHR Biomedical Research Unit in Nutrition, Diet & Lifestyle. Salmon was donated by the University of Bergen, Norway.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "The women were allocated to one of two groups according to a previously generated random number table".
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers responsible for assessing outcome measures (both laboratory and clinical) remained blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Enrolled 123 (62 salmon, 61 control). At delivery: 107 (87%): 53 (85%) salmon, 54 (89%) control. Birth samples: 101 (82%): 51 (82%) salmon, 50 (82%) control. 6-month clinic visit: 86 (70%): 48 (77%) salmon, 38 (62%) control.

Noakes 2012 (Continued)

Selective reporting (reporting bias)	High risk	Trial registered at clinicaltrials.gov as NCT00801502. Only limited data were reported on some of the prespecified review outcomes.
Other bias	Low risk	There is no obvious risk of other bias.

Olsen 1992

Methods	Randomised controlled trial. Olsen 1992 was the main trial with 16 publications. All 16 publications are included in the references to included studies.
Participants	Setting: Denmark. Pregnant women were recruited from the midwife clinic at 30 weeks' gestation. Excluded were women with a history of placental abruption in a previous pregnancy or a serious bleeding episode in the present pregnancy, women who used prostaglandin inhibitors regularly, multiple pregnancies, allergy to fish, and regular intake of fish oil (n = 533).
Interventions	Intervention: 4 x 1 g fish oil capsules daily containing 32% EPA and 23% DHA to provide 1.28 g EPA and 0.92 g DHA. Control group 1: 4 x 1 g capsules of olive oil daily. Control group 2: no supplement. Duration of intervention: 30th week of gestation until delivery.
Outcomes	1. Olsen 1992 reported Primary outcome - pregnancy duration. Secondary outcomes included side effects and complications including postpartum bleeding. 2. Olsen 2008 reported Primary outcome - asthma at 16 years of age. Secondary outcomes - combined outcome of asthma, atopic dermatitis and allergic rhinitis at 16 years of age. Medically diagnosed (from a mandatory registry that recorded diagnoses from hospitals in Denmark) allergy outcomes.
Notes	For this systematic review control groups 1 and 2 were combined to compare with the intervention group (see 'Risk of bias' table).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "Women were randomly assigned to the three groups in the ratio 2/1/1. Randomisation was stratified by parity and arranged in balanced blocks of between 8 and 12".

Olsen 1992 (Continued)

Allocation concealment (selection bias)	Low risk	Quote "Sealed, opaque envelope for that study number contained a randomisation number that either identified a particular package of oil capsules or showed that the woman should receive no oil supplement".
Blinding of participants and personnel (performance bias) All outcomes	High risk	While group 1 and 2 were blinded, group 3 received no supplement and were therefore unblinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent evaluation, registry based diagnosis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomised 533 (intervention 266; olive oil 136; and no oil 131). Assessed at 16 years 528 (99%) (intervention 263; olive oil 136; and no oil 129).
Selective reporting (reporting bias)	High risk	Trial registered at ClinicalTrials.gov identifier: NCT01353807. Most of the prespecified outcomes were reported in this trial according to their protocol. However, outcomes of interest to the review are not reported completely. Only limited data were reported on some of the prespecified review outcomes.
Other bias	Low risk	Placebo group and no oil group were combined in the review. Analyses were conducted with the n-3 LCPUFA supplementation group compared to olive oil control group separately to n-3 LCPUFA supplementation group compared to no supplement control group, although the direction of effect differed it made little difference to the meta-analysis.

Ramakrishnan 2010

Methods	Randomised controlled trial. Ramakrishnan 2010 was the main trial with 14 publications. All 14 publications are included in the references to included studies.
Participants	Setting: Mexico. Women were recruited at the Mexican Institute of Social Security (Instituto Mexicano del Seguro Social [IMSS]) General Hospital in Cuernavaca, Mexico, and 3 small health clinics within the IMSS system in Cuernavaca during routine prenatal care visits. Women were recruited for inclusion in the study if they were in gestation week 18 to 22, were aged 18 to 35 years, planned to deliver at the IMSS General Hospital in Cuernavaca, planned to predominantly breastfeed for at least 3 months, and planned to live in the area for 2 years after delivery. Women were excluded, if they had a (1) high-risk pregnancy, (2) lipid metabolism/ absorption disorders, (3) regular intake of fish oil or DHA supplements, or (4) chronic use of certain medications. (n = 1094)
Interventions	Intervention: 2 200 mg capsules daily of DHA rich algal oil concentrate, providing 400 mg of DHA per day. Control: 2 200 mg corn oil and soy oil capsules daily without DHA.
Outcomes	Ramakrishnan 2010 reported Primary outcome measures: birth size and gestational age. Imhoff-Kunsch 2011

Ramakrishnan 2010 (Continued)

Outcome measures: immune function and morbidity.

Parental reports of wheeze were reported at 1 month, 3 months and 6 months of age . A non-validated questionnaire was used to collect data.

Upper respiratory tract infections and fever were reported at 1 month, 3 months and 6 months of age.

[Escamilla-Nunez 2014](#)

Outcome measures: respiratory symptoms in children at 18 months of age (reported as incidence rate according to atopy).

Notes

Contacted authors to obtain incidence of 18 month allergy outcomes.

The research was supported by NIH (HD-043099) and the March of Dimes foundation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "All eligible women were randomly assigned to either the treatment or the control group by use of a computer generated list created by the study biostatistician at Emory University. We used block randomization to create balanced replicates of 4 treatments (2 colors for DHA and 2 for control) using a block size of 8".
Allocation concealment (selection bias)	Unclear risk	It is likely that participants and investigators enrolling participants could not foresee assignment because the assignment codes were placed in sealed envelopes and kept in a sealed location administered by a faculty member of the university who was not involved in the study. It is not stated if they were sequentially numbered nor if they were opaque.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants and members of the study team were blinded to the treatment scheme throughout the intervention period of the study. Capsules were similar in appearance and taste.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "Data were unblinded for the analytical study team after the last infant in the study was born and had reached the age of 6 months at which time the participants were no longer taking supplements".
Incomplete outcome data (attrition bias) All outcomes	Low risk	1094 randomised, 834 assessed at 6 months - 76% follow-up rate, similar between intervention (77%) and control (76%) At 18 months, 869 assessed according to mother atopy and treatment group - 82% follow-up rate, similar between intervention (80%) and control (78%). 54 randomised but did not begin treatment, 67 withdrew after beginning treatment (lack of family support, moved from area, disliked flavour, heartburn, nausea).
Selective reporting (reporting bias)	High risk	ClinicalTrials.gov Identifier:NCT00646360. Most of the prespecified outcomes were reported in this trial according to their protocol. However, outcomes of interest to the review are reported incompletely and so cannot be used.
Other bias	Low risk	No obvious risk of other bias.

AA: arachidonic acid

ALA: alpha-linolenic acid
 BMI: body mass index
 DHA: docosahexaenoic acid
 EPA: eicosapentaenoic acid
 g: gram
 IgE: immunoglobulin E
 LA: linolenic acid
 PUFA: polyunsaturated fatty acids
 SPT: skin prick test
 vs: versus

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bergmann 2008	Excluded because the trial did not report allergy outcome of the infants and/or children.
Campos-Martinez 2012	Excluded because this trial published as an abstract and did not report allergy outcome of the infants and/or children.
Carlson 2013	Excluded because the trial did not report allergy outcome of the infants and/or children.
Colombo 2004	Excluded because the trial did not report allergy outcome of the infants and/or children.
Courville 2011	Excluded because this trial did not report allergy outcome of the infants and/or children.
Granot 2011	Excluded because the trial did not report allergy outcome of the infants and/or children.
Hauner 2009	Excluded because the trial does not report allergy outcome of the infants and/or children.
Helland 2001	Excluded because the trial did not report allergy outcome of the infants and/or children.
Innis 2007	Excluded because the trial did not report allergy outcome of the infants and/or children.
Judge 2007	Excluded because the trial did not report allergy outcome of the infants and/or children.
Karlsson 2010	Excluded because the trial did not report allergy outcome of the infants and/or children.
Knudsen 2006	Excluded because the trial reported only timing of spontaneous delivery.
Krauss-Etschmann 2007	Excluded because the trial did not report allergy outcome of the infants and/or children.
Martin-Alvarez 2012	Excluded because the trial published as an abstract and did not report allergy outcome of the infants and/or children.
Pena-Quintana 2011	Excluded because this trial published as an abstract and did not report allergy outcome of the infants and/or children.
Ribeiro 2012	Excluded because the trial did not report allergy outcome of the infants and/or children.

Characteristics of ongoing studies [ordered by study ID]

[Bisgaard 2012](#)

Trial name or title	
	Fish oil supplementation during pregnancy for prevention of asthma, eczema and allergies in childhood: interventional trial in the COPSAC2010

Bisgaard 2012 (Continued)

Methods	Randomised controlled trial.
Participants	Pregnant women from week 24.
Interventions	n-3 fatty acid start from week 24 gestation to 1 week after delivery. Olive oil start from week 26 gestation to 1 week after delivery.
Outcomes	Primary outcome measures: development of wheezy disorder from 0 to 3 years of age [time-frame: 3 years]. Development of eczema from 0 to 3 years of age [time frame: 3 years]. Sensitisation at 18 months of age [time frame: 18 months] Secondary outcome measures: development of asthma exacerbations from 0 to 3 years of age [time frame: 3 years]. Infections from 0 to 3 years of age [time frame: 3 years]. Growth [time frame: 0 to 3 years of age]. Cognitive, language and motor development [time frame: 2½ years].
Starting date	November 2008.
Contact information	Hans Bisgaard, MD, DMSc, Copenhagen University Hospital of Copenhagen, Gentofte, Denmark, 2820.
Notes	ClinicalTrials.gov identifier: NCT00798226.

Duchen 2012

Trial name or title	Combined dietary supplementation with <i>Lactobacillus reuteri</i> and omega-3 PUFA during pregnancy and postnatally in relation to development of IgE-associated disease during infancy
Methods	Randomised controlled trial.
Participants	Pregnant women.
Interventions	Dietary supplement: placebo. Dietary supplement: omega-3 fatty acids. Dietary supplement: refined coconut and peanut oil without <i>L. reuteri</i> . Dietary supplement: <i>L. reuteri</i> .
Outcomes	Primary outcome measures: IgE-associated disease [time frame: 2 years of age]. A food reaction is defined as gastrointestinal symptoms, hives, aggravated eczema or wheezing following ingestion of a certain food with recovery after food elimination from the diet and reoccurrence of symptoms after ingestion of the particular food. Eczema is characterised as reoccurring, itching eczematous and lichenified or nummular dermatitis. Doctor diagnosed wheezing at least 3 times during the first 2 years is required for the diagnosis of asthma. If specific positive SPT or serum IgE antibodies is present, the food reaction, eczema is defined as IgE associated. Secondary outcome measures: maternal gastrointestinal function [time frame: 20th gestational week to 6 months postpartum]. Maternal gastrointestinal function will be addressed by validated diary cards. The mothers will record every single stool, stool consistency, and corresponding defecatory symptoms (urgency, straining, and feeling of incomplete evacuation) for 7 days at gestational week 25 and 35. Stool consistency will be defined by the Bristol Stool Form Scale. The mothers will also record every meal, and episodes (start and ending time) of abdominal pain and bloating.

Duchen 2012 (Continued)

Starting date	March 2012.
Contact information	Karel M Duchén, MD, PhD, Allergicentrum, Universitetssjukhuset, Linköping, Sweden, 58185. Tel +46-10-103 1355.
Notes	ClinicalTrials.gov Identifier: NCT01542970.

Laitinen 2013

Trial name or title	Nutrition and pregnancy intervention study
Methods	Randomised controlled trial.
Participants	Pregnant obese women.
Interventions	Dietary supplement: comparison of probiotics, fish oil and their combination to placebo.
Outcomes	<p>Primary outcome measures: prevalence of GDM [time frame: assessed at gestational weeks 24-28]. Fasting glucose levels [time frame: assessed at the third trimester of pregnancy]. Prevalence of allergy in child [time frame: assessed at 12 and 24 months of age]. Secondary outcome measures: need for medication for management of gestational diabetes mellitus GDM (insulin or metformin) [time frame: during pregnancy].</p> <p>Body composition of mother [time frame: during and after pregnancy]. Immunologic and metabolic markers [time frame: during and after pregnancy]. Fecal microbiota [time frame: before, during and after intervention]. Other outcome measures: body composition, growth, development and metabolic markers of the child [time frame: 0 to 24 months of age].</p>
Starting date	September 2013.
Contact information	Kirsi Laitinen, Adjunct professor, Turku University Hospital, Turku, Finland, 20521, + 358 02 333 6063, kirsi.laitinen@utu.fi
Notes	ClinicalTrials.gov identifier: NCT01922791.

Liu 2013

Trial name or title	The effects of polyunsaturated fatty acids (PUFA) on allergic/atopic dermatitis
Methods	November 2013.
Participants	Pregnant women between 16 and 20 weeks.
Interventions	Dietary supplement: DHA + EPA. Dietary supplement: high olive oil. Dietary supplement: DHA.
Outcomes	<p>Primary outcome measures: lipid analysis [time frame: baseline, delivery, within 1 week after delivery, 6 weeks postpartum, 4 months postpartum]. Metabolomics study of PUFA [time frame: baseline, delivery, within 1 week after delivery, 6 weeks postpartum, 4 months postpartum, 12 months postpartum]. Skin prick test to common allergens [time frame: 4 months postpartum, 12 months postpartum].</p>

Liu 2013 (Continued)

Clinical assessment of IgE-mediated allergic eczema [time frame: 4 months postpartum, 12 months postpartum].
 Secondary outcome measures: fatty acid desaturase (FADS) phenotypes [time frame: baseline].
 Immunoglobulin E (IgE) antibodies [time frame: baseline].
 Immunological biomarkers [time frame: 4 months postpartum, 12 months postpartum].
 Medically-confirmed adverse events collected throughout the study period [time frame: 12 months postpartum].

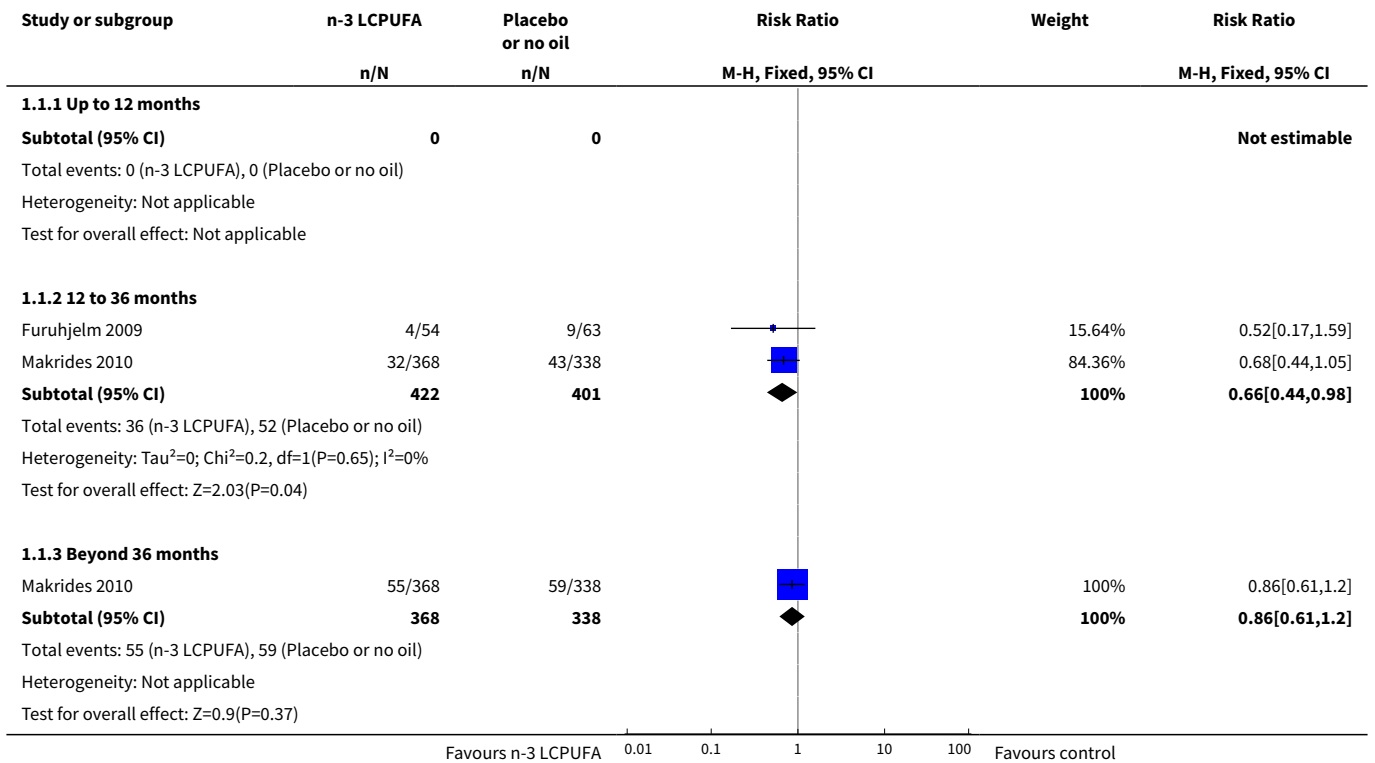
Starting date	November 2013.
Contact information	Huimin Liu, International Peace Maternity and Child Health Hospital of China welfare Institute, Shanghai, Shanghai, China, 200030, 86-20-82156129, huimin.liu@mjn.com
Notes	ClinicalTrials.gov Identifier:NCT01936194.

GDM: gestational diabetes mellitus
 DHA: docosahexaenoic acid
 EPA: eicosapentaenoic acid
 PUFA: polyunsaturated fatty acids
 SPT: skin prick test

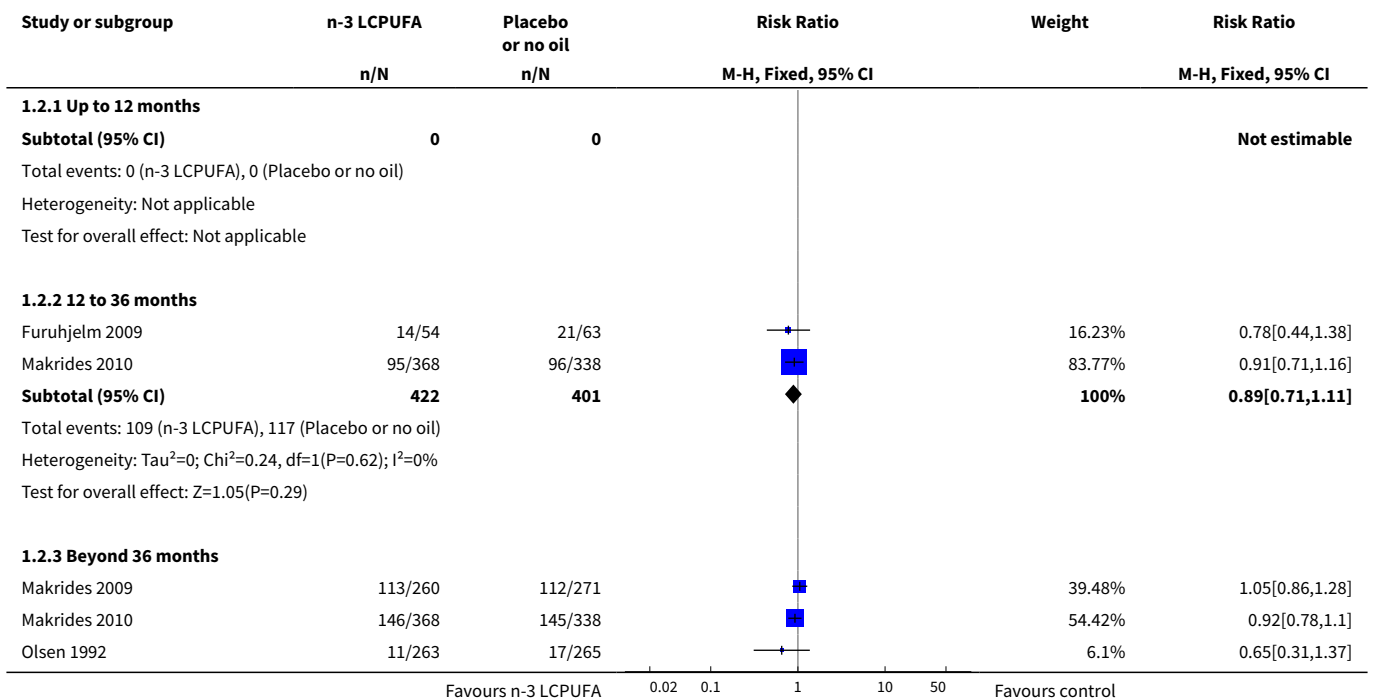
DATA AND ANALYSES
Comparison 1. n-3 LCPUFA supplementation versus placebo or no supplementation - any allergy

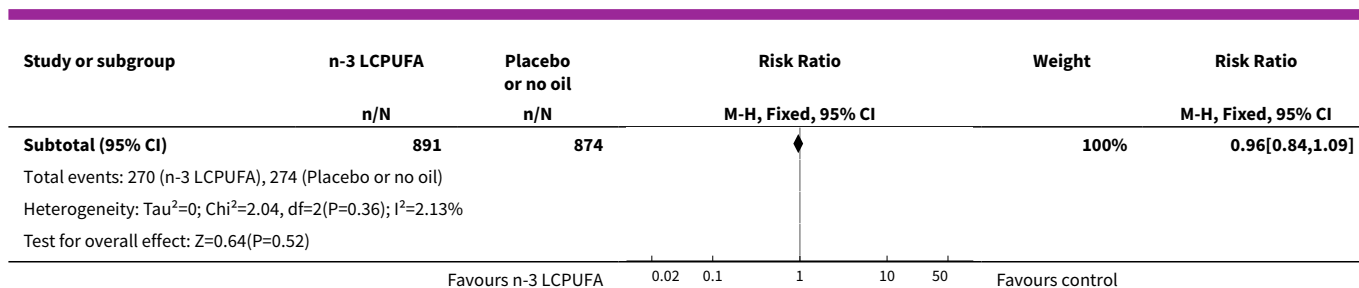
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergies (with sensitisation): medically diagnosed IgE mediated	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Up to 12 months	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 12 to 36 months	2	823	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.44, 0.98]
1.3 Beyond 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.61, 1.20]
2 Any allergies (+/- sensitisation): medically diagnosed/parental re-reported	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Up to 12 months	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 12 to 36 months	2	823	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.71, 1.11]
2.3 Beyond 36 months	3	1765	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.09]

Analysis 1.1. Comparison 1 n-3 LCPUFA supplementation versus placebo or no supplementation - any allergy, Outcome 1 Any allergies (with sensitisation): medically diagnosed IgE mediated.



Analysis 1.2. Comparison 1 n-3 LCPUFA supplementation versus placebo or no supplementation - any allergy, Outcome 2 Any allergies (+/- sensitisation): medically diagnosed/parental reported.



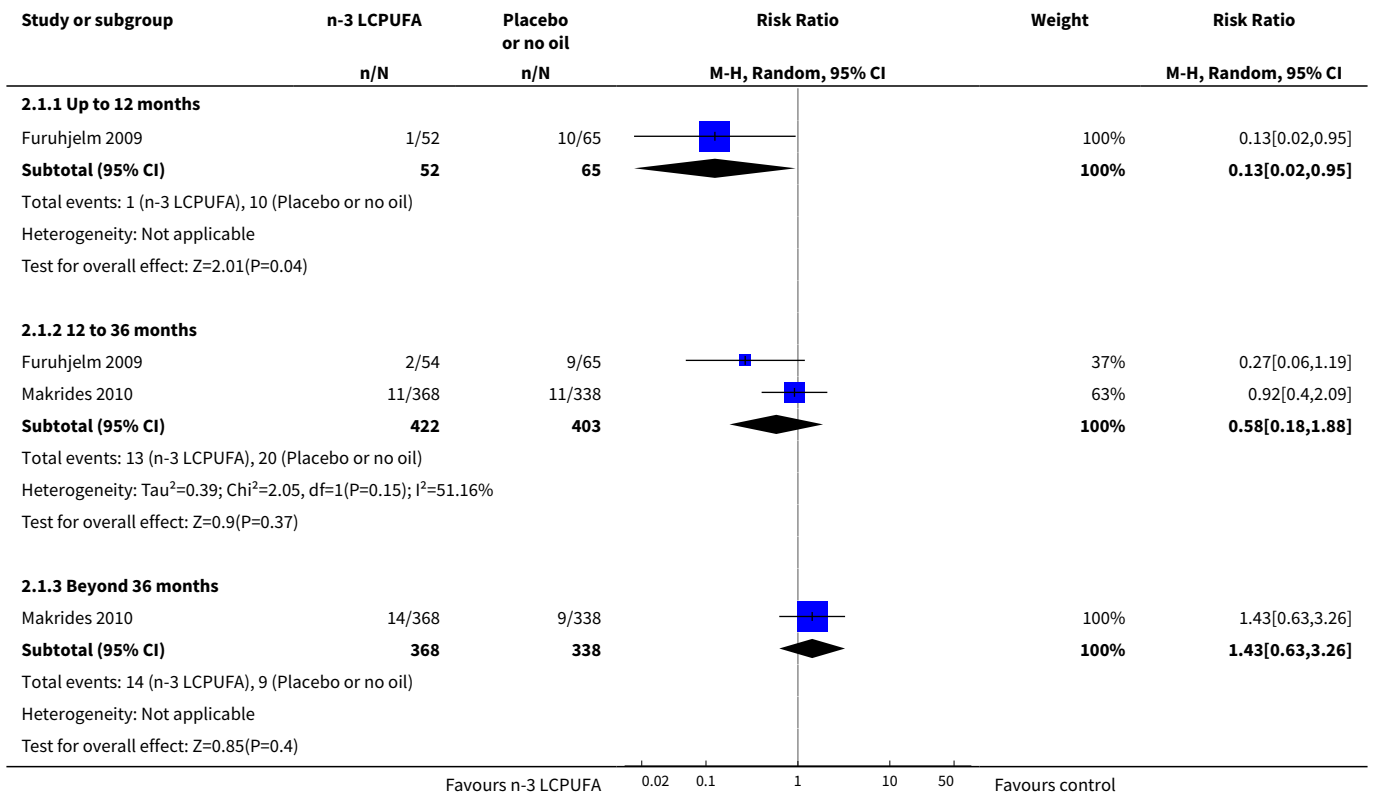


Comparison 2. n-3 LCPUFA supplementation versus placebo or no supplementation - specific forms of allergy

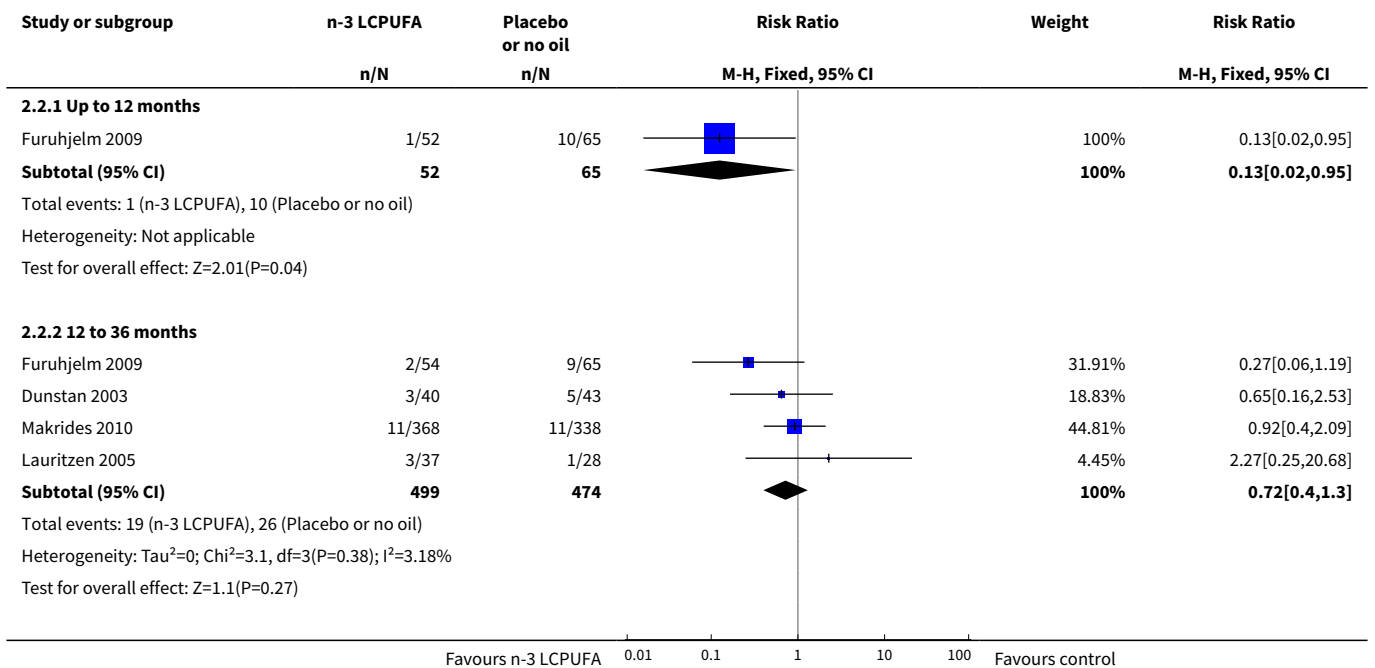
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Food allergies (with sensitisation): medically diagnosed IgE mediated	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Up to 12 months	1	117	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.02, 0.95]
1.2 12 to 36 months	2	825	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.18, 1.88]
1.3 Beyond 36 months	1	706	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.63, 3.26]
2 Food allergies (+/- sensitisation): medically diagnosed/parental reported	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Up to 12 months	1	117	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.02, 0.95]
2.2 12 to 36 months	4	973	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.40, 1.30]
2.3 Beyond 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.63, 3.26]
3 Atopic dermatitis/Eczema (with sensitisation): medically diagnosed IgE mediated	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Up to 12 months	1	117	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.13, 1.11]
3.2 12 to 36 months	2	823	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.39, 0.95]
3.3 Beyond 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.57, 1.23]
4 Atopic dermatitis/Eczema (+/- sensitisation): medically diagnosed/parental reported	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Up to 12 months	2	203	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.22, 2.62]

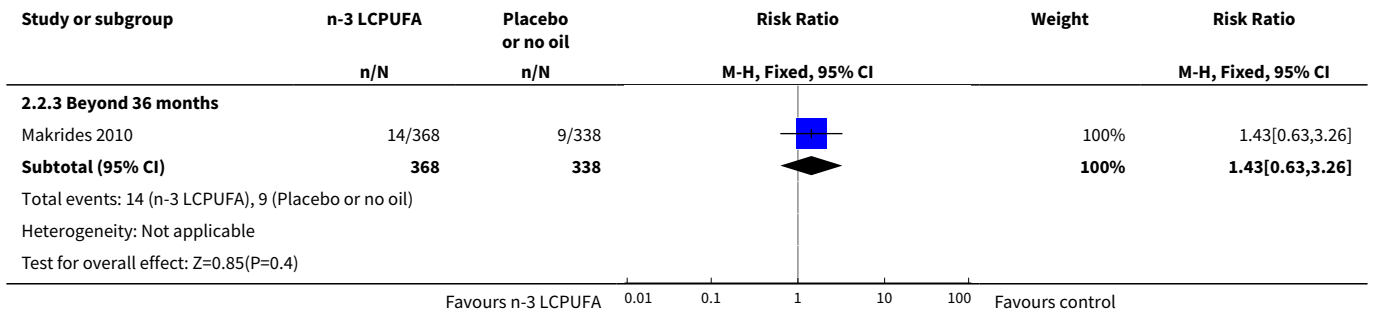
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 12 to 36 months	4	973	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.69, 1.33]
4.3 Beyond 36 months	2	1237	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.68, 1.13]
5 Allergic rhinitis/Hay fever (with sensitisation): medically diagnosed IgE mediated	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Up to 12 months	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 12 to 36 months	2	825	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.07, 3.06]
5.3 Beyond 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.44, 1.54]
6 Allergic rhinitis/Hay fever (+/- sensitisation): medically diagnosed/parental reported	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Up to 12 months	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 12 to 36 months	2	805	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.25, 1.12]
6.3 Beyond 36 months	2	1169	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.81, 1.30]
7 Asthma/Wheeze (with sensitisation): medically diagnosed IgE mediated	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Up to 12 months	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 12 to 36 months	2	824	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.21, 3.49]
7.3 Beyond 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.34, 3.58]
8 Asthma/Wheeze (+/- sensitisation): medically diagnosed/parental reported	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Up to 12 months	1	83	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.54, 2.94]
8.2 12 to 36 months	4	955	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.73, 1.18]
8.3 Beyond 36 months	3	1697	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.13]

Analysis 2.1. Comparison 2 n-3 LCPUFA supplementation versus placebo or no supplementation - specific forms of allergy, Outcome 1 Food allergies (with sensitisation): medically diagnosed IgE mediated.

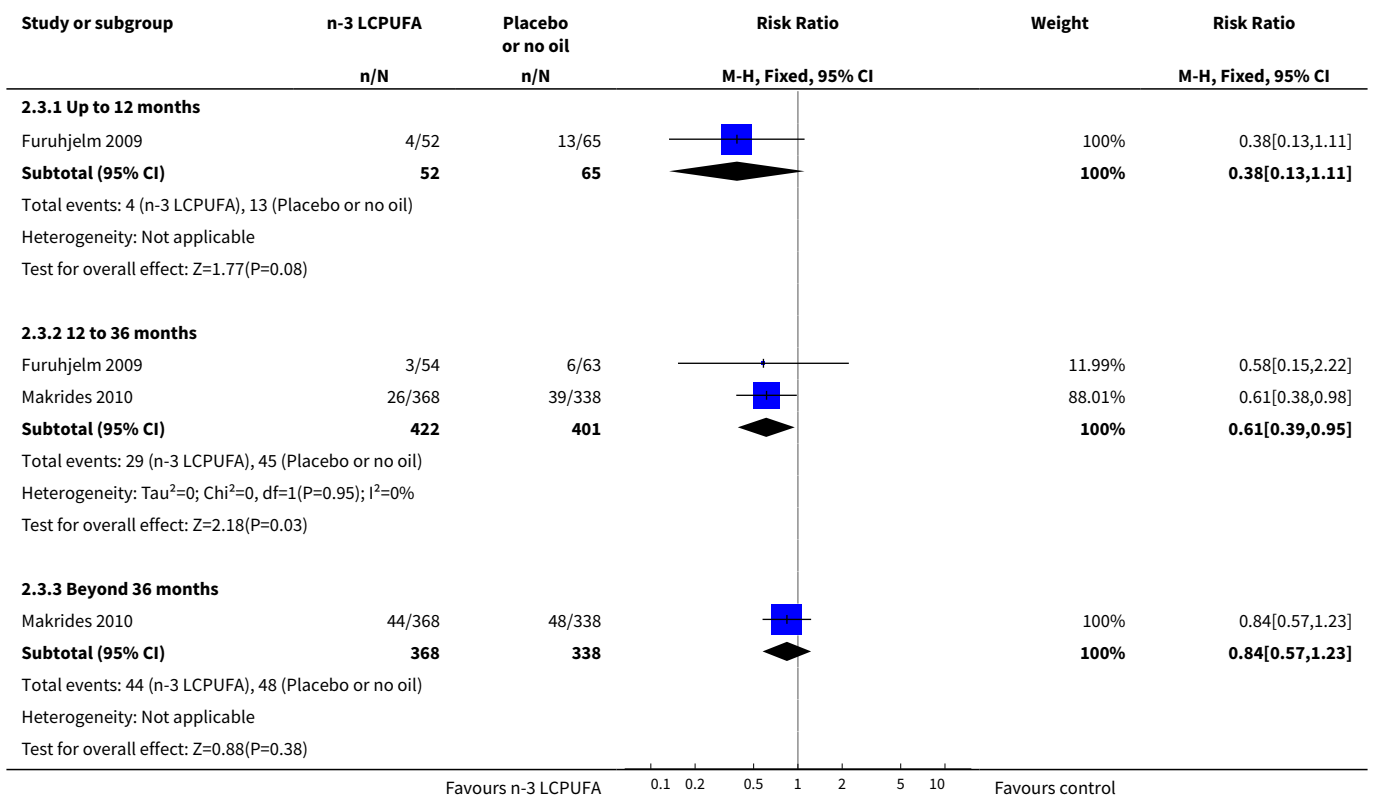


Analysis 2.2. Comparison 2 n-3 LCPUFA supplementation versus placebo or no supplementation - specific forms of allergy, Outcome 2 Food allergies (+/- sensitisation): medically diagnosed/parental reported.

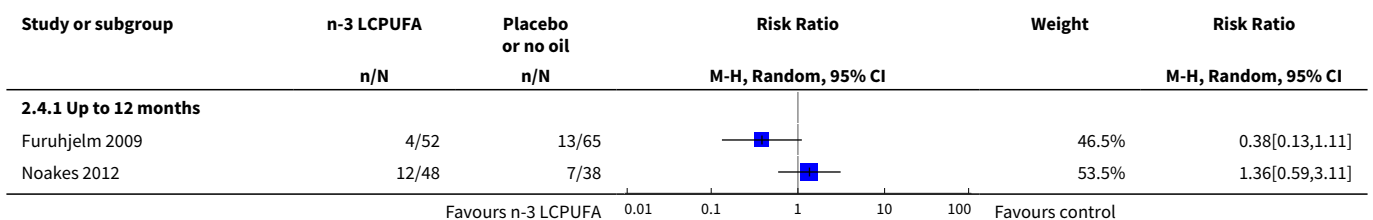


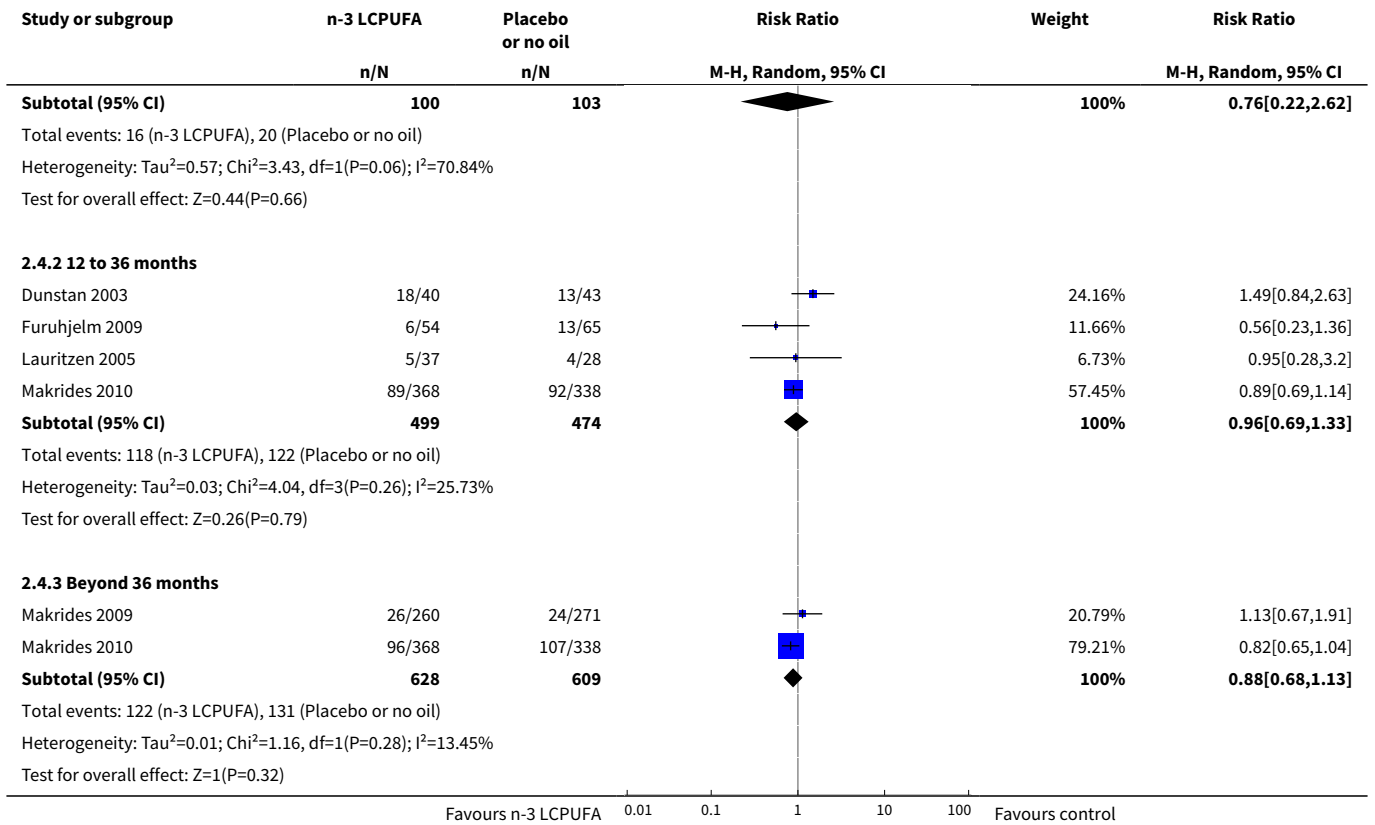


Analysis 2.3. Comparison 2 n-3 LCPUFA supplementation versus placebo or no supplementation - specific forms of allergy, Outcome 3 Atopic dermatitis/Eczema (with sensitisation): medically diagnosed IgE mediated.

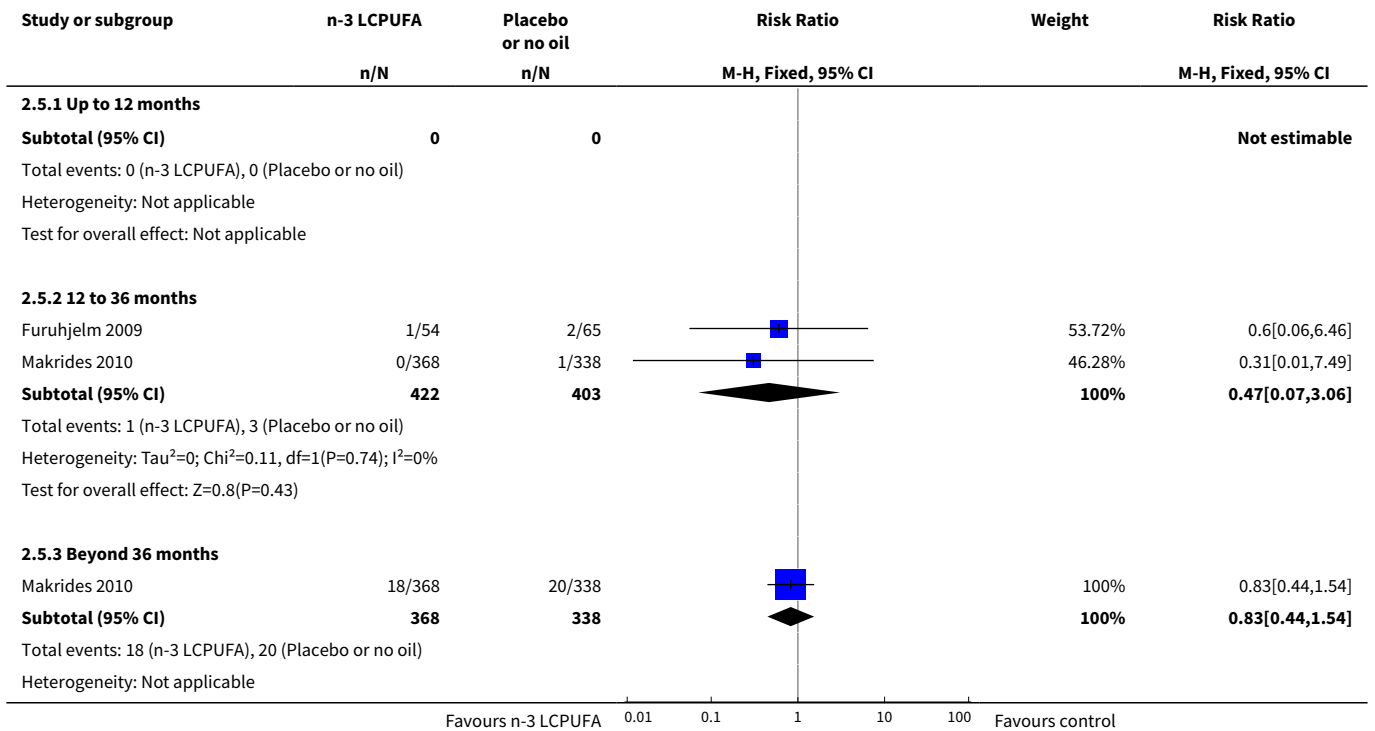


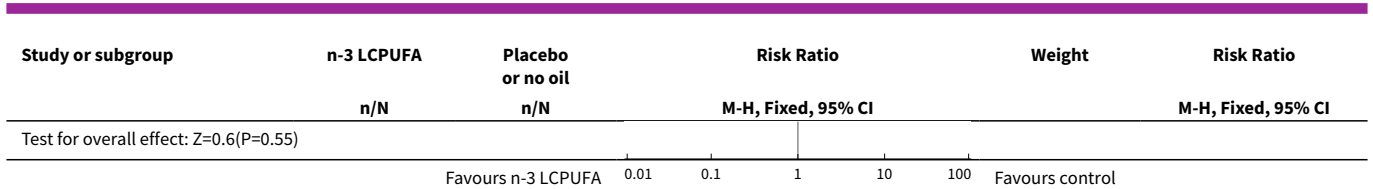
Analysis 2.4. Comparison 2 n-3 LCPUFA supplementation versus placebo or no supplementation - specific forms of allergy, Outcome 4 Atopic dermatitis/Eczema (+/- sensitisation): medically diagnosed/parental reported.



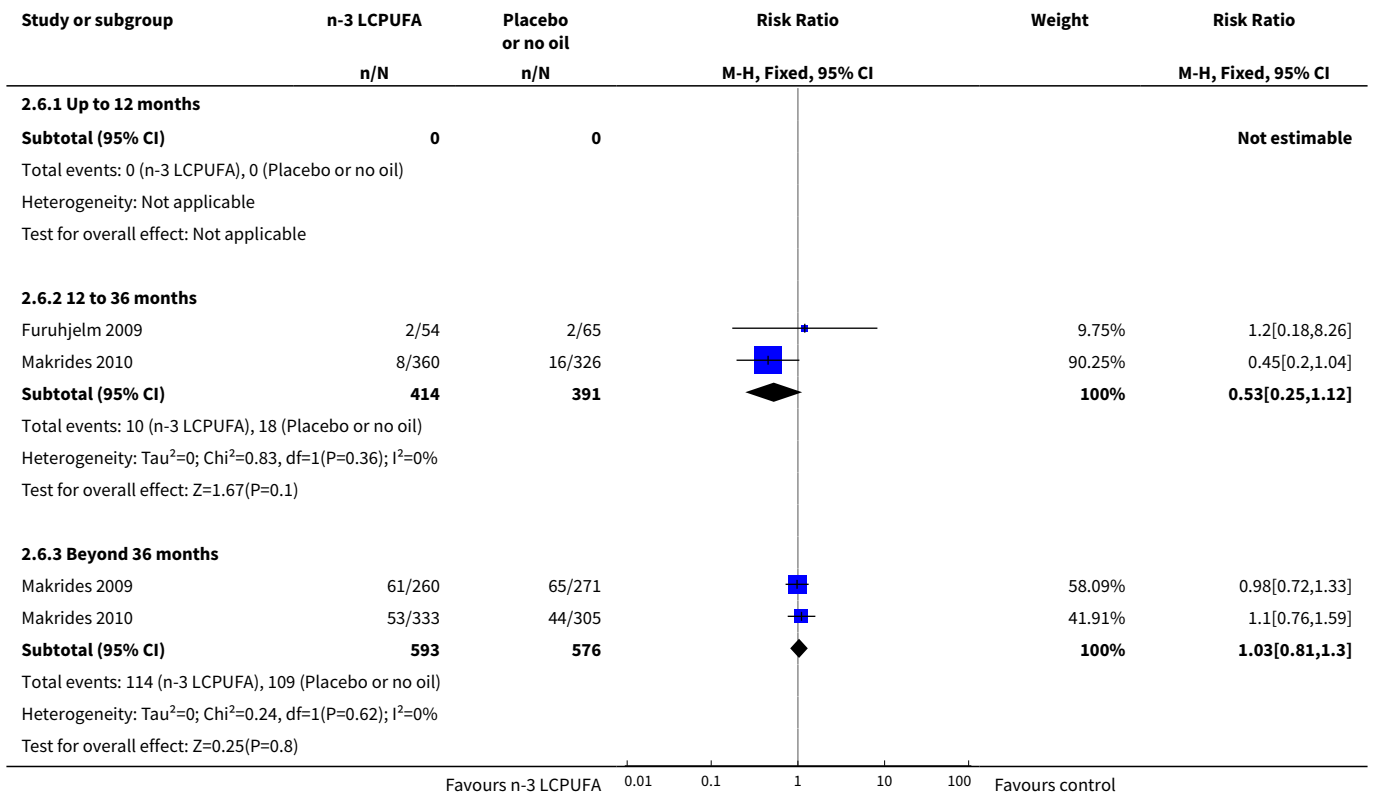


Analysis 2.5. Comparison 2 n-3 LCPUFA supplementation versus placebo or no supplementation - specific forms of allergy, Outcome 5 Allergic rhinitis/Hay fever (with sensitisation): medically diagnosed IgE mediated.

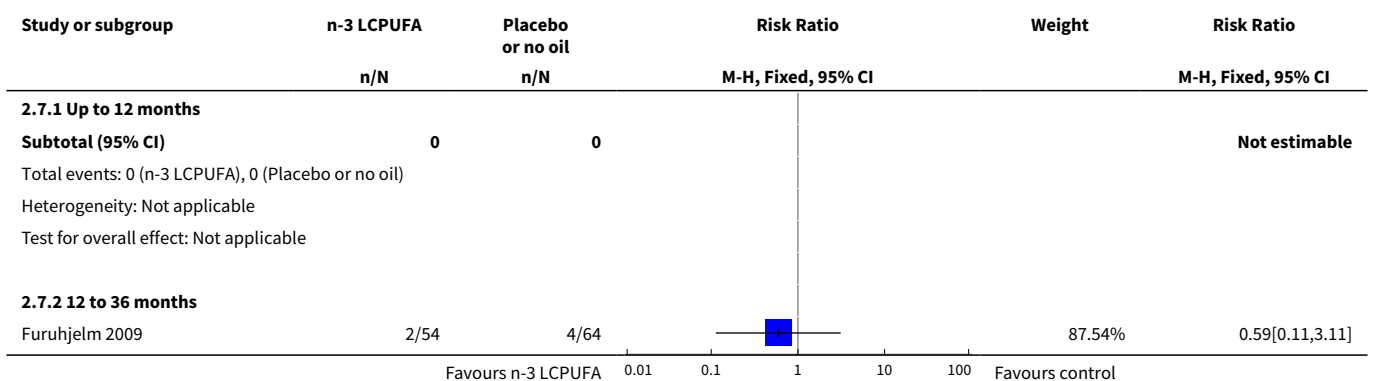


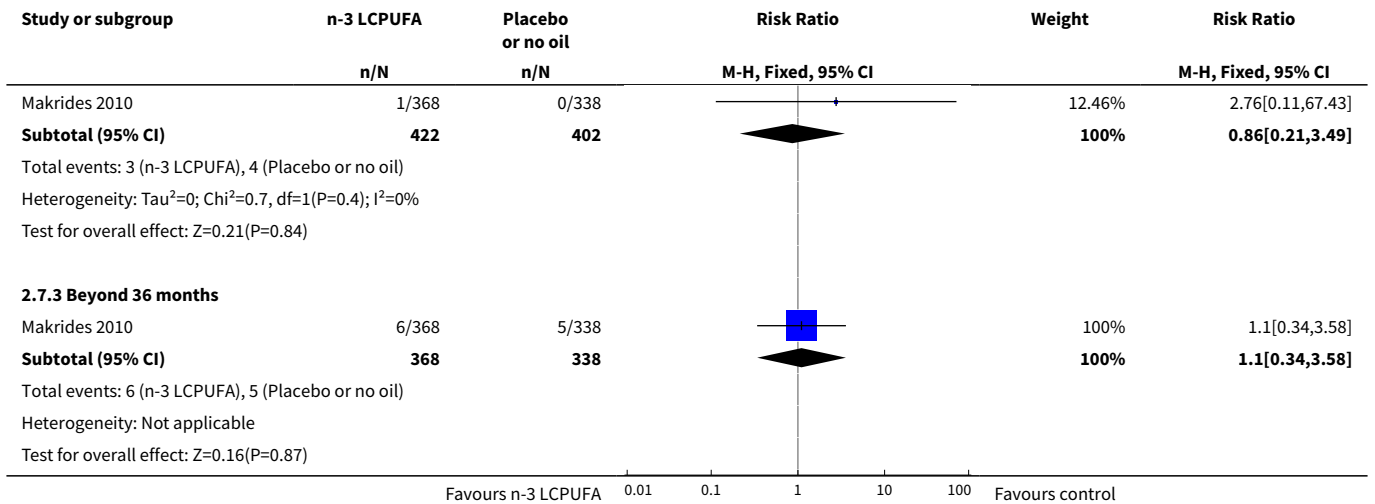


Analysis 2.6. Comparison 2 n-3 LCPUFA supplementation versus placebo or no supplementation - specific forms of allergy, Outcome 6 Allergic rhinitis/Hay fever (+/- sensitisation): medically diagnosed/parental reported.

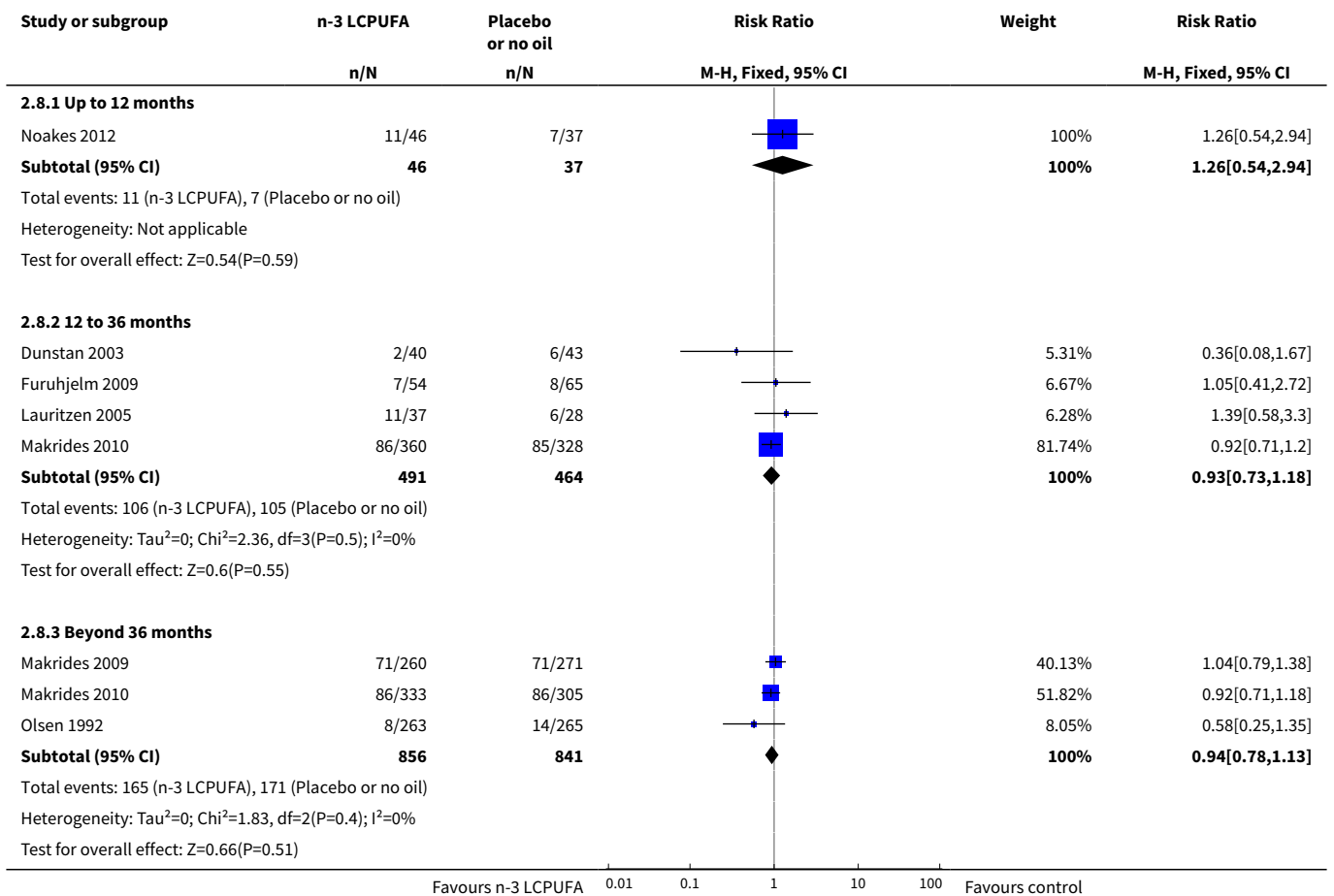


Analysis 2.7. Comparison 2 n-3 LCPUFA supplementation versus placebo or no supplementation - specific forms of allergy, Outcome 7 Asthma/Wheeze (with sensitisation): medically diagnosed IgE mediated.





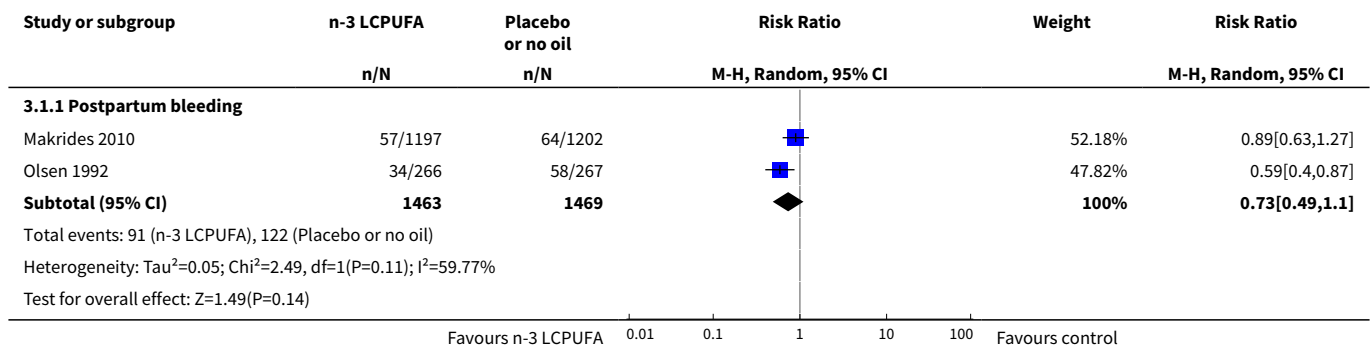
Analysis 2.8. Comparison 2 n-3 LCPUFA supplementation versus placebo or no supplementation - specific forms of allergy, Outcome 8 Asthma/Wheeze (+/- sensitisation): medically diagnosed/parental reported.



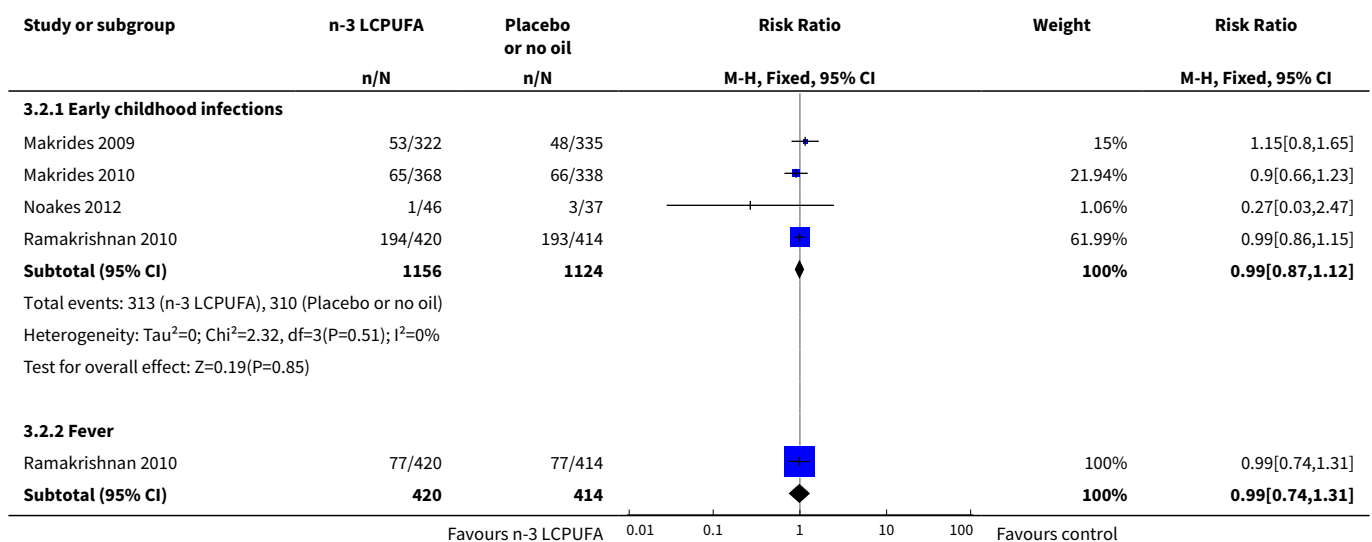
Comparison 3. n-3 LCPUFA supplementation versus placebo or no supplementation - maternal and infant safety

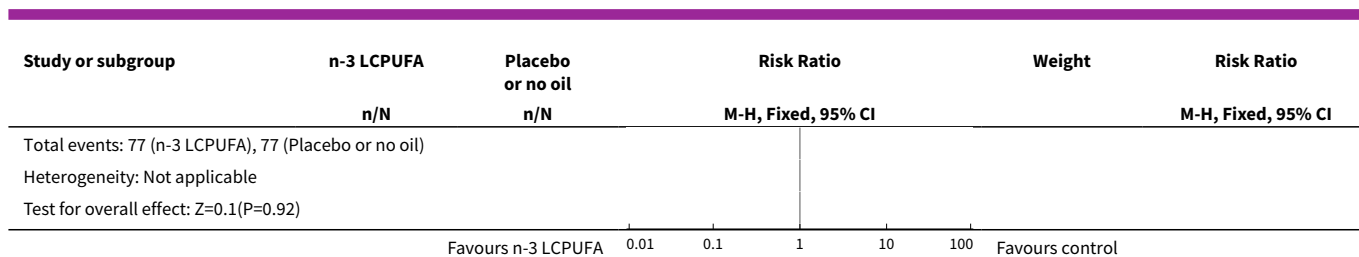
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal safety	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Postpartum bleeding	2	2932	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.49, 1.10]
2 Infants safety	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Early childhood infections	4	2280	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.87, 1.12]
2.2 Fever	1	834	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.74, 1.31]

Analysis 3.1. Comparison 3 n-3 LCPUFA supplementation versus placebo or no supplementation - maternal and infant safety, Outcome 1 Maternal safety.



Analysis 3.2. Comparison 3 n-3 LCPUFA supplementation versus placebo or no supplementation - maternal and infant safety, Outcome 2 Infants safety.



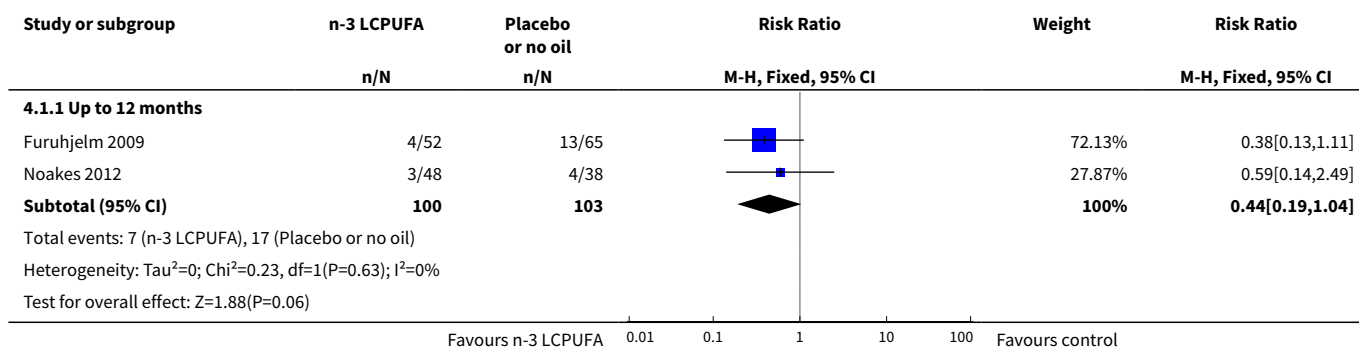


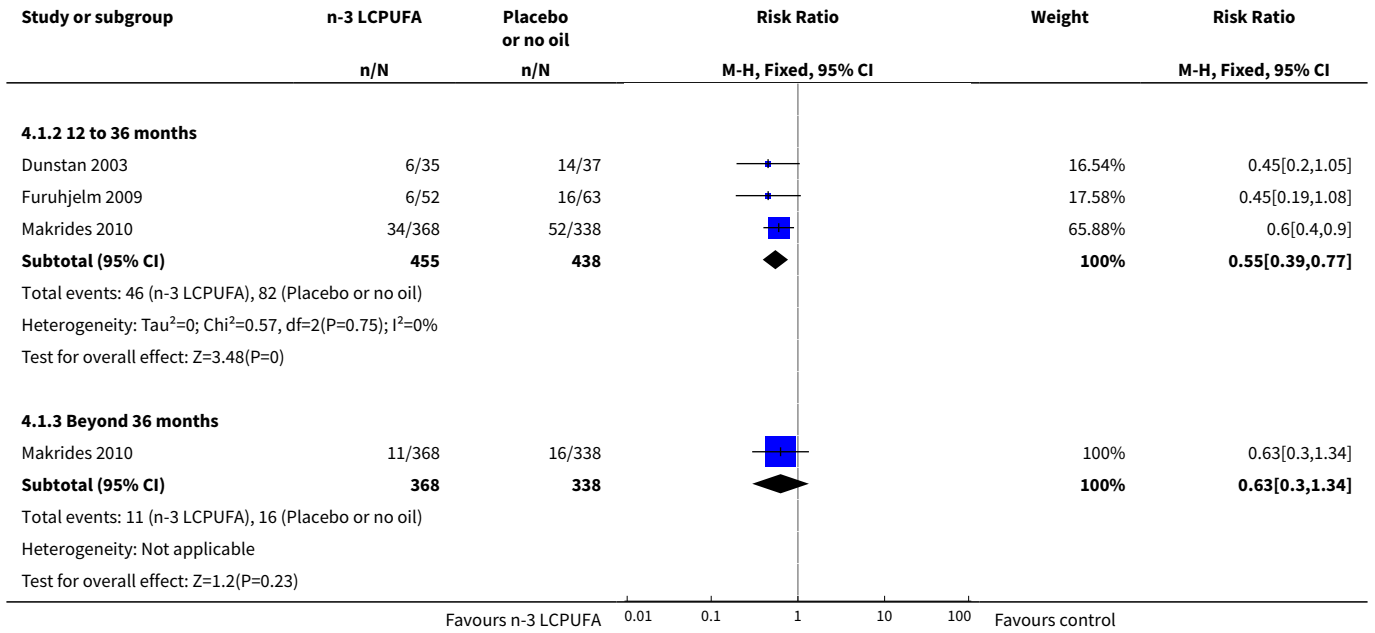
Comparison 4. n-3 LCPUFA supplementation versus placebo or no supplementation - allergen sensitisation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Skin prick test results - egg	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Up to 12 months	2	203	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.19, 1.04]
1.2 12 to 36 months	3	893	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.39, 0.77]
1.3 Beyond 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.30, 1.34]
2 Skin prick test results - cows' milk	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Up to 12 months	2	205	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.24, 2.29]
2.2 12 to 36 months	3	897	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.20, 2.34]
2.3 Beyond 36 months	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Skin Prick Test results - peanut	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Up to 12 months	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 12 to 36 months	2	778	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.34, 1.08]
3.3 Beyond 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.30, 1.18]
4 Skin prick test results - wheat	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Up to 12 months	1	117	Risk Ratio (M-H, Fixed, 95% CI)	3.74 [0.16, 89.85]
4.2 12 to 36 months	2	783	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.29, 6.84]
4.3 Beyond 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	2.76 [0.56, 13.56]
5 Skin prick test results - fish	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Up to 12 months	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 12 to 36 months	1	666	Risk Ratio (M-H, Fixed, 95% CI)	6.36 [0.33, 122.65]

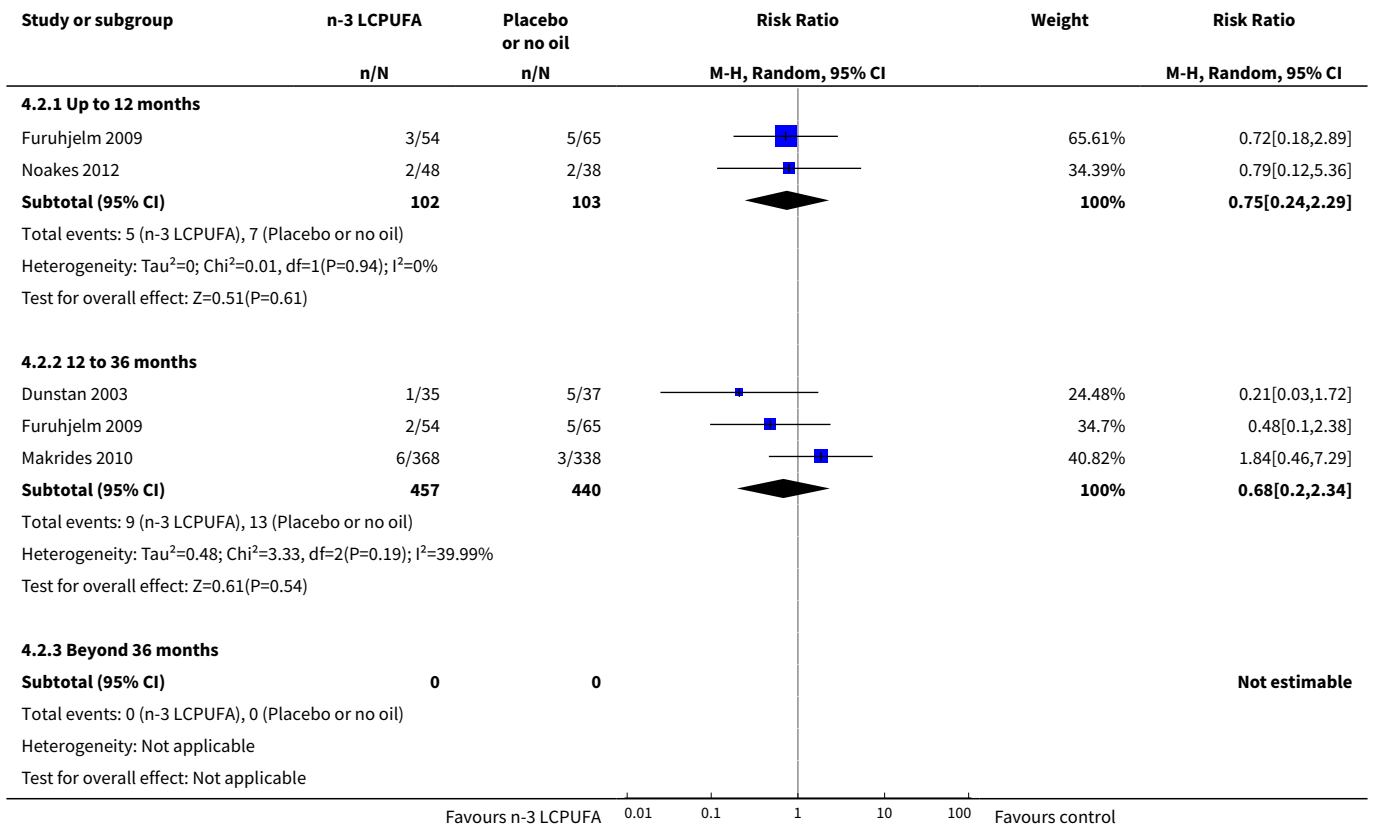
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 Beyond 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [0.17, 20.17]
6 Skin prick test results - inhalant allergen (pollens)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Up to 12 months	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 12 to 36 months	2	779	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.08, 2.30]
6.3 Beyond 36 months	1	580	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.44, 1.34]
7 Skin prick test results - house dust mite	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Up to 12 months	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 12 to 36 months	2	738	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.18, 3.28]
7.3 Beyond 36 months	1	580	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.48, 1.46]
8 Skin prick test results - cat	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Up to 12 months	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.05, 12.25]
8.2 12 to 36 months	2	738	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.39, 2.94]
8.3 Beyond 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [0.98, 3.75]
9 Skin prick test results - any allergen	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Up to 12 months	2	201	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.32, 1.09]
9.2 12 to 36 months	3	892	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.53, 0.94]
9.3 Beyond 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.74, 1.22]

Analysis 4.1. Comparison 4 n-3 LCPUFA supplementation versus placebo or no supplementation - allergen sensitisation, Outcome 1 Skin prick test results - egg.

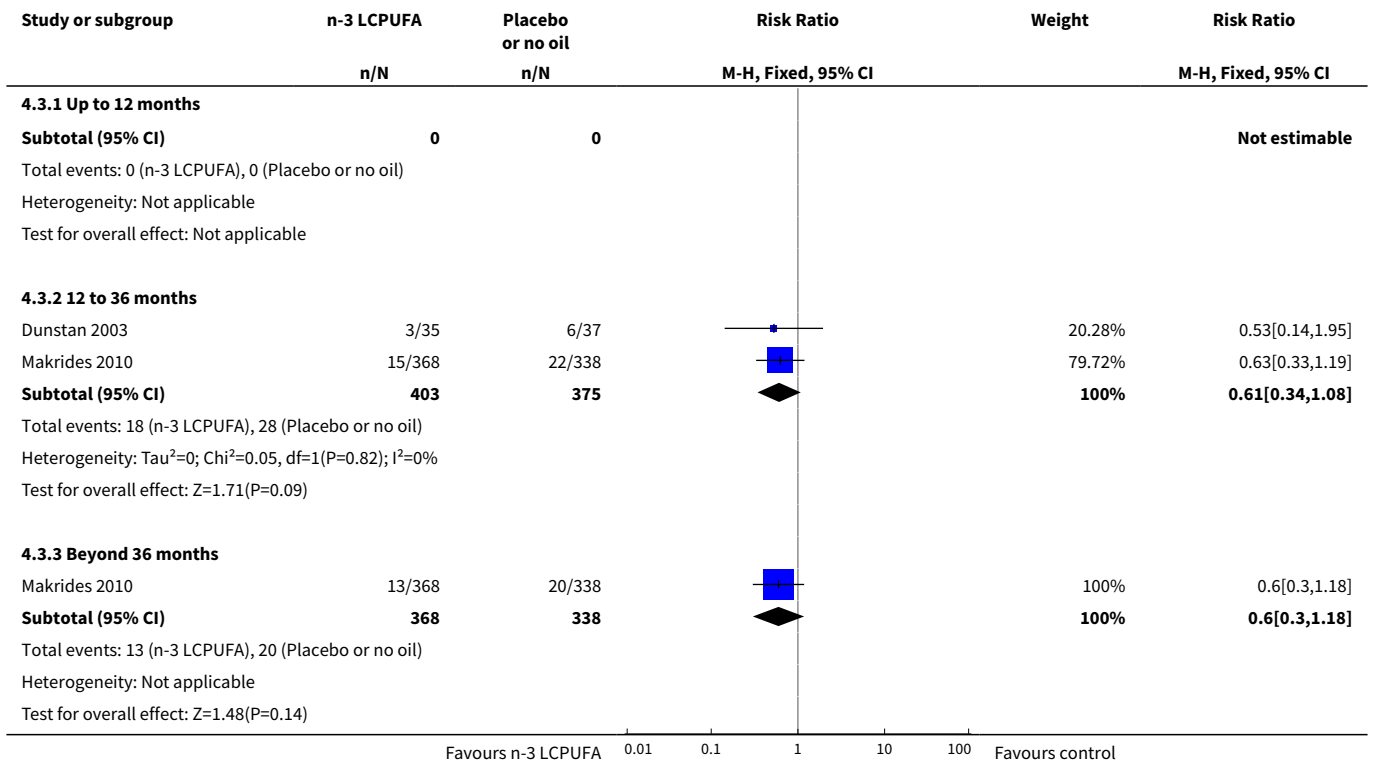




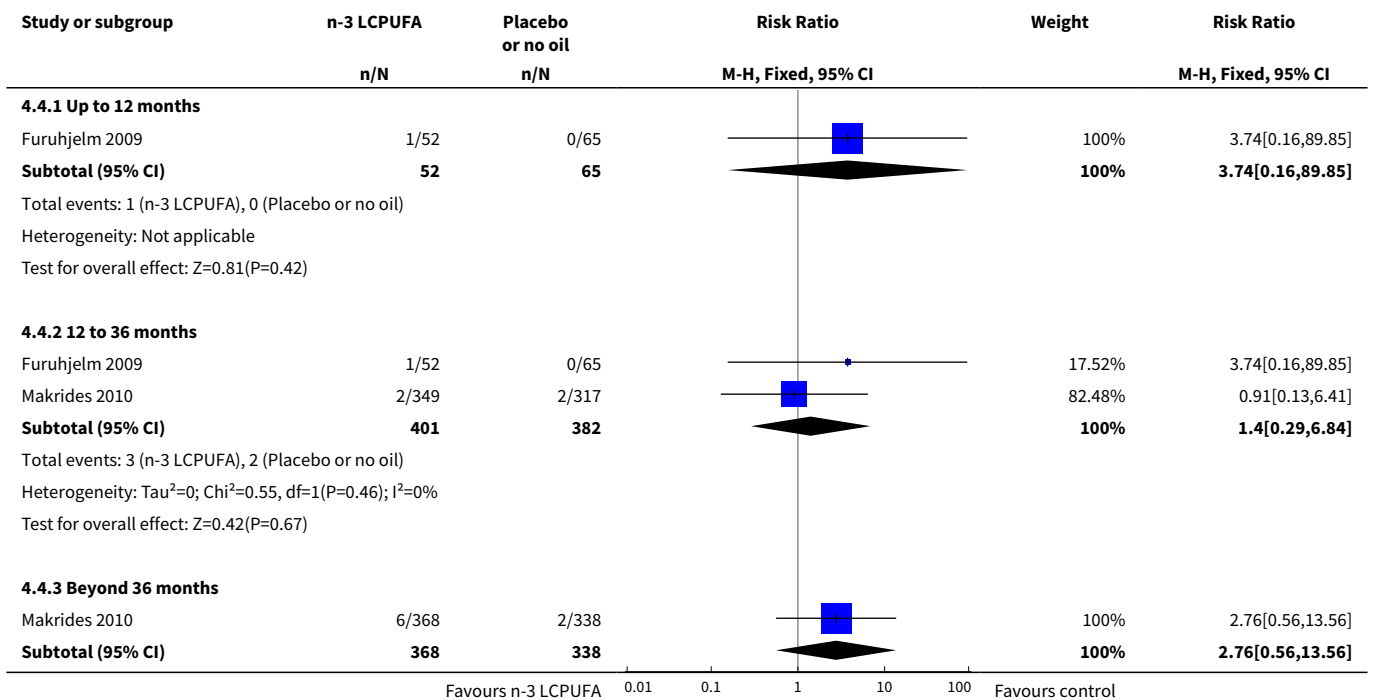
Analysis 4.2. Comparison 4 n-3 LCPUFA supplementation versus placebo or no supplementation - allergen sensitisation, Outcome 2 Skin prick test results - cows' milk.

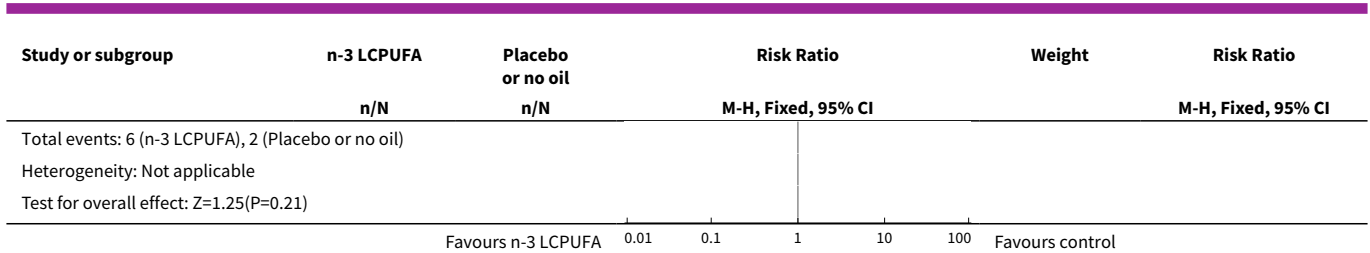


Analysis 4.3. Comparison 4 n-3 LCPUFA supplementation versus placebo or no supplementation - allergen sensitisation, Outcome 3 Skin Prick Test results - peanut.

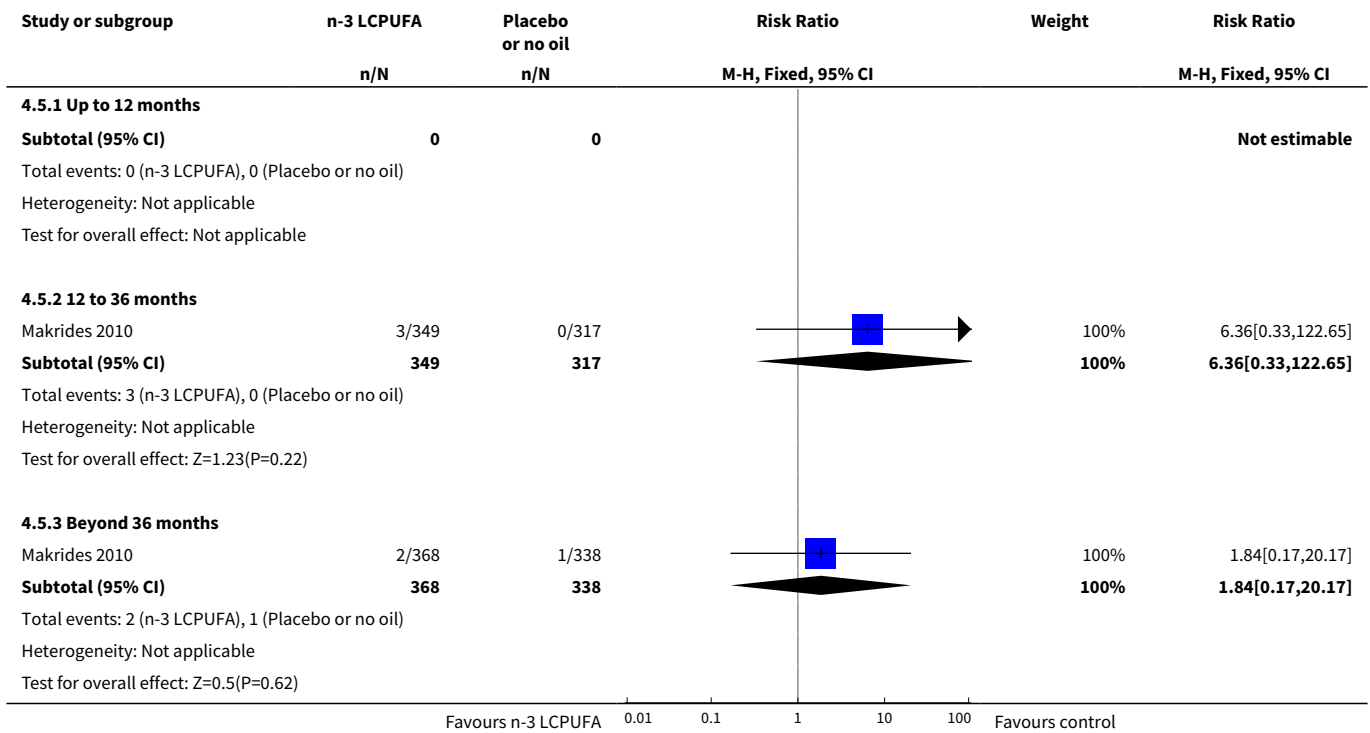


Analysis 4.4. Comparison 4 n-3 LCPUFA supplementation versus placebo or no supplementation - allergen sensitisation, Outcome 4 Skin prick test results - wheat.

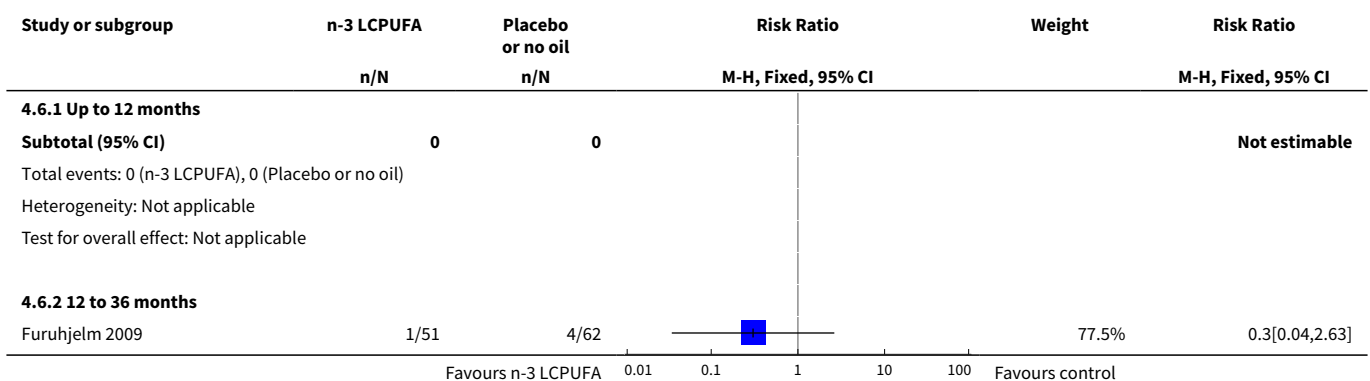


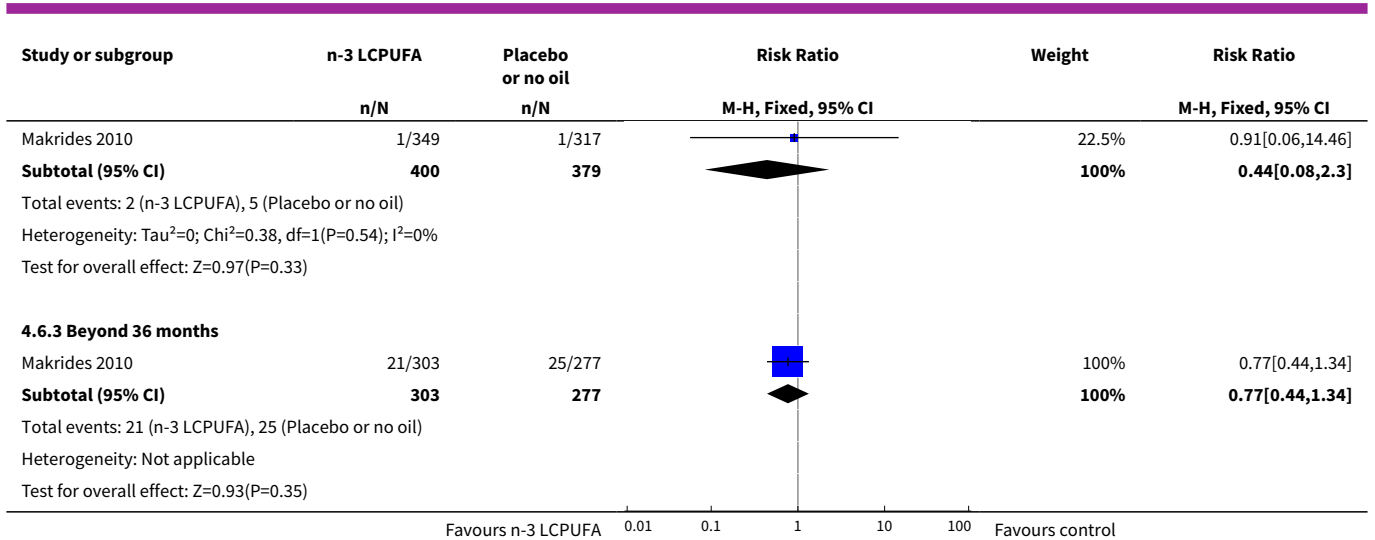


Analysis 4.5. Comparison 4 n-3 LCPUFA supplementation versus placebo or no supplementation - allergen sensitisation, Outcome 5 Skin prick test results - fish.

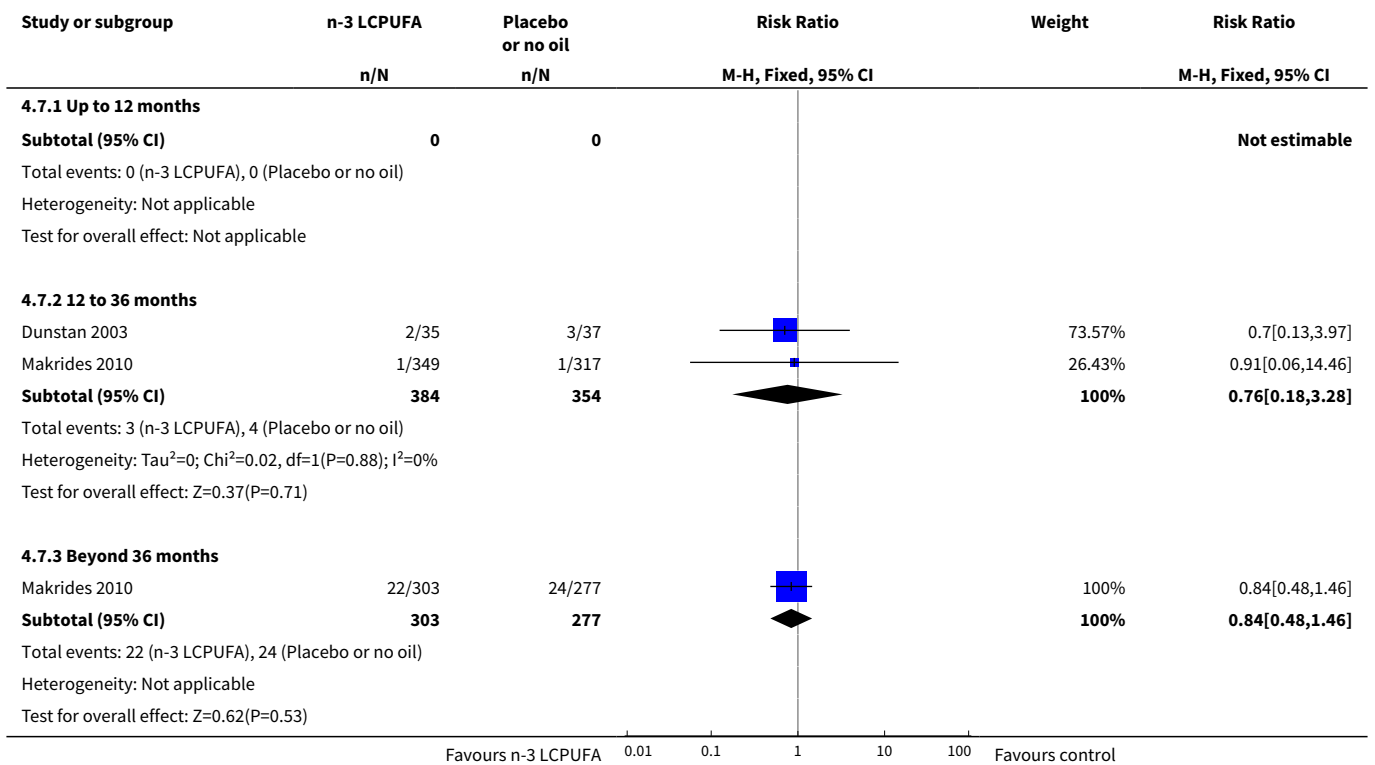


Analysis 4.6. Comparison 4 n-3 LCPUFA supplementation versus placebo or no supplementation - allergen sensitisation, Outcome 6 Skin prick test results - inhalant allergen (pollens).

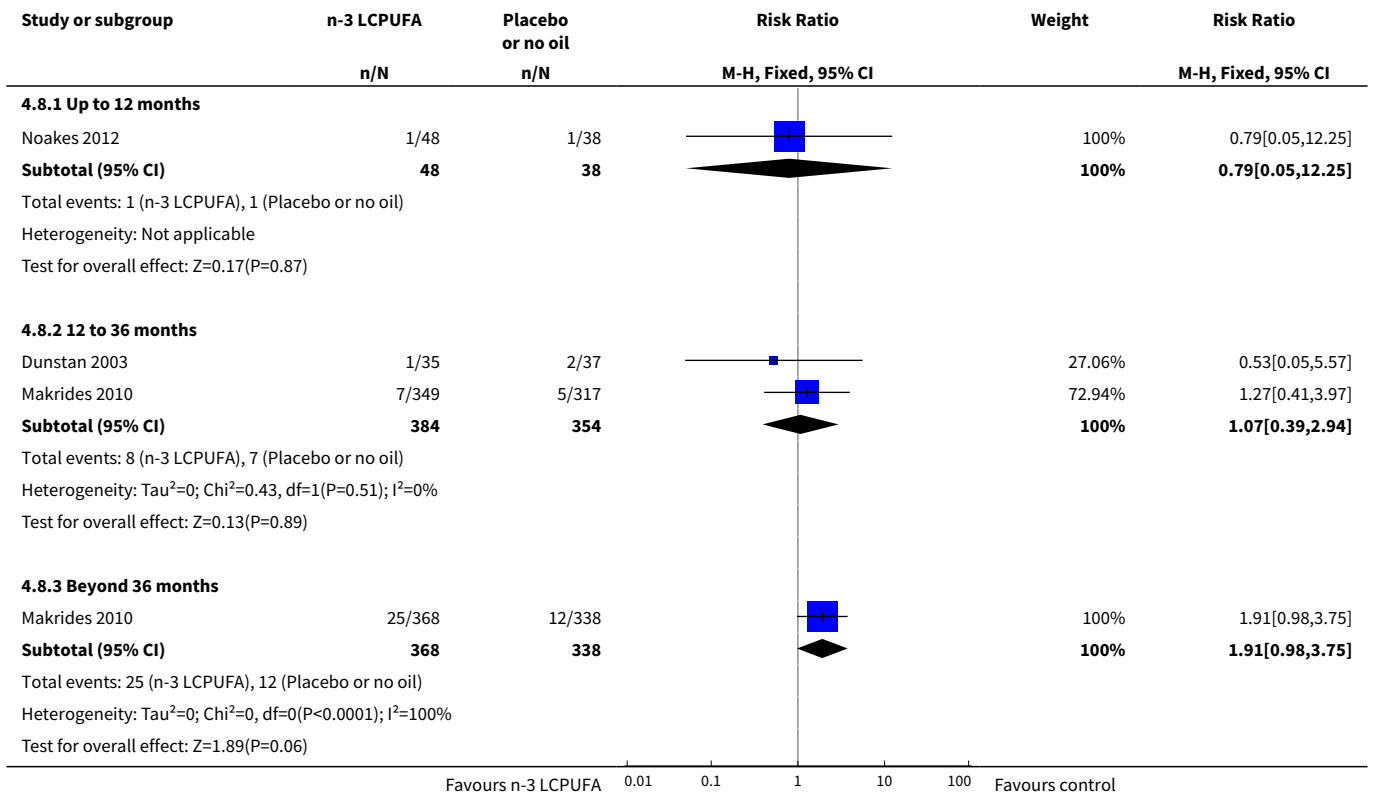




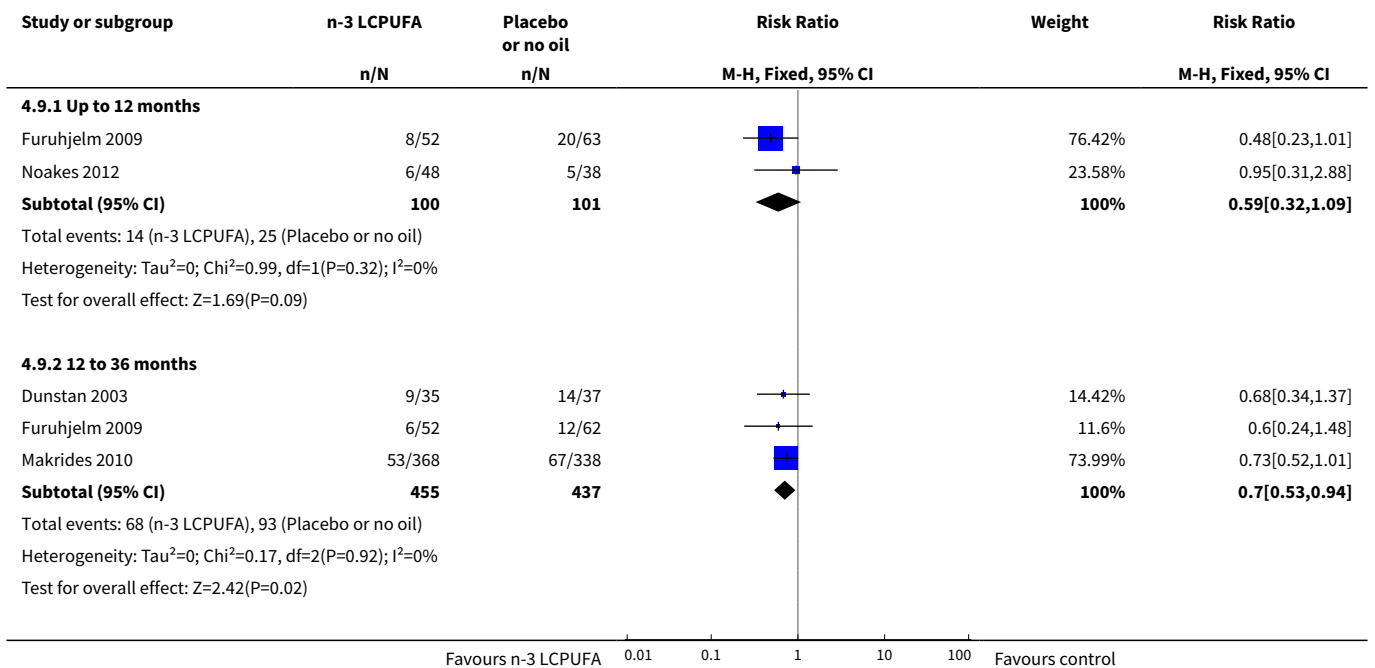
Analysis 4.7. Comparison 4 n-3 LCPUFA supplementation versus placebo or no supplementation - allergen sensitisation, Outcome 7 Skin prick test results - house dust mite.

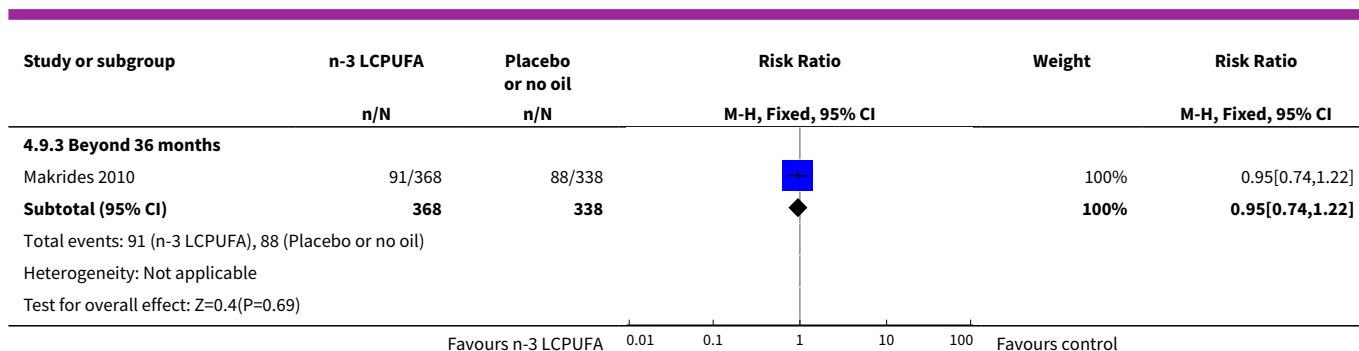


Analysis 4.8. Comparison 4 n-3 LCPUFA supplementation versus placebo or no supplementation - allergen sensitisation, Outcome 8 Skin prick test results - cat.



Analysis 4.9. Comparison 4 n-3 LCPUFA supplementation versus placebo or no supplementation - allergen sensitisation, Outcome 9 Skin prick test results - any allergen.



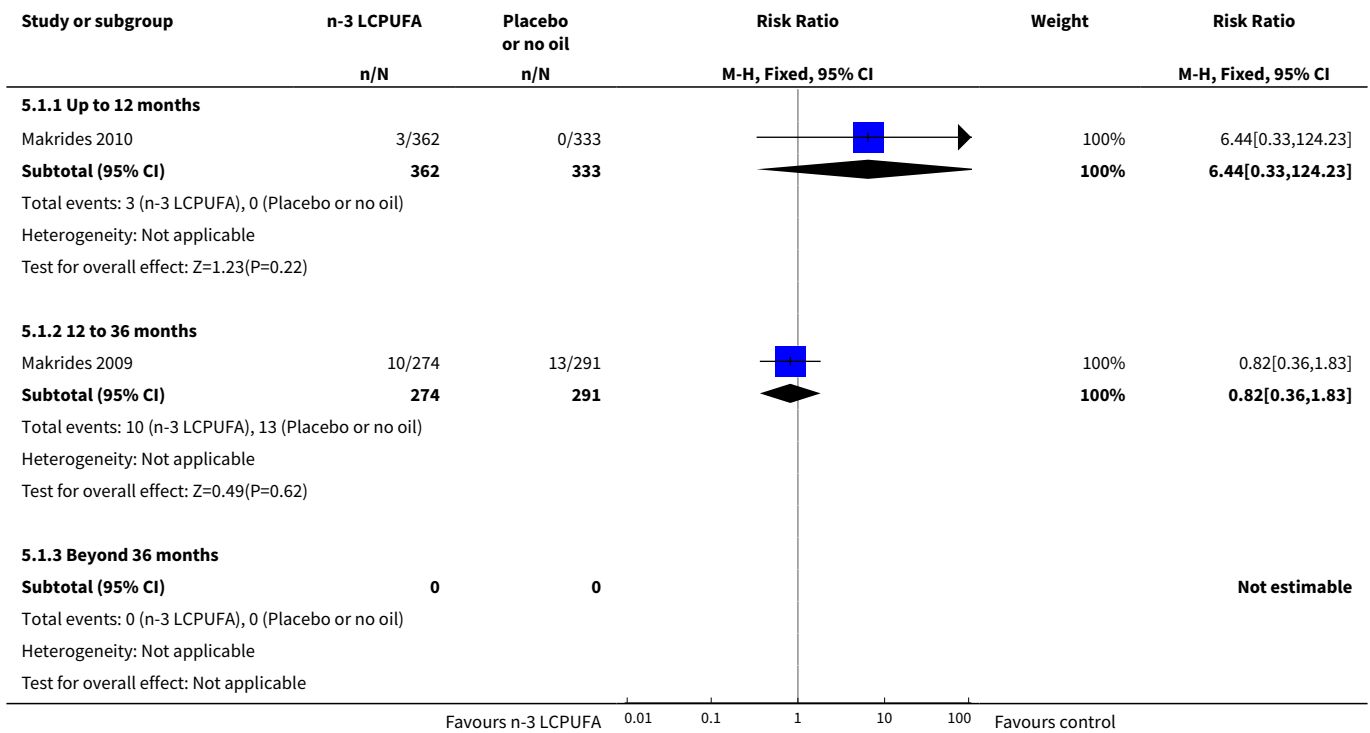


Comparison 5. n-3 LCPUFA supplementation versus placebo or no supplementation - parent's reports of allergy (non-validated questionnaire)

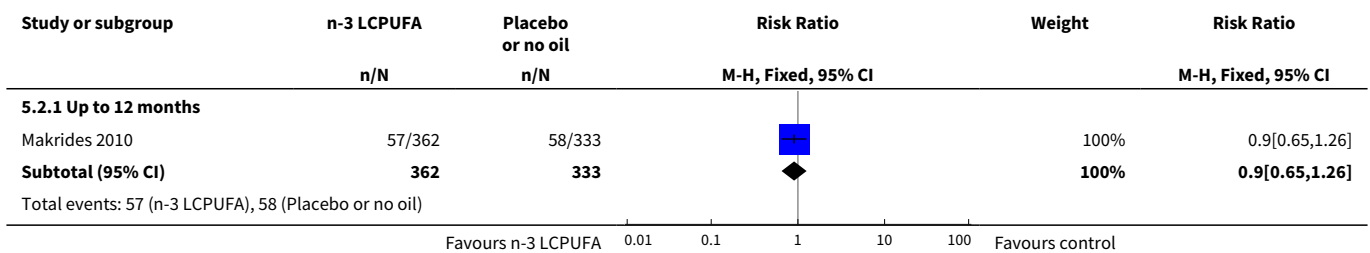
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Food allergies: parental reported (non-validated questionnaires)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Up to 12 months	1	695	Risk Ratio (M-H, Fixed, 95% CI)	6.44 [0.33, 124.23]
1.2 12 to 36 months	1	565	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.36, 1.83]
1.3 Beyond 36 months	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Eczema: parental reported (non-validated questionnaires)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Up to 12 months	1	695	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.26]
2.2 12 to 36 months	2	1263	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.74, 1.13]
2.3 Beyond 36 months	2	746	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.77, 1.18]
3 Allergic rhinitis/Hay fever: parental reported (non-validated questionnaires)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Up to 12 months	1	695	Risk Ratio (M-H, Fixed, 95% CI)	4.60 [0.22, 95.48]
3.2 12 to 36 months	1	565	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.26, 1.96]
3.3 Beyond 36 months	1	109	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.78, 3.12]
4 Asthma/Wheeze: parental reported (non-validated questionnaires)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Up to 12 months	2	1529	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.73, 1.56]
4.2 12 to 36 months	3	2134	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.79, 1.11]
4.3 Beyond 36 months	2	745	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.72, 1.45]

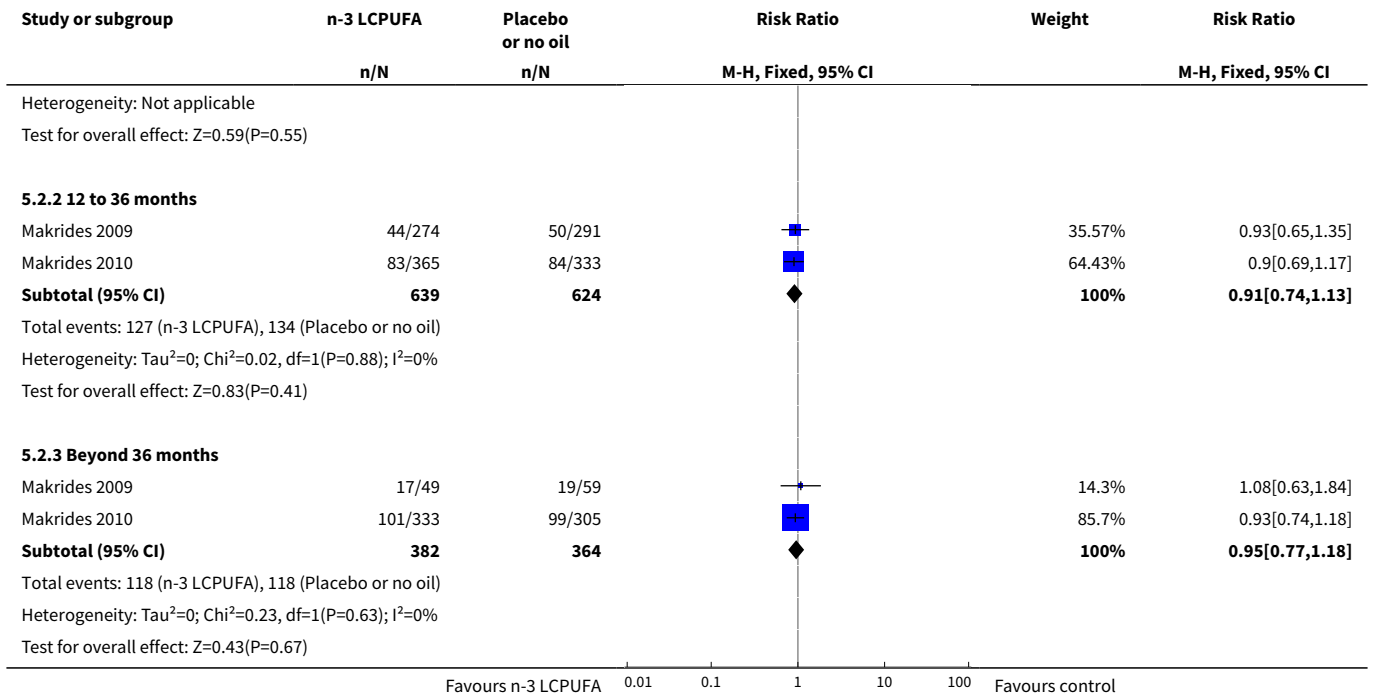
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Any allergies: parental reported (non-validated questionnaires)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Up to 12 months	1	695	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.26]
5.2 12 to 36 months	1	565	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.74, 1.21]
5.3 Beyond 36 months	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.64, 1.30]

Analysis 5.1. Comparison 5 n-3 LCPUFA supplementation versus placebo or no supplementation - parent's reports of allergy (non-validated questionnaire), Outcome 1 Food allergies: parental reported (non-validated questionnaires).

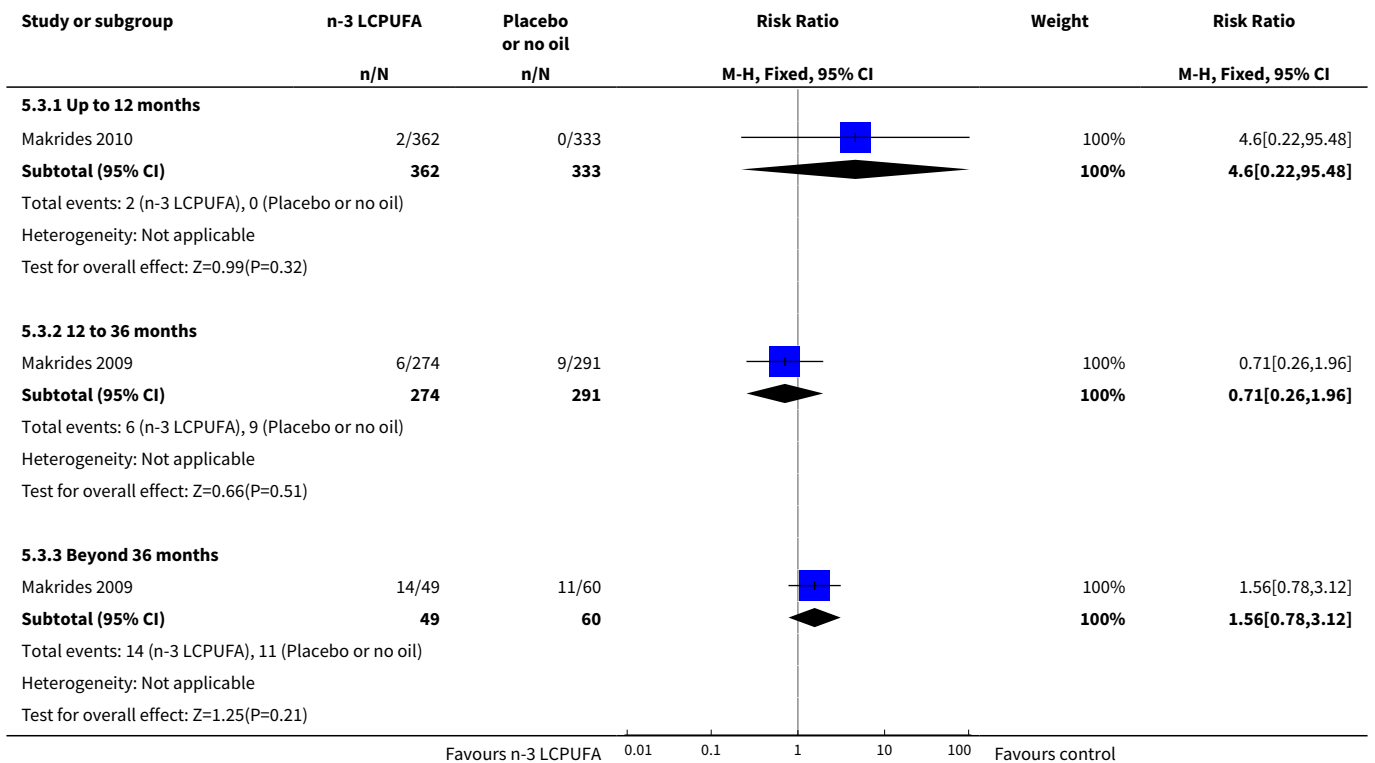


Analysis 5.2. Comparison 5 n-3 LCPUFA supplementation versus placebo or no supplementation - parent's reports of allergy (non-validated questionnaire), Outcome 2 Eczema: parental reported (non-validated questionnaires).

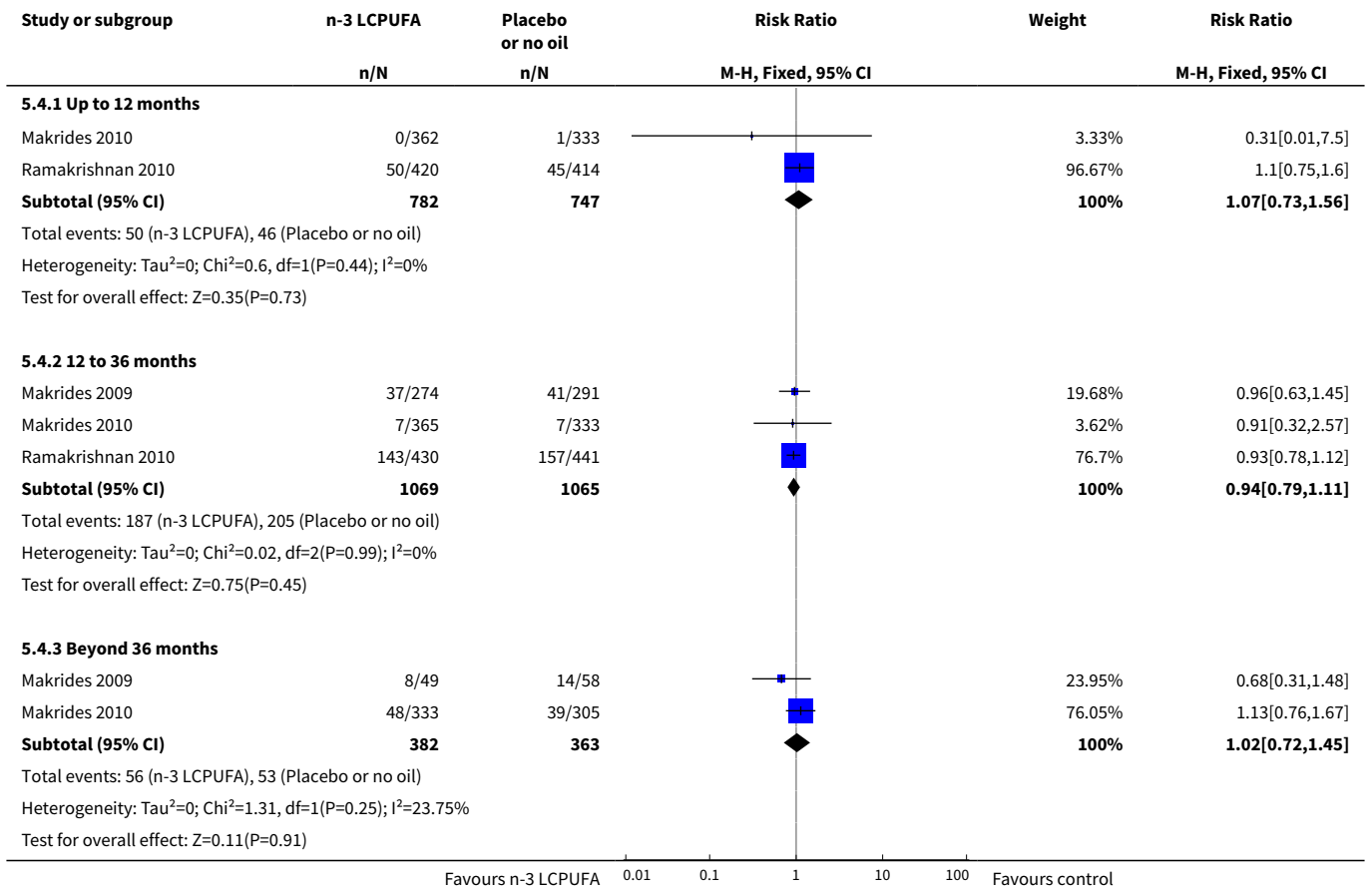




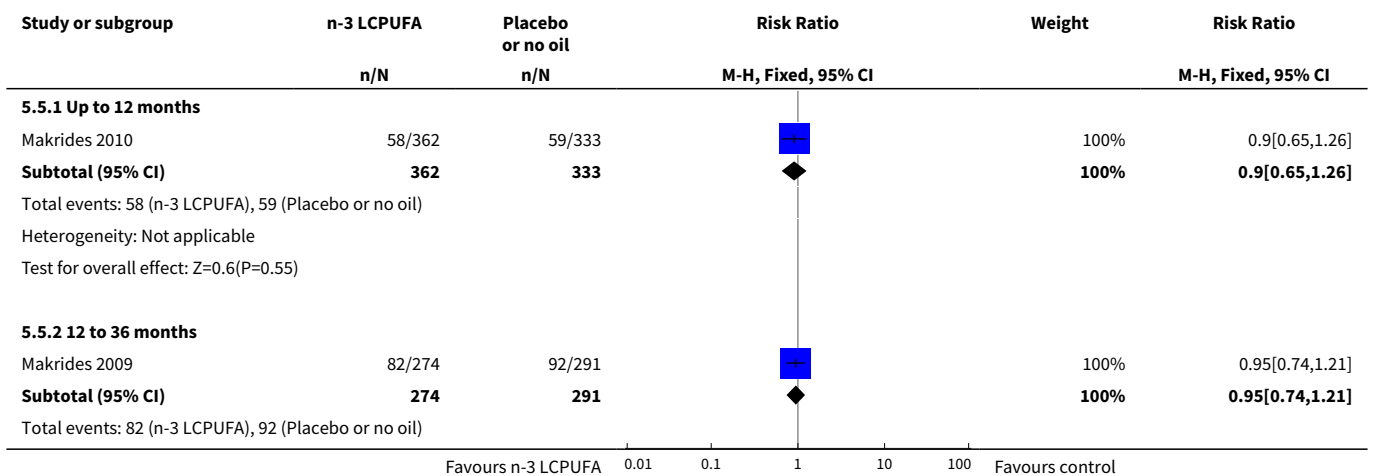
Analysis 5.3. Comparison 5 n-3 LCPUFA supplementation versus placebo or no supplementation - parent's reports of allergy (non-validated questionnaire), Outcome 3 Allergic rhinitis/Hay fever: parental reported (non-validated questionnaires).

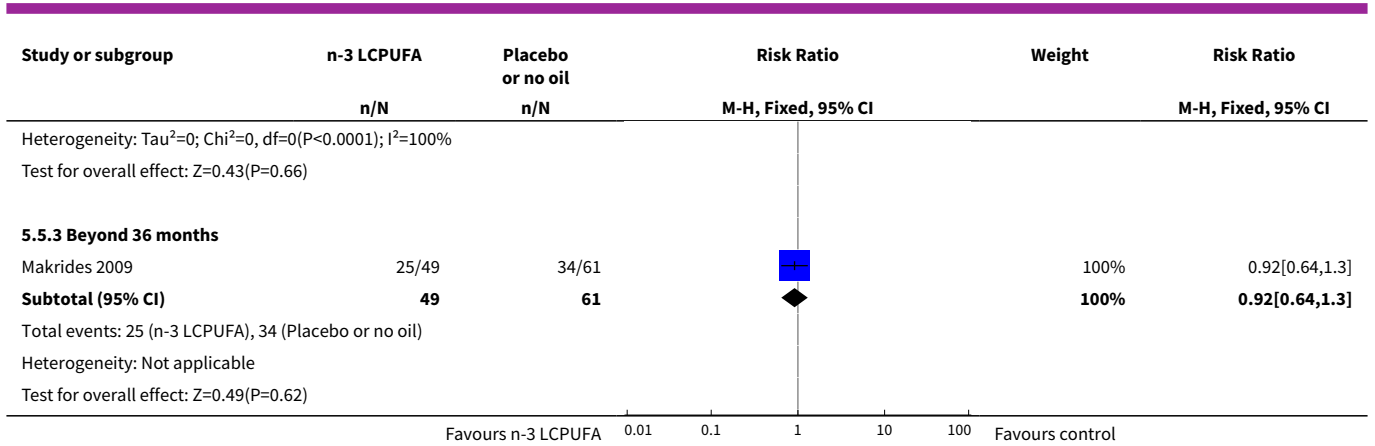


Analysis 5.4. Comparison 5 n-3 LCPUFA supplementation versus placebo or no supplementation - parent's reports of allergy (non-validated questionnaire), Outcome 4 Asthma/Wheeze: parental reported (non-validated questionnaires).



Analysis 5.5. Comparison 5 n-3 LCPUFA supplementation versus placebo or no supplementation - parent's reports of allergy (non-validated questionnaire), Outcome 5 Any allergies: parental reported (non-validated questionnaires).

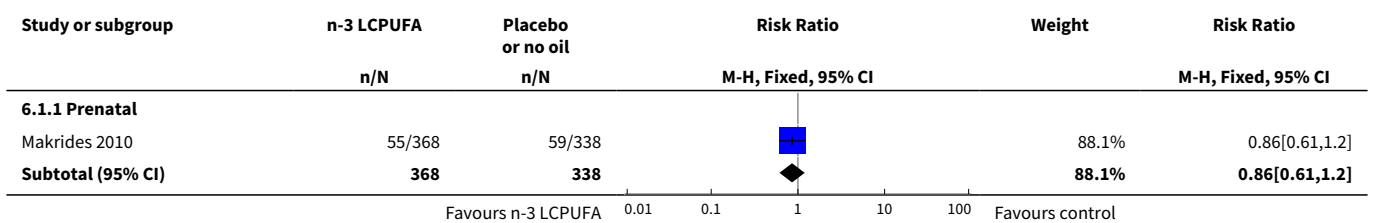


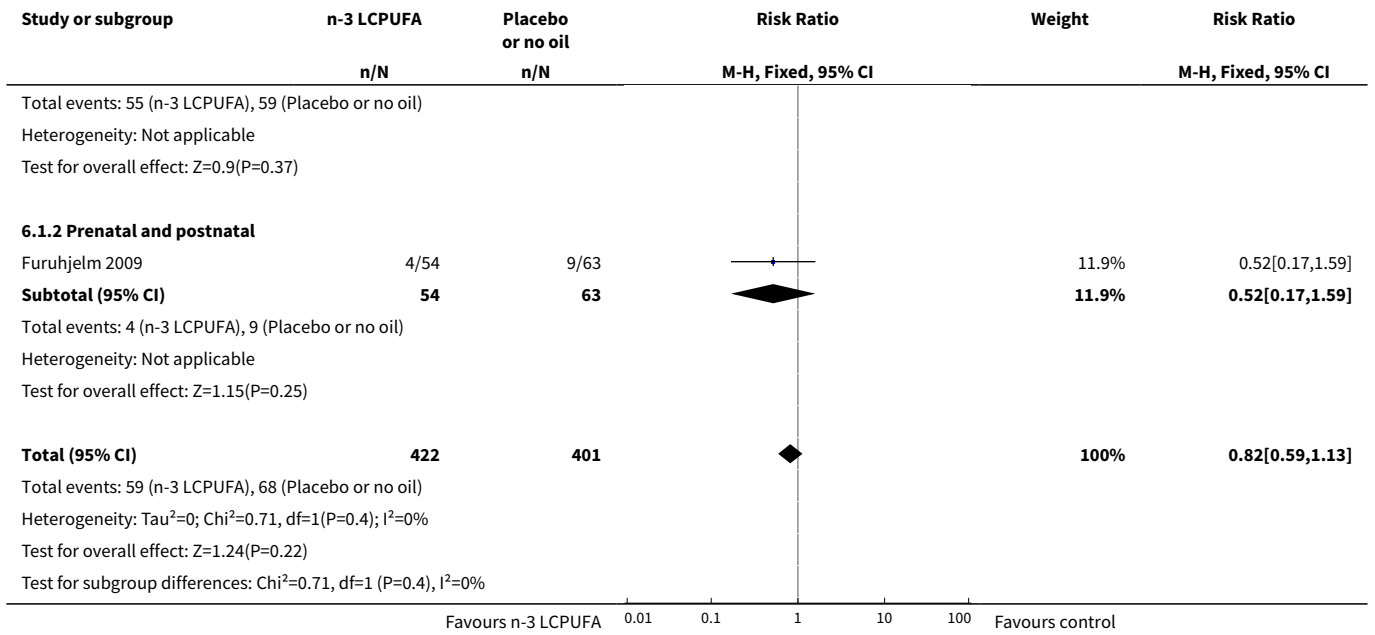


Comparison 6. Timing of supplementation - prenatal versus postnatal versus pre and postnatal subgroup

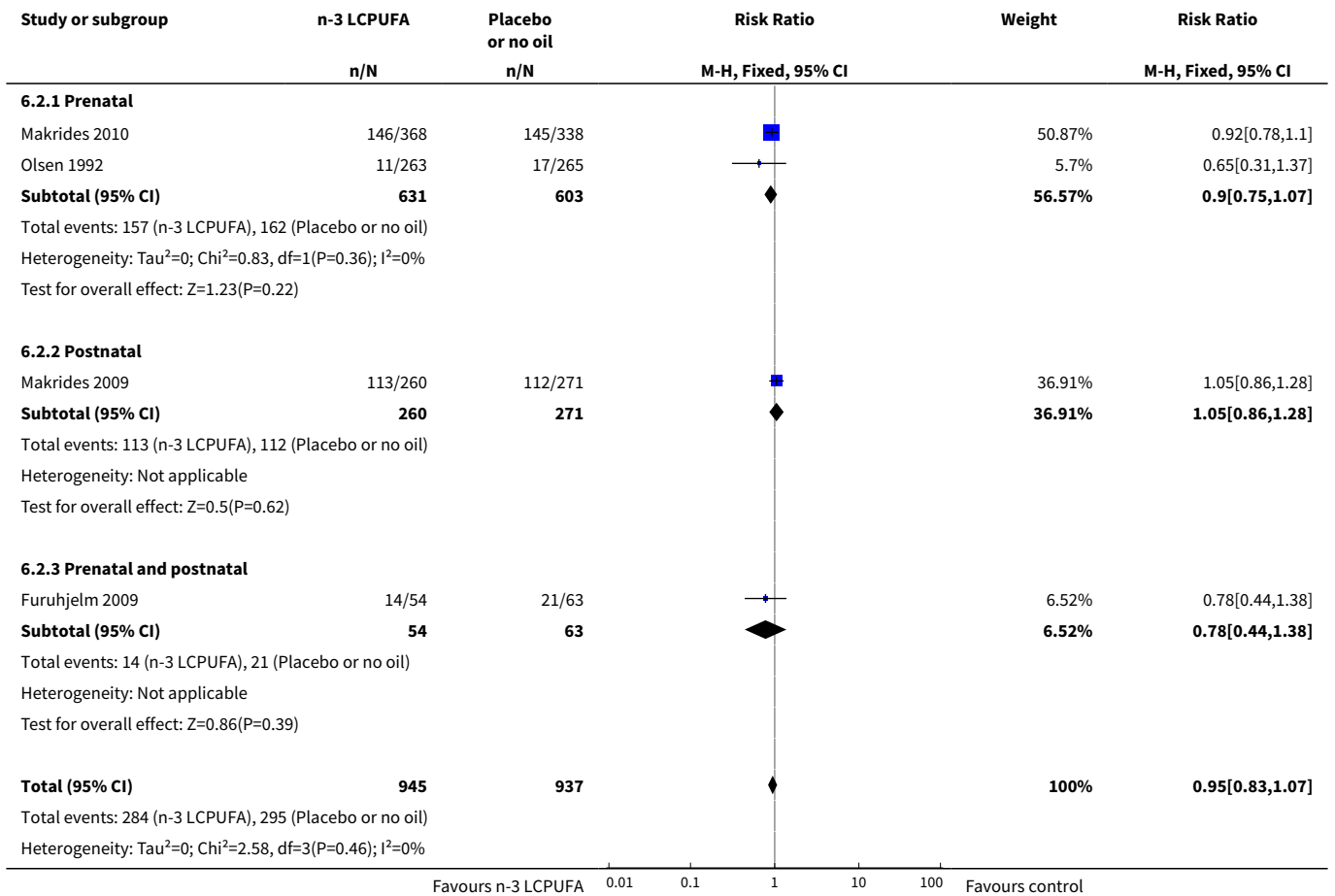
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergies: last available time (with sensitisation): medically diagnosed IgE mediated	2	823	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.59, 1.13]
1.1 Prenatal	1	706	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.61, 1.20]
1.2 Prenatal and postnatal	1	117	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.17, 1.59]
2 Any allergies: last available time (+/- sensitisation): medically diagnosed/parental reported	4	1882	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.83, 1.07]
2.1 Prenatal	2	1234	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.75, 1.07]
2.2 Postnatal	1	531	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.86, 1.28]
2.3 Prenatal and postnatal	1	117	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.44, 1.38]

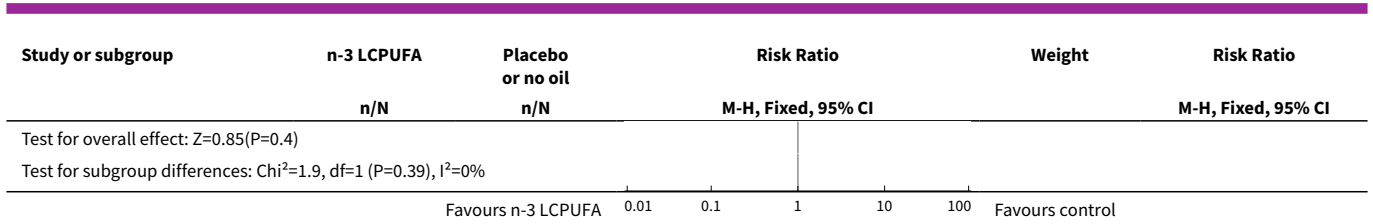
Analysis 6.1. Comparison 6 Timing of supplementation - prenatal versus postnatal versus pre and postnatal subgroup, Outcome 1 Any allergies: last available time (with sensitisation): medically diagnosed IgE mediated.





Analysis 6.2. Comparison 6 Timing of supplementation - prenatal versus postnatal versus pre and postnatal subgroup, Outcome 2 Any allergies: last available time (+/- sensitisation): medically diagnosed/parental reported.

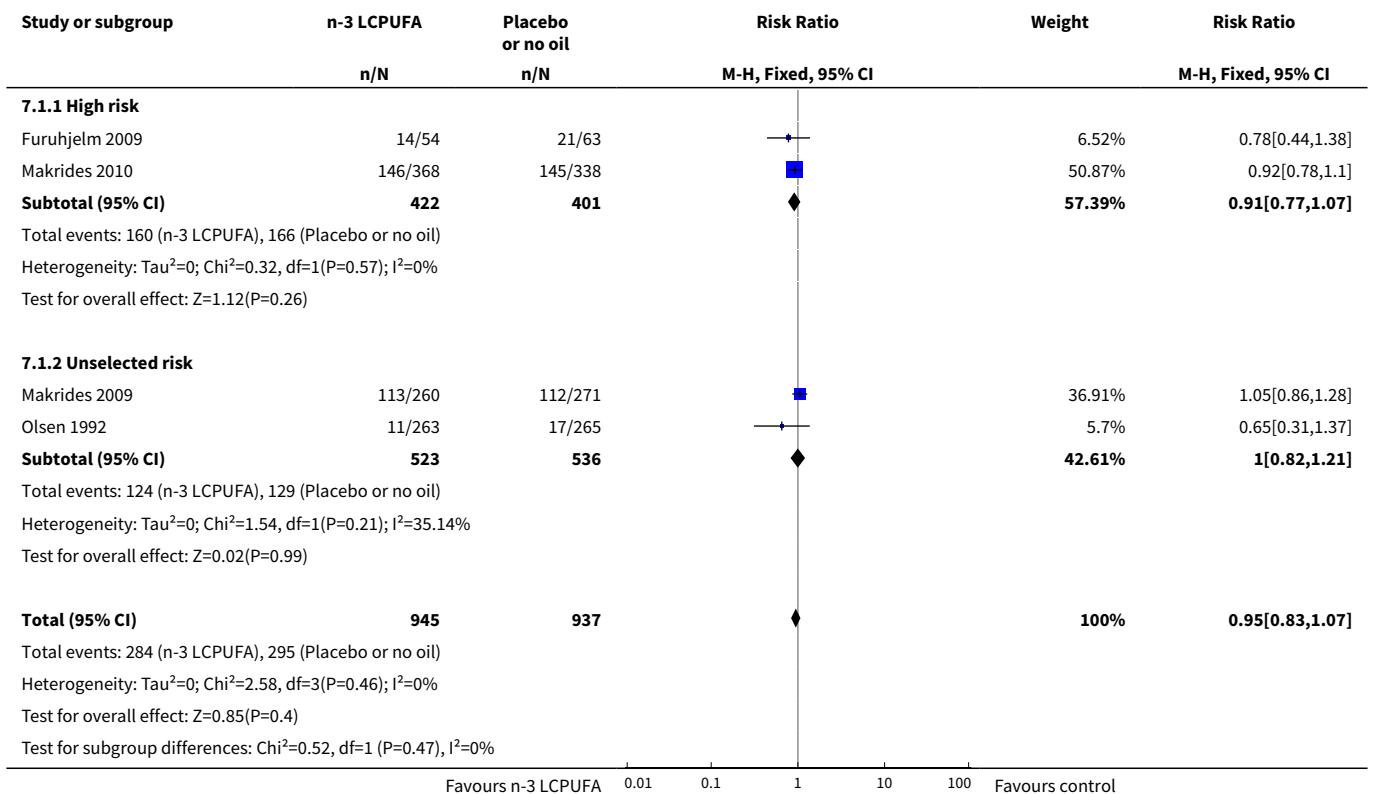




Comparison 7. Allergy risk - high risk versus unselected risk subgroup

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy: last available time	4	1882	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.83, 1.07]
1.1 High risk	2	823	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.77, 1.07]
1.2 Unselected risk	2	1059	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.82, 1.21]

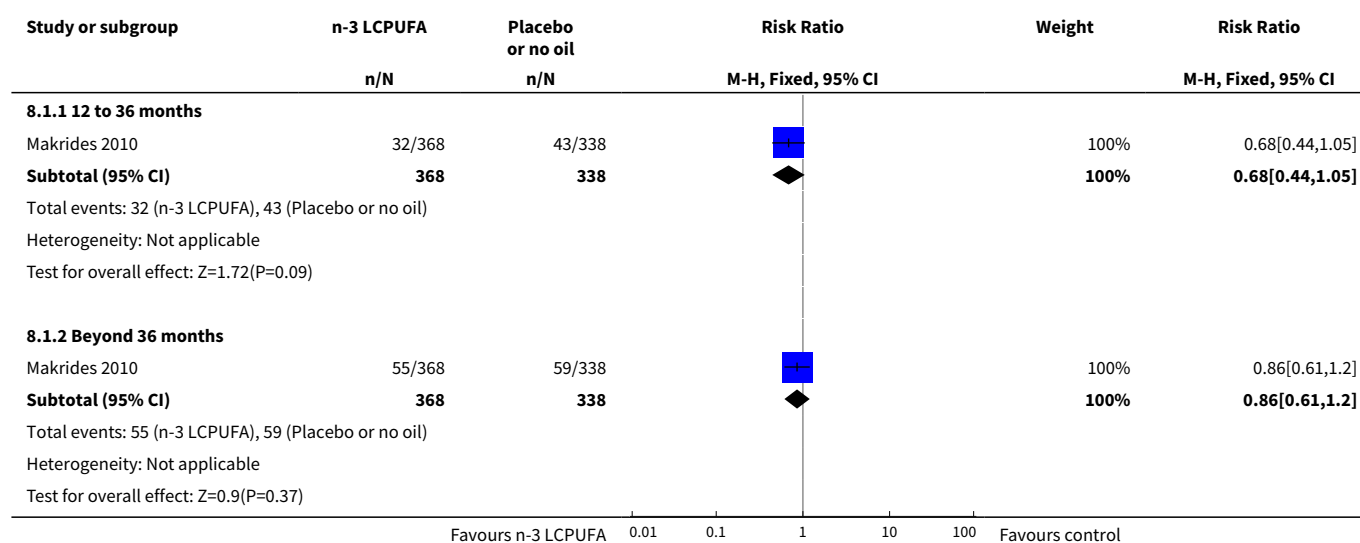
Analysis 7.1. Comparison 7 Allergy risk - high risk versus unselected risk subgroup, Outcome 1 Any allergy: last available time.



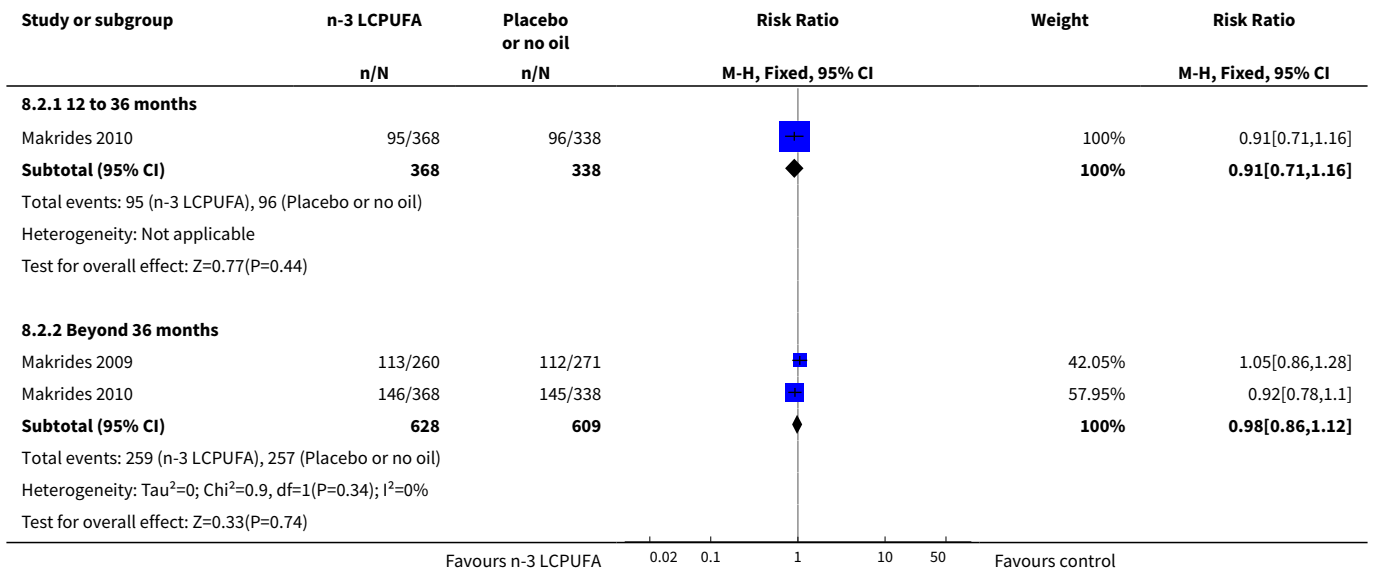
Comparison 8. n-3 LCPUFA supplementation versus placebo or no supplementation - sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergies (with sensitisation): medically diagnosed IgE mediated	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 12 to 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.44, 1.05]
1.2 Beyond 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.61, 1.20]
2 Any allergies (+/- sensitisation): medically diagnosed/parental reported	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 12 to 36 months	1	706	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.71, 1.16]
2.2 Beyond 36 months	2	1237	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.86, 1.12]

Analysis 8.1. Comparison 8 n-3 LCPUFA supplementation versus placebo or no supplementation - sensitivity analysis, Outcome 1 Any allergies (with sensitisation): medically diagnosed IgE mediated.



Analysis 8.2. Comparison 8 n-3 LCPUFA supplementation versus placebo or no supplementation - sensitivity analysis, Outcome 2 Any allergies (+/- sensitisation): medically diagnosed/parental reported.



ADDITIONAL TABLES
Table 1. The effects of n-3 LCPUFA supplementation on IgE-mediated allergies using pooled analysis RR (M-H, Fixed/Random, 95% CI)

Allergy (IgE mediated)	Assessed Age	No of studies	No of participants	n-3 LCPUFA		Placebo		Effect Estimate RR [95% CI]
				Events	Total	Events	Total	
Food allergy	< 12 months	1	117	1	52	10	65	0.13 [0.02 to 0.95] *
	12-36 months	2	825	13	422	20	403	0.58 [0.18 to 1.88] ^R
	≥ 36 months	1	706	14	368	9	338	1.43 [0.63 to 3.26]
Eczema	< 12 months	1	117	4	52	13	65	0.38 [0.13 to 1.11]
	12-36 months	2	823	29	422	45	401	0.61 [0.39 to 0.95] *
	≥ 36 months	1	706	44	368	48	338	0.84 [0.57 to 1.23]
Allergic rhinitis	< 12 months	0	0					NE
	12-36 months	2	825	1	422	3	403	0.47 [0.07 to 3.06]
	≥ 36 months	1	706	18	368	20	338	0.83 [0.44 to 1.54]
Asthma	< 12 months	0	0					NE
	12-36 months	2	824	3	422	4	402	0.86 [0.21 to 3.49]
	≥ 36 months	1	706	6	368	5	338	1.10 [0.34 to 3.58]
Any allergies	< 12 months	0	0					NE
	12-36 months	2	823	36	422	52	401	0.66 [0.44 to 0.98] *
	≥ 36 months	1	706	55	368	59	338	0.86 [0.61 to 1.20]

*significant P < 0.05, ** significant P < 0.005, NE = Not estimable, ^R= Random-effects estimate

Table 2. The effects of n-3 LCPUFA supplementation on all allergies using pooled analysis RR (M-H, Fixed, 95% CI)

Assessed Age	No of studies	No of participants	n-3 LCPUFA	Placebo
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Table 2. The effects of n-3 LCPUFA supplementation on all allergies using pooled analysis RR (M-H, Fixed, 95% CI)

<i>Allergy</i> (IgE mediated or not)				<i>Events</i>		<i>Total</i>		<i>Effect Estimate</i>
				<i>Events</i>	<i>Total</i>	<i>Events</i>	<i>Total</i>	<i>RR [95% CI]</i>
<i>Food allergy</i>	< 12 months	1	117	1	52	10	65	0.13 [0.02, 0.95] *
	12-36 months	4	973	19	499	26	474	0.72 [0.40 to 1.30]
	≥ 36 months	1	706	14	368	9	338	1.43 [0.63 to 3.26]
<i>Eczema</i>	< 12 months	2	203	16	100	20	103	0.76 [0.22 to 2.62] ^R
	12-36 months	4	973	118	499	122	474	0.96 [0.69 to 1.33] ^R
	≥ 36 months	2	1237	122	628	131	609	0.88 [0.68 to 1.13] ^R
<i>Allergic rhinitis</i>	< 12 months	0	0					NE
	12-36 months	2	805	10	414	18	391	0.53 [0.25 to 1.12]
	≥ 36 months	2	1169	114	593	109	576	1.03 [0.81 to 1.30]
<i>Asthma</i>	< 12 months	1	83	11	46	7	37	1.26 [0.54 to 2.94]
	12-36 months	4	955	106	491	105	464	0.93 [0.73 to 1.18]
	≥ 36 months	3	1697	165	856	171	841	0.94 [0.78 to 1.13]
<i>Any allergies</i>	< 12 months	0	0					NE
	12-36 months	2	823	109	422	117	401	0.89 [0.71 to 1.11]
	≥ 36 months	3	1765	270	891	274	874	0.96 [0.84 to 1.09]

*significant P < 0.05, ** significant P < 0.005, NE= Not estimable, ^R= Random-effects estimate

Table 3. The effects of n-3 LCPUFA supplementation on skin prick results for allergens using pooled analysis RR (M-H, Fixed, 95% CI)

<i>Skin prick results</i>	<i>Assessed Age</i>	<i>No of studies</i>	<i>No of participants</i>	<i>n-3 LCPUFA</i>		<i>Placebo</i>		<i>Fixed Effect estimate</i>
				<i>Events</i>	<i>Total</i>	<i>Events</i>	<i>Total</i>	<i>RR [95% CI]</i>

Table 3. The effects of n-3 LCPUFA supplementation on skin prick results for allergens using pooled analysis RR (M-H, Fixed, 95% CI) (Continued)

<i>Egg</i>	< 12 months	2	203	7	100	17	103	0.44 [0.19 to 1.04]
	12-36 months	3	893	46	455	82	438	0.55 [0.39 to 0.77] **
	≥ 36 months	1	706	11	368	16	338	0.63 [0.30 to 1.34]
<i>Cow's milk</i>	< 12 months	2	205	5	102	7	103	0.75 [0.24 to 2.29] ^R
	12-36 months	3	897	9	457	13	440	0.68 [0.20 to 2.34] ^R
	≥ 36 months	0	0					NE
<i>Peanut</i>	< 12 months	0	0					NE
	12-36 months	2	778	18	403	28	375	0.61 [0.34 to 1.08]
	≥ 36 months	1	706	13	368	20	338	0.60 [0.30 to 1.18]
<i>Wheat</i>	< 12 months	1	117	1	52	0	65	3.74 [0.16 to 89.85]
	12-36 months	2	783	3	401	2	382	1.40 [0.29 to 6.84]
	≥ 36 months	1	706	6	368	2	338	2.76 [0.56 to 13.56]
<i>Fish</i>	< 12 months	0	0					NE
	12-36 months	1	666	3	349	0	317	6.36 [0.33 to 122.65]
	≥ 36 months	1	706	2	368	1	338	1.84 [0.17 to 20.17]
<i>Inhalant allergens (pollens)</i>	< 12 months	0	0					NE
	12-36 months	2	779	2	400	5	379	0.44 [0.08 to 2.30]
	≥ 36 months	1	580	21	303	25	277	0.77 [0.44 to 1.34]
<i>House dust mite</i>	<12 months	0	0					NE
	12-36 months	2	738	3	384	4	354	0.76 [0.18 to 3.28]
	≥36 months	1	580	22	303	24	277	0.84 [0.48 to 1.46]

Table 3. The effects of n-3 LCPUFA supplementation on skin prick results for allergens using pooled analysis RR (M-H, Fixed, 95% CI) (Continued)

<i>Cat</i>	< 12 months	1	86	1	48	1	38	0.79 [0.05 to 12.25]
	12-36 months	2	738	8	384	7	354	1.07 [0.39 to 2.94]
	≥ 36 months	1	706	25	368	12	338	1.91 [0.98 to 3.75]
<i>Any allergen (one or more allergen)</i>	< 12 months	2	201	14	100	25	101	0.59 [0.32 to 1.09]
	12-36 months	3	892	68	455	93	437	0.70 [0.53 to 0.94] *
	≥ 36 months	1	706	91	368	88	338	0.95 [0.74 to 1.22]

*significant P < 0.05, ** significant P < 0.005, NE = Not estimable

APPENDICES

Appendix 1. PubMed search strategy

1. pregnancy[mh]
2. pregnan*[tiab]
3. maternal exchange*[tiab]
4. transplacental exposure*[tiab]
5. gestat*[tiab]
6. fetal Development [mesh]
7. Fetal Development [tiab]
8. Fetal Programming* [tiab]
9. fetal growth[tiab]
10. Foetal Development [tiab]
11. Foetal Programming* [tiab]
12. foetal growth[tiab]
13. Gestational Age*[tiab]
14. Fetal Age*[tiab]
15. foetal age*[tiab]
16. Breast Feeding[mh]
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19. lactating mother*[tiab]
20. breastfeeding[tiab]
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26. docosahexaenoic acid*[tiab]
27. cod liver oil[tiab]
28. omega 3 fatty acid*[tiab]
29. n 3 fatty acid*[tiab]
30. eicosapentaenoic acid[tiab]
31. n 3 pufa)
32. 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31

33. hypersensitivity[mh]
34. hypersensitiv*[tiab]
35. allerg*[tiab]
36. environmental illness*[tiab]
37. atopic dermatitis[tiab]
38. anaphyla*[tiab]
39. atopic dermatitis[tiab]
40. eczema[tiab]
41. urticaria*[tiab]
42. hives[tiab]
43. 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42
44. 23 AND 32 AND 43
45. randomized controlled trial[pt]
46. controlled clinical trial[pt]
47. randomized controlled trials[mh]
48. random allocation[mh]
49. double-blind method[mh]
50. single-blind method[mh]
51. clinical trial[pt]
52. clinical trials[mh]
53. clinical trial[tw]
54. ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw]))
55. (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design [mh:noexp] OR comparative study[pt] OR evaluation studies as topic[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control[tw] OR controlled[tw] OR prospectiv*[tw] OR volunteer*[tw])
56. 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55
57. NOT animals[mh] NOT (human[mh] and animals[mh])
58. 44 AND 56
59. 58 NOT 57

Appendix 2. CINAHL (via EBSCOhost) search strategy

1. (((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR (placebo* OR random* OR "research design*" OR "comparative stud*" OR "evaluation stud*" OR "follow-up stud*" OR control OR controlled OR prospectiv* OR volunteer*)) NOT (animals NOT human))
2. (pregnan* OR "maternal exchange*" OR "transplacental exposure*" OR gestat* OR "fetal development" OR "fetal programming*" OR "fetal growth" OR "foetal development" OR "foetal programming*" OR "foetal growth" OR "fetal age*" OR "foetal age*" OR "breast feeding" OR "breast fed" OR "lactating mother*" OR breastfeeding OR postpartum)
3. ("fish oil*" OR "docosahexaenoic acid*" OR "cod liver oil" OR "omega 3 fatty acid*" OR "n 3 fatty acid*" OR "eicosapentaenoic acid" OR "n 3 pufa")
4. (hypersensitiv* OR allerg* OR "environmental illness*" OR "atopic dermatitis" OR anaphyla* OR eczema OR urticaria* OR hives)
5. 1 AND 2 AND 3 AND 4

Appendix 3. Scopus search strategy

1. (pregnan* OR "maternal exchange" OR "transplacental exposure" OR gestat* OR "fetal development" OR "fetal programming" OR "fetal growth" OR "foetal development" OR "foetal programming" OR "foetal growth" OR "Gestational Age" OR "fetal age" OR "foetal age" OR "breast feeding" OR "breast fed" OR "lactating mother" OR breastfeeding OR postpartum)
2. ("fish oil" OR "docosahexaenoic acid" OR "cod liver oil" OR "omega 3 fatty acid" OR "n 3 fatty acid" OR "eicosapentaenoic acid" OR "n 3 pufa")
3. (hypersensitivit* OR allerg* OR "environmental illness" OR "atopic dermatitis" OR anaphyla* OR "atopic dermatitis" OR eczema OR urticaria* OR hives)
4. ("randomized controlled trial" OR "randomised controlled trial" OR "random allocation" OR "double blind" OR "single blind" OR "clinical trial*" OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR placebo* OR "comparative stud" OR "follow up stud" OR "prospective stud" OR rct OR "systematic review" OR "meta analys" OR metaanalys*)
5. 1 AND 2 AND 3 AND 4

Appendix 4. Web of Knowledge search strategy

1. pregnan*
2. "maternal exchange"
3. "transplacental exposure"
4. gestat*
5. "Fetal Development"
6. "Fetal Programming"
7. "fetal growth"
8. "Foetal Development"
9. "Foetal Programming"
10. "foetal growth"
11. "Gestational Age"
12. "Fetal Age"
13. "foetal age"
14. "breast feeding"
15. "breast fed"
16. "lactating mother"
17. breastfeeding
18. postpartum
19. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18
20. "fish oil"
21. "docosahexaenoic acid"
22. "cod liver oil"
23. "omega 3 fatty acid"
24. "n 3 fatty acid"
25. "eicosapentaenoic acid"

26. "n 3 pufa"
27. 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26
28. hypersensitivit*
29. allerg*
30. "environmental illness"
31. "atopic dermatitis"
32. anaphyla*
33. "atopic dermatitis"
34. eczema
35. urticaria*
36. hives
37. 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36
38. 19 AND 27 AND 372124
39. ("randomized controlled trial*" OR "controlled clinical trial*" OR "randomised controlled trial*" OR "random allocation*" OR "double blind" OR "single blind" OR "clinical trial*" OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR placebo* OR "comparative stud*" OR "follow up stud*" OR "prospective stud*" OR rct OR "systematic review*" OR "meta analys*" OR metaanalys*)
40. 38 AND 39

Appendix 5. ClinicalTrials.gov search strategy

<http://clinicaltrials.gov>

(hypersensitivity OR hypersensitive OR allergy) AND ("fish oil" OR docosahexaenoic OR "omega 3 fatty acid") AND (pregnancy OR pregnant OR postpartum OR fetal OR foetal OR "breast feeding" OR breastfeeding)

Appendix 6. Data analysis

Data and analyses

Comparison 1: n-3 LCPUFA supplementation versus placebo or no supplementation - any allergy

[Analysis 1.1](#); [Analysis 1.2](#)

Comparison 2: Secondary Outcomes: n-3 LCPUFA supplementation versus placebo or no supplementation - specific type of allergy

[Analysis 2.1](#); [Analysis 2.2](#); [Analysis 2.3](#); [Analysis 2.4](#); [Analysis 2.5](#); [Analysis 2.6](#); [Analysis 2.7](#); [Analysis 2.8](#)

Comparison 3: Secondary Outcomes: n-3 LCPUFA supplementation versus placebo or no supplementation - maternal and infant safety

[Analysis 3.1](#); [Analysis 3.2](#)

Comparison 4: Secondary Outcomes: n-3 LCPUFA supplementation versus placebo or no supplementation - allergen sensitisation

[Analysis 4.1](#); [Analysis 4.2](#); [Analysis 4.3](#); [Analysis 4.4](#); [Analysis 4.5](#); [Analysis 4.6](#); [Analysis 4.7](#); [Analysis 4.8](#); [Analysis 4.9](#)

Comparison 5: Secondary Outcomes: n-3 LCPUFA supplementation versus placebo or no supplementation - parent's reports of allergy

[Analysis 5.1](#); [Analysis 5.2](#); [Analysis 5.3](#); [Analysis 5.4](#); [Analysis 5.5](#)

Comparison 6: Subgroup: Timing of supplementation

[Analysis 6.1](#); [Analysis 6.2](#)

Comparison 7: Subgroup: Allergy risk

[Analysis 7.1](#)

Comparison 8: Sensitivity analysis

[Analysis 8.1](#); [Analysis 8.2](#)

CONTRIBUTIONS OF AUTHORS

AWG and MM were responsible for conceiving the review. AWG, MM and CTC designed, developed and wrote the review. MM and CTC provided a methodological perspective and a clinical perspective and provided general advice on the review. AWG and CTC were responsible for co-ordinating the review.

DECLARATIONS OF INTEREST

Maria Makrides (MM) serves on scientific advisory boards for Nestle, Fonterra and Nutricia. Associated honoraria are paid to the Women's and Children's Health Research Institute to support conference travel and continuing education for post graduate students and early career researchers. MM is an investigator on two trials included in this review ([Makrides 2009](#); [Makrides 2010](#)).

Carmel T Collins is an investigator on two trials included in this review ([Makrides 2009](#); [Makrides 2010](#)).

Anoja W Gunaratne (AWG) was involved in the follow-up at 7 years corrected age of [Makrides 2009](#) and at 3 years of age of [Makrides 2010](#).

The [Makrides 2009](#) and [Makrides 2010](#) trials were independently assessed for inclusion, risk of bias and data extracted by AWG and a third party (Karen Best).

SOURCES OF SUPPORT

Internal sources

- Women's & Children's Health Research Institute, The University of Adelaide, Adelaide, Australia.

External sources

- NHMRC Center for Research Excellence in Food for Future Australians (ID App1035530), Australia.
- Maria Makrides was supported by a Fellowship from National Health Medical Research Council (NHMRC) (ID App1061704), Australia.
- Carmel T Collins was supported by a Postdoctoral Research Fellowship from the MS McLeod Research Fund of the Women's and Children's Hospital Foundation, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Due to different methods of reporting across trials, we deemed it inappropriate to conduct analyses of cumulative allergies across time points.
2. In the protocol we specified the primary outcome only as allergy. We have refined this for the review, with any allergy being our primary outcome (medically diagnosed IgE mediated; and medically diagnosed IgE mediated and/or parental report). Specific forms of allergy (food allergy, eczema, allergic rhinitis and asthma/wheeze) are now secondary outcomes.
3. Trials that reported 'wheeze' were included in the allergy outcomes for asthma, with the outcome being changed to asthma/wheeze.
4. The data were reported at last time point in the subgroup analysis comparisons.
5. Maternal safety was added as a secondary safety outcome (e.g. postpartum haemorrhage or infection) due to the theoretical risk of harm associated with higher doses of n-3 LCPUFA.
6. In the [Objectives](#), we made it clearer that the aim of this review was to assess the effect of maternal n-3 LCPUFA supplementation in mothers during pregnancy and/or lactation on the allergy outcomes of in their children.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Age Factors; Fatty Acids, Omega-3 [*administration & dosage]; Food Hypersensitivity [prevention & control]; Hypersensitivity [*prevention & control]; Immunoglobulin E [immunology]; Postnatal Care; Prenatal Care; Randomized Controlled Trials as Topic

MeSH check words

Child, Preschool; Female; Humans; Infant; Infant, Newborn; Pregnancy