

Review article

Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis

Background: There is conflicting evidence on the use of omega 3 and omega 6 supplementation for the prevention of allergic diseases. We conducted a systematic review evaluating the effectiveness of omega 3 and 6 oils for the primary prevention of sensitization and development of allergic disorders.

Methods: We searched The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, LILACS, PsycInfo, AMED, ISI Web of Science and Google Scholar for double-blind randomized controlled trials. Two authors independently assessed articles for inclusion. Meta-analyses were undertaken using fixed effects modelling, or random effects modelling in the event of detecting significant heterogeneity.

Results: Of the 3129 articles identified, 10 reports (representing six unique studies) satisfied the inclusion criteria. Four studies compared omega 3 supplements with placebo and two studies compared omega 6 supplements with placebo. There was no clear evidence of benefit in relation to reduced risk of allergic sensitization or a favourable immunological profile. Meta-analyses failed to identify any consistent or clear benefits associated with use of omega 3 [atopic eczema: RR = 1.10 (95% CI 0.78–1.54); asthma: RR = 0.81 (95% CI 0.53–1.25); allergic rhinitis: RR = 0.80 (95% CI 0.34–1.89) or food allergy RR = 0.51 (95% CI 0.10–2.55)] or omega 6 oils [atopic eczema: RR = 0.80 (95% CI 0.56–1.16)] for the prevention of clinical disease.

Conclusions: Contrary to the evidence from basic science and epidemiological studies, our systematic review and meta-analysis suggests that supplementation with omega 3 and omega 6 oils is probably unlikely to play an important role as a strategy for the primary prevention of sensitization or allergic disease.

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Over recent decades there has been a dramatic increase in allergic diseases worldwide (1). These conditions now pose a substantial disease burden on individuals and healthcare organizations internationally (2, 3). There is thus considerable interest in identifying interventions that have the ability to prevent or modify disease course and there is an increasing body of evidence from randomized controlled trials (RCTs) investigating a number of pharmacological and non-pharmacological interventions. This evidence is, however on the whole disparate making it difficult for patients, professionals and policy makers to come to any firm conclusions on the effectiveness of these interventions.

One such intervention is the use of essential fatty acids (EFA) for the prevention and treatment of symptoms of eczema, rhinitis and asthma. There are two families of EFAs that have attracted greatest interest in relation to the aetiology and treatment of allergic disease: these are omega 3 and omega 6 oils. Some of the substances found in omega 6 oils are precursors of a group of substances

called eicosanoids, which may play an important part in the inflammatory and immunological pathophysiology of atopic disease (4). Fish oils are particularly rich in omega 3 fatty acids, and the potential anti-inflammatory active ingredient in these is eicosapentaenoic acid, which may reduce airway inflammation and bronchoconstriction (5).

Studies have shown that omega 3 dietary supplementation during pregnancy can modify immune responses in infants and may reduce subsequent infant allergy (6). Also, high levels of omega 3 fatty acids in the diet have found to be associated with a decreased risk of allergic sensitization and allergic rhinitis (7), and regular fish consumption before the age of 12 months appears to be associated with a reduced risk of allergic sensitization to food and inhalant allergens during the first 4 years of life (8, 9). Also relevant is that studies have shown that breast milk low in omega 3 fatty acids may be a risk factor for atopic dermatitis in the infant (10). Conversely, however, studies have also found that omega 3 fatty acid supplementation alone does not improve asthma symptoms (11) and that there is little

evidence to recommend that people with asthma supplement or modify their dietary intake of omega 3 fatty acids in order to improve asthma control (7) or hay fever symptoms (12). A more recent study suggested that it is at present impossible to determine whether or not omega 3 fatty acids are an efficient adjuvant or monotherapy for children or adults with asthma (13).

Evidence for the role of omega 6 oil in atopic dermatitis is also somewhat conflicting; for example, one study showed that early supplementation with omega 6 in children at high familial risk did not prevent the expression of atopy as reflected by total serum IgE, but it tended to alleviate the severity of atopic dermatitis in later infancy (14). Further, out of 24 people who had taken a dietary supplement of evening primrose oil for atopic dermatitis (omega 6), 13% found that it helped their skin (15). However, the study by Kitz et al. found that omega 6 supplementation did not prevent atopic disease although it did seem to reduce total IgE in the first year of life (16).

The evidence is also unclear in relation to the treatment of allergic diseases in general. For example, one study found that these supplements did not prevent the onset of atopy, eczema or asthma in high-risk children (17) whereas another concluded that careful manipulation of dietary omega 3 and 6 may play a key role in the successful management of inflammation associated with atopic diseases (18).

There is thus at present conflicting evidence on both the use of omega 3 and omega 6 supplementation (separately and in combination) for the prevention and treatment of allergic diseases. Whilst systematic reviews evaluating the effectiveness of omega 3 and omega 6 as a *treatment* agent for those with *established* allergic disease are currently in progress (4, 5) there is at present no systematic summary of the literature evaluating the role of omega 3 and omega 6 fatty acids for the *primary prevention* of allergic disorders.

We aimed to conduct a systematic review evaluating the effectiveness of omega 3 and 6 oils for the primary prevention of sensitization, eczema/atopic dermatitis, allergic rhinitis, asthma and other allergic disorders.

Methods

We conducted a systematic review of the literature using standard internationally agreed upon approaches for identifying and appraising RCT evidence. This involved formulating a clearly described search strategy for identifying all double-blind placebo RCTs investigating the effectiveness of omega 3 and 6 oil supplements for the primary prevention of eczema/atopic dermatitis, allergic rhinitis, asthma and other allergic disorders. We included both completed and ongoing work and used a standardized approach to assessing study quality, data abstraction and synthesis that sought to minimize the risk of drawing erroneous conclusions and to maximize transparency. Our review protocol was subjected to international peer review by the funding body.

RCTs were identified by using a detailed search strategy for the following databases: The Cochrane Central Register of Controlled

Trials (CENTRAL, from 1966 to 2008) in *The Cochrane Library* (last update); MEDLINE (from 1966 to 2008); EMBASE (from 1966 to 2008); LILACS (from 1982 to 2008); PsycInfo (from 1966 to 2008); AMED (from 1985 to 2008); ISI Web of Science. (from 1966 to 2008); and Google Scholar (from 2000 to 2008).

Titles and abstracts of trials identified from the searches were checked by two reviewers (CA and UN). The full texts of all RCTs of possible relevance were independently assessed by two reviewers (CA and UN). Any disagreements were resolved by discussion between the authors and if resolution could not be achieved a third reviewer arbitrated (AS).

The bibliographies of eligible studies were scrutinized for possible additional RCTs. Unpublished and ongoing trials were identified through searching the metaRegister of Controlled Trials, Clinical-Trials.gov and the UK NHS National Research Register. We also contacted omega fatty acid manufacturers and corresponded with experts in the field. No language restrictions were imposed.

The methodological quality of included RCTs was independently assessed by two reviewers and documented following the Cochrane approach using the methods detailed in section six of the Cochrane Handbook for Systematic Reviews of Interventions (19). In essence, this involved concentrating on using the following five parameters to assess quality: allocation concealment; method of allocation to treatment; documentation of exclusions; completeness of follow-up; and methods of documentation of complications. Each parameter of trial quality was graded according to: A – low risk of bias; B – moderate risk of bias and C – high risk of bias. An overall assessment for each controlled trial using these three criteria was then made.

Reviewers were not masked to study details. We assessed the agreement of reviewers on methodological quality assessment and any disagreements were resolved by discussion. The quality assessment also included an evaluation of the following components for each included study since there is evidence that these are associated with biased estimates of treatment effect (20). Each study was assessed using the 0–5 scale described by Jadad et al. (21).

Data extraction was performed independently by CA and checked by UN using a customized data extraction form. Discrepancies were resolved by discussion, with arbitration by AS if necessary.

Inclusion and exclusion criteria

Types of participants. We were interested in studies of individuals judged to be both at high- and low-risk of developing eczema/atopic dermatitis, allergic rhinitis, asthma and/or other allergic disorders. Studies involving children and adults with an existing allergic condition were excluded.

Types of intervention. We were interested in studies that had investigated omega 3 and 6 oil supplements used either in isolation or in combination.

Statistical analysis

We considered the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. We assumed significant heterogeneity if the I^2 was greater than 40% (i.e. more than 40% of the variability in outcome between trials could not be explained by sampling variation) (22). We undertook meta-analysis using the fixed-effects model (in the absence of statistical heterogeneity) and a random-effects model (if such heterogeneity was likely). However, if there were only two studies in the analysis, the I^2

could not be calculated, so we used the more conservative approach and undertook random effects modelling.

We used StatsDirect (23) for data analysis and quantitative data synthesis undertaking separate analyses for omega 3 and omega 6 oil supplements. We calculated individual and pooled relative risks (RR) with 95% confidence intervals (95% CI).

Evidence of publication bias using funnel plots could not be explored for any outcome other than asthma as there were insufficient numbers of trials. Similarly, with the exception of the data for asthma, these data could not be explored further using Begg (24) and Egger (25) tests. There were insufficient numbers of trials to meaningfully undertake sensitivity analyses based on assessment of study quality.

Results

We identified a total of 3129 articles of potential interest; of these, a total of 23 articles that related to 19 studies were identified for detailed assessment. After reviewing the methodology of these studies, we excluded 13 further papers leaving a total of 10 eligible reports relating to six individual trials (see Fig. 1).

The six trials that met the inclusion criteria were all double-blind studies; all studies enrolled high-risk individuals with two of these studies also enrolling low-risk individuals (see Table 1). Of these studies, four trials (eight reports) compared omega 3 marine fatty acid supplements with placebo (6, 17, 26–31). These four trials enrolled 679 participants. Two studies compared omega 6 fatty acid supplementation with a placebo (14, 16) and there were a total number of 259 participants in these two studies. Our searches for unpublished material identified a further eight studies in progress (see Fig. 2).

Incidence of eczema/atopic dermatitis

The incidence of eczema/atopic dermatitis was reported in three of the studies that looked at omega 3 (total 664 subjects) (6, 17, 28) and the two studies that looked at omega 6 (total 259 subjects) (14, 16) as assessed by a qualified clinician.

The pooled data for risk of developing eczema/atopic dermatitis following omega 3 fatty acid supplementation showed a non-significant increased risk in those that received the intervention compared to those receiving placebo (RR = 1.10; 95% CI 0.78–1.54; see Fig. 3). The pooled relative risk for development of eczema/atopic dermatitis in those receiving omega 6 fatty acids compared to placebo was 0.80 (95% CI 0.56–1.16; see Fig. 4) indicating that omega 6 supplementation had a non-significant protective effect.

Incidence of asthma

Four studies assessed asthma incidence in 1078 subjects in either high- or low-risk individuals receiving omega 3 supplementation (17, 27, 28, 30). The Begg and Egger

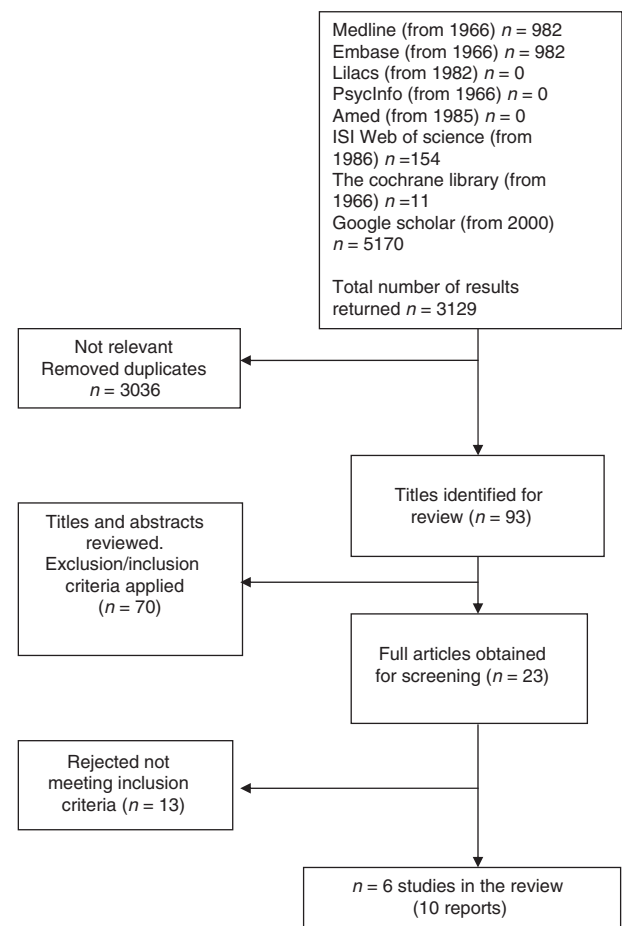


Figure 1. PRISMA diagram of published studies.

tests showed a slight effect of publication bias [Begg-Mazumdar: Kendall's tau = -0.667 $P = 0.083$ (low power); Egger = -2.668 (95% CI = -6.35 to 1.01) $P = 0.089$]. Since the I^2 was greater than 40% we used the random effect model to analyse these data. The pooled analysis revealed a non-significant risk reduction (RR = 0.81; 95% CI 0.53–1.25; see Fig. 5).

Incidence of allergic rhinitis

Two studies investigated allergic rhinitis incidence in 599 subjects; both assessed the effectiveness of omega 3 supplementation (17, 27). The results showed a non-significant risk reduction (RR = 0.80; 95% CI 0.34–1.89; see Fig. 6) in those receiving omega 3 supplementation when compared to those receiving placebo.

Incidence of food allergy

Two studies investigated food allergy incidence in 148 subjects in those receiving omega 3 supplementation

Table 1. Constituents and details of the included primary prevention trials

Study	Omega	High or low risk?	Intervention	Control	Who took the supplement?	Duration	Quality assessment
Dunstan et al. 2003a	Omega 3	High	Fish oil	Olive oil	Breastfeeding mothers	20 weeks gestation until delivery	Quality score = 5 Quality assessment = A
Dunstan et al. 2003b	Same as above study	High					
Denburg et al. 2008	Same as Dunstan et al. study	High					
Lauritzen et al. 2005	Omega 3	High and low	Fish oil	Olive oil	Breastfeeding mothers	First 4 months	Quality score = 5 Quality assessment = A
Marks et al. 2006	Omega 3	High	Canola and tuna based oils in diet	Polyunsaturated oils low in n-3 fatty acids	Newborns	6 months	Quality score = 5 Quality assessment = A
Peat et al. 2004	Same as Marks et al. study	High					
Mihrshahi et al. 2003	Same as Marks et al. study	High					
Olsen et al. 2008	Omega 3	High and low	Fish oil	Olive oil	Pregnant mothers	30 weeks gestation until delivery	Quality score = B Quality assessment = 3
Kitz et al. 2005	Omega 6	High	Whey hydrolysate formula supplemented with GLA	Whey hydrolysate formula	Breastfeeding mothers or formula fed newborns	First 6 months	Quality score = 5 Quality assessment = A
Van Gool et al. 2003	Omega 6	High	Borage oil (GLA)	Sunflower oil	Formula fed newborns	First 6 months	Quality score = 5 Quality assessment = A

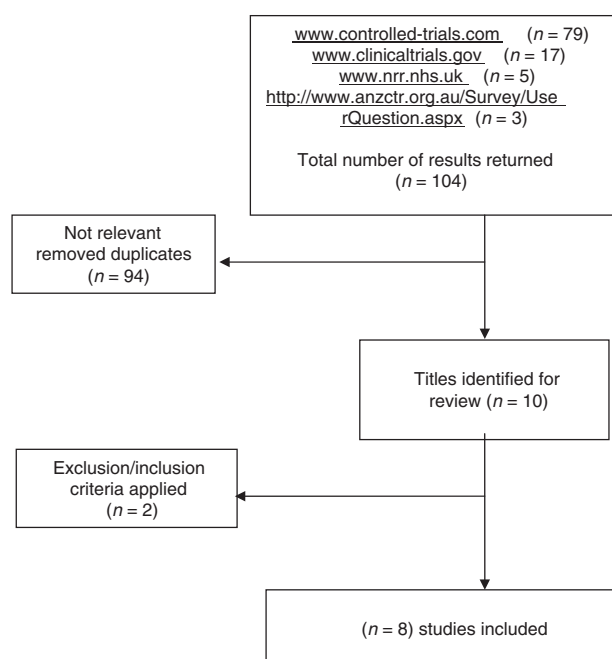


Figure 2. PRISMA diagram of unpublished studies.

(27, 28). The pooled assessment revealed a non-significant risk reduction (RR = 0.51; 95% CI 0.10–2.55; Fig. 7) in those receiving supplementation when compared to those receiving placebo.

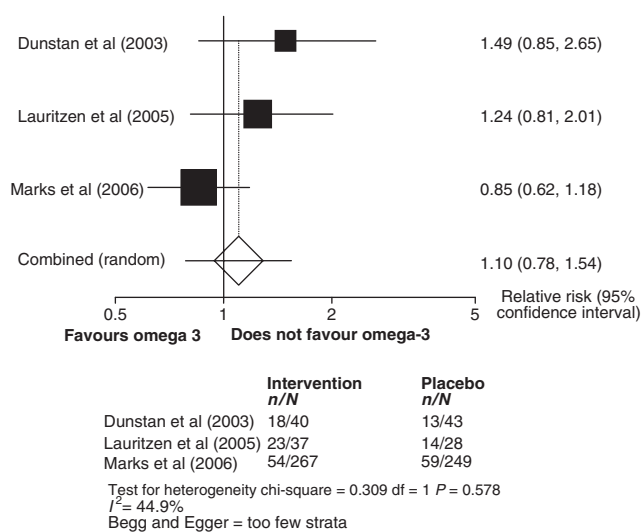


Figure 3. Comparison of omega 3 supplementation vs placebo (double-blind RCTs) for eczema/atopic dermatitis (random effects model).

Sensitization to common allergens

Two studies assessed sensitization using skin prick tests (SPT) (17, 27). Marks et al. (17) measured atopy as a positive SPT to any of salmon, peanuts, cow's milk, egg white, egg yolk, tuna, house dust mite (HDM, *Dermatophagoides pteronyssinus*), cockroach, cat, *Alternaria*

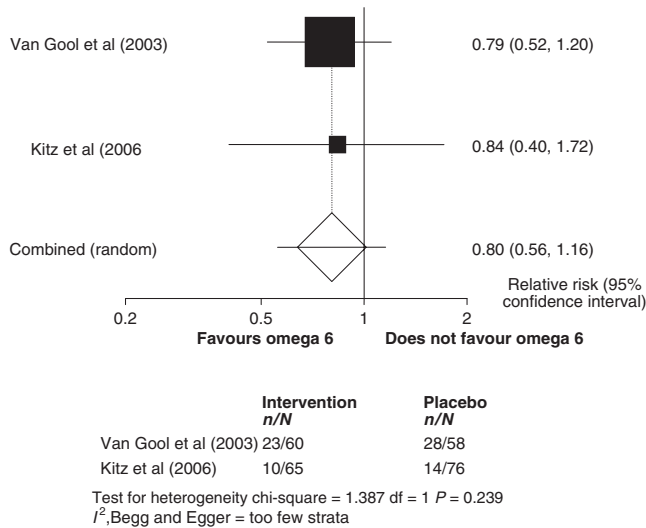


Figure 4. Comparison of omega 6 supplementation vs placebo (double-blind RCTs) for eczema/atopic dermatitis (random effects model).

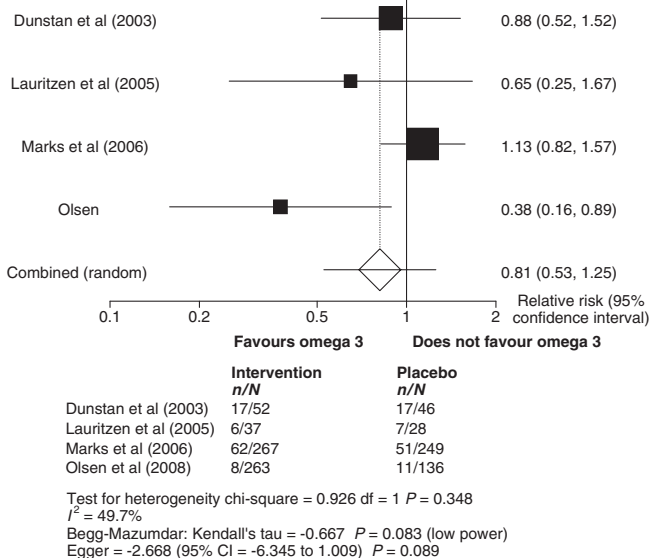


Figure 5. Comparison of omega 3 supplementation vs placebo (double-blind RCTs) for asthma (random effects model).

alternata, rye grass and grass mix. Glycerol and histamine phosphate were used as positive and negative controls. Wheal sizes that were ≥ 2 mm and also greater than the negative control were classified as positive. Dunstan et al. (27) tested for egg, milk, peanut, HDM and cat using the same positive and negative controls and wheal diameter as Marks et al.

The SPT for 'any atopy', which was carried out in 560 subjects, revealed a non-significant protective effect (RR = 0.92; 95% CI 0.76–1.11). This thus showed that 'any positive SPT' was slightly higher in those that

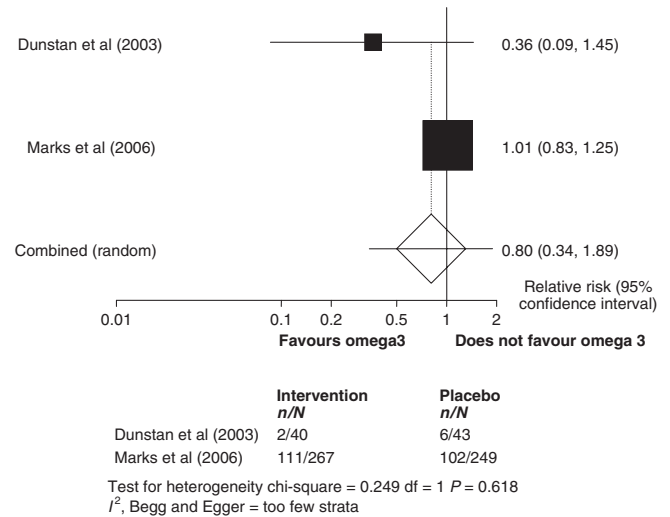


Figure 6. Comparison of omega 3 supplementation vs placebo (double-blind RCTs) for allergic rhinitis (random effects model).

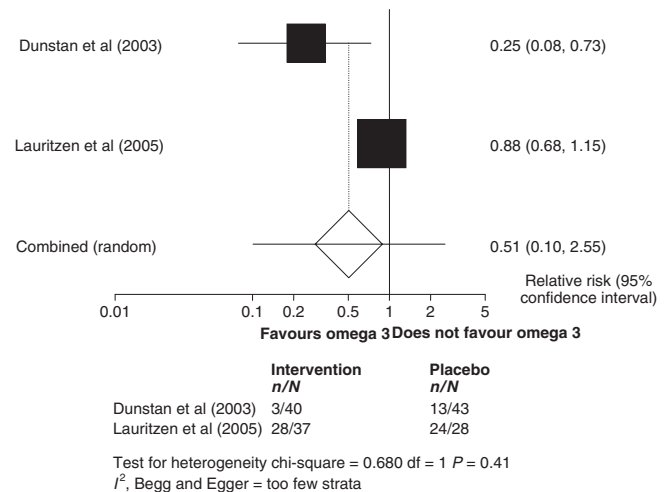


Figure 7. Comparison of omega 3 supplementation vs placebo (double-blind RCTs) for food allergy (random effects model).

received the placebo compared to those that received the omega 3 supplement.

Dunstan et al. (6, 27) and Marks et al. (17) reported individual data for SPT to HDM in 560 subjects receiving omega 3 supplementation, which revealed a small non-significant increase in risk of sensitization in those receiving supplementation (RR = 1.04; 95% CI 0.81–1.34) compared to those receiving placebo.

Two studies using omega 3 supplementation (17, 28, 31) and two using omega 6 (14, 16) supplementation reported IgE results. In one study (omega 3 supplementation) at 3 years (31), there was no significant difference ($P = 0.09$) in the geometric mean total IgE concentrations between those that received the supplement [31.0 kIU/l (95% CI

25.0–38.4)] and those in the placebo [40.1 kIU/l (95% CI 32.5–49.5)]. Similar results were found at 5 years ($P = 0.3$) (17). The study by Lauritzen et al. (28) (omega 3 supplementation) measured total plasma IgE levels (titre value) and it was approximately the same for those that received the intervention [8.9 (titre value 8.0–9.2)] and the control [8.8 (titre value 7.3–9.2)] $P > 0.05$.

Van Gool et al. (14) (omega 6 supplementation) reported a non-significant increase ($P = 0.24$) in mean total IgE at aged 1 year (9.31, $\pm$ SD 4.45) in those receiving supplementation when compared to those in the control group (6.87, $\pm$ SD 3.56). Kitz et al. (16) found that atopic subjects that received omega 6 supplementation had significantly lower IgE levels than those that did not receive the supplementation ($P < 0.01$). In the non-

atopic subjects, no significant effect of omega 6 supplementation on IgE levels was found.

Severity of allergic disease

Three studies used the validated SCORing Atopic Dermatitis (SCORAD) to assess atopic dermatitis/eczema severity in those receiving omega (6, 26, 27) and omega 6 (14, 16) supplementation. Data were not amenable to meta-analyses because of differences in reporting approach. The findings from each study are therefore considered individually below.

Dunstan et al. (6, 27) (omega 3 supplementation) found that in those with atopic eczema/dermatitis, those receiving omega 3 were 10 times less likely to have severe

Table 2. Unpublished studies

Clinical trials identifier and author	Study population	Intervention	Main outcomes	Location
NCT00380926 http://www.controlled-trials.com	Allergic sensitization to house dust mite as proven by skin test and specific IgE Normal lung function, episodic asthma	n-3 Fish oil supplement	lung function, symptom score, exhalative nitric oxide, metacholine testing	Germany
NCT00676468 http://www.controlled-trials.com Mickleborough et al. 2008	Males and females with exercise-induced bronchoconstriction	n-3 Fish oil supplement	sulfoleucotriens, eosinophilic cationic protein, sputum eosinophils, safety lab parameters (clinical chemistry, haematology, haemostasis)	USA
NCT00621829 http://www.controlled-trials.com Zeki et al. 2008	Children and adults patients >18 years or older with moderate and severe asthma (as diagnosed by lung specialist physician), based on the NIH NAEPP 1997 guidelines, who do not have an acute exacerbation at the time of enrolment and are on the same asthma medications for at least 1 month	n-3 Fish oil supplement	Asthma exacerbations 3 months	USA
NCT00325208 http://www.ClinicalTrials.gov Fewtrell MS, 2005	Preterm infants	Long-chain PUFA supplement of formula milk	– cognitive and neurological status – anthropometry – Atopy- asthma/eczema – blood pressure	UK
N0231193482 http://www.nrr.nhs.uk/ Calder P, 2007	Pregnant women	Oily fish consumption	– markers of risk in cord blood – manifestations of atopy at 6 months	UK
NCT00379171 http://www.ClinicalTrials.gov Michaelsen et al.	Healthy infants from 8 to 12 months	An Intervention Study With Milk Types and LC-PUFA Supplements in 9- to 12-month-old infants	Secondary Outcome Measures: Allergy status; Faeces samples: Calprotectin, IgA and composition of the intestinal microbiota	Denmark
ACTRN12606000281594 http://www.anzctr.org.au/Survey/UserQuestion.aspx Prescott et al.	Infants whose maternal asthma or hay fever, and atopy was confirmed by skin testing (to common allergens)	n-3 Fish oil supplement	Allergic sensitization and Allergic disease assessed at 1, 2.5 and 5 years of age. Effects on immune development	Australia
NCT00631046 http://www.ClinicalTrials.gov Michaelsen et al.	Singleton infants, 8–19 months	n-3 Fish oil supplement	Assess the effect of n-3 LCPUFA on growth and body composition. Secondary outcome: Allergy status	Denmark

disease (SCORAD > 25) compared to controls (OR = 0.09; 95% CI 0.01–0.94; $P = 0.045$). Van Gool et al. (14) (omega 6 supplementation) showed a favourable trend in SCORAD in the omega 6 supplemented group (mean $\pm$ SD, 6.32 ± 5.32) compared to the control (8.28 ± 6.54). Kitz et al. (16) used SCORAD in their final diagnosis of atopic eczema/dermatitis (omega 6 supplementation), but scores were not reported.

Only one study reported lung function results for asthma (17) and this did not show a significant beneficial effect of omega 3 supplementation on lung function at 5 years (Fev1/FVC ratio baseline: Control = 0.95; Intervention = 0.95/% change in FEV1: Control = 3.4%; Intervention = 3.5/% change in resistance of the respiratory system: Control = –15.6%; intervention = –13.8%).

Immunological outcomes

Two of the studies that investigated omega 3 supplements reported immunological and fatty acid data, however, these data were not suitable for meta-analyses because of reporting differences. We therefore consider the findings from each of these studies individually below.

Dunstan et al. (6, 27) found that all neonatal cytokines [interleukin (IL)-5, IL-13, IL-10 and interferon γ (IFN γ)] responses (to all allergens) were lower for the omega 3 group. However, the IL-10 in response to cat allergen was significantly lower in the fish oil supplemented group

compared with the control group (mean difference, –0.543; 95% CI –1.076 to –0.010; $P = 0.046$). Lauritzen et al. (28) reported that IFN γ levels in the omega 3 group were fourfold higher than in the control (olive oil) group ($P = 0.034$), but IL-10 was similar for both groups.

Two studies measured plasma fatty acids after omega 3 supplementation. One study aimed to modify the dietary ratio of omega 3 to omega 6 as there is evidence that omega 6 fatty acids compete with omega 3 fatty acids (32). The authors measured plasma fatty acids (using gas chromatography) and reported the proportion of total fatty acids that were omega 3 and omega 6 respectively at 3 years (31) and 5 years (17). The ratio of omega 3 to omega 6 was much lower in the intervention group [1 : 5.6 (at 3 years) and 1 : 5.8 (at 5 years)] compared to the placebo group [1 : 7.7 (at 3 years) and 1 : 7.4 (at 5 years); ($P < 0.001$ for all comparisons)].

The second study (28) reported that at 4 months, omega 3 polyunsaturated fatty acids (PUFA) levels were higher in the fish oil group compared to control ($P < 0.0001$), but there were no significant differences in outcomes at the two-and-a-half year assessment.

None of the studies reported any data on health economics or adverse events.

All of the experts in the field that we contacted responded and agreed with our included published and list of ongoing studies; one expert however alerted us to two additional ongoing studies (see Table 2).

Table 3. Summary of results for omega (a) 3 and (b) 6 trials

Outcome	Summary
(a)	
Incidence: Eczema/atopic dermatitis	Incidence higher in those that received the intervention compared to those that received the placebo [RR: 1.10 (95% CI: 0.78–1.54)].
Incidence: Asthma	Incidence higher in those that received the placebo compared to those that received intervention [RR: 0.81 (95% CI: 0.53–1.25)].
Incidence: Allergic rhinitis	Incidence higher in those that received the placebo compared to those that received intervention [RR: 0.80 (95% CI: 0.34–1.89)].
Incidence: Food allergy	Incidence higher in those that received the placebo compared to those that received intervention [RR: 0.51 (95% CI: 0.10–2.55)].
SPT: Any allergy	'Any positive SPT' was slightly higher in those that received the placebo compared to those that received the intervention [0.92 (95% CI: 0.76–1.11)].
SPT: HDM	Increase in the risk of sensitization in those receiving the intervention compared to placebo [RR: 1.04 (95% CI: 0.81–1.34)].
Total IgE	No difference in IgE between placebo and intervention groups.
SCORAD	Those receiving intervention 10 times less likely to have a SCORAD >25 compared to placebo.
Lung function	No significant beneficial effect of intervention on lung function at 5 years.
Neonatal cytokines: IL-5, IL-13, IL-10 and IFN γ	Responses (to all allergens) were lower for the intervention group compared to placebo. IFN γ fourfold higher in intervention group than placebo.
Plasma fatty acids	The ratio of omega 3 to omega 6 was much lower in the intervention group than placebo at 5 years.
Outcome	Details
(b)	
Incidence: Eczema/atopic dermatitis	Incidence higher in those that received the placebo compared to those that received the intervention [RR: 0.80 (95% CI 0.56–1.16)].
Total IgE	Non significant increase in mean total IgE at aged 1 year in those receiving supplementation compared to those in the control group. Significantly lower IgE levels in intervention group (high risk) than those that did not receive the supplementation.
SCORAD	SCORAD: Score is less in the intervention group compared to placebo

Discussion

Our systematic review and meta-analysis suggest that supplementation with omega 3 and/or 6 oils is unlikely to be associated with a marked reduction in risk of developing sensitization or indeed allergic disease (Table 3 a,b). These interventions cannot therefore at present be recommended as a preventative strategy.

The basic sciences and epidemiological literature investigating the relationship between omega 3 and 6 oils and allergic disease development has overall been suggestive of benefits, but our systematic review has revealed that the results from well-conducted experimental studies have been far less conclusive. This work thus underscores the importance of RCT evidence in guiding decisions regarding interventional measures as it is only such study designs that are able to overcome the chief limitations of epidemiological studies, namely the difficulties in controlling for unknown confounding factors and the risk of bias. This is particularly relevant in the context of intervention decisions for primary prevention strategies, where the intervention is being given to healthy individuals and the burden of proof required before deciding to intervene is appropriately high.

The main strength of this work lies in the detailed search strategy – including the search for unpublished and ongoing work – the rigorous and transparent methods employed, and the quantitative synthesis of data only where this was considered clinically and statistically

appropriate. Despite the extensive searches undertaken there remains the possibility however that we may have failed to locate some relevant evidence, this representing the main potential limitation of this work.

Conclusions

There is as yet no clear evidence to support the use of omega 3 and omega 6 fatty acids for the primary prevention of atopic allergic disease development or indeed sensitization. Future trials should seek to build on the findings of this systematic review and meta-analysis and in so doing ensure that they study the impact of these interventions on mechanistic, clinical and health services endpoints.

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