National Institute for Health and Care Excellence

Final

Addendum to Clinical Guideline 72, Attention deficit hyperactivity disorder

Clinical Guideline Addendum 72.1

Methods, evidence and recommendations

February 2016

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Developed by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Contents

Clinical guidelines update

The NICE Clinical Guidelines Update Team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the new surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

The NICE guideline on attention deficit hyperactivity disorder (ADHD, NICE clinical guideline CG72) was reviewed in 2015 as part of NICE's routine surveillance programme to decide whether it required updating. The surveillance report identified new evidence relating to the effects of diet on ADHD. The full report can be found here: https://www.nice.org.uk/guidance/cg72/resources/attention-deficit-hyperactivity-disorder-adhd-surveillance-review-decision3.

There has been considerable interest in the effect of diet on ADHD. The original NICE guideline on ADHD recommended that children and young people with ADHD should be referred to a dietician for advice on diet if there is a clear link (from a food diary) between behaviour and a particular type of food or drink. NICE also recommended that the elimination of colourings and additives from the diets of children and young people with ADHD should not be routinely advised, and there are no current recommendations on the routine elimination of other substances. The 2015 NICE surveillance review found new evidence that assessed the effectiveness of a 'few food' diet and may have an impact on current recommendations. A 'few food' diet is a type of restriction/elimination diet, where certain foods are either restricted, or removed from the diet completely. When following a 'few food' diet, a diet is limited to 1 or a small number of foods from each food group; for example a diet could be restricted to rice, meat, vegetables, pears and water.

Polyunsaturated fatty acids (PUFAs) have also been proposed as a possible treatment for ADHD. N-3 PUFAs are present in the diet in oily fish, whereas N-6 PUFAs can be found in nuts, poultry and cereals. Both N-3 and N-6 PUFAs can be consumed as dietary supplements, which are available from pharmacies, health food shops, and supermarkets. N-3 PUFAs can also be prescribed by healthcare professionals, although ADHD is not a licensed indication. The original NICE guideline on ADHD recommended that dietary fatty acid supplementation should not be used for the treatment of ADHD in children and young people. The aim of this update was to review new evidence in this area.

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be

cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

Recommendations in this addendum fall into the following categories:

- **[new 2016]** if the evidence has been reviewed and the recommendation has been added or updated, or
- **[2016]** if the evidence has been reviewed but no change has been made to the recommended action.

1.2 Recommendations

1. Do not advise elimination of artificial colouring and additives from the diet as a generally applicable treatment for children and young people with ADHD. [2016]
2. Ask about foods or drinks that appear to influence hyperactive behaviour as part of the clinical assessment of ADHD in children and young people, and:
    - if there is a clear link, advise parents or carers to keep a diary of food and drinks taken and ADHD behaviour
    - if the diary supports a relationship between specific foods and drinks and behaviour, offer referral to a dietitian
    - ensure that further management (for example, specific dietary elimination) is jointly undertaken by the dietitian, mental health specialist or paediatrician, and the parent or carer and child or young person. [2016]
3. Advise the family members or carers of children with ADHD that there is no evidence about the long-term effectiveness or potential harms of a 'few food' diet for children with ADHD, and only limited evidence of short-term benefits. [new 2016]
4. Do not advise or offer dietary fatty acid supplementation for treating ADHD in children and young people. [2016]

1.3 Patient-centred care

This guideline offers best practice advice on the care of children and young people with attention deficit hyperactivity disorder (ADHD).

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the person is under 16, their family or carers should also be

given information and support to help the child or young person make decisions about their treatment. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have the capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good service user experience. All healthcare professionals and social care practitioners working with people using adult NHS mental health services should follow the recommendations in Service user experience in adult mental health.

If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's Transition: getting it right for young people.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people ADHD. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

1.49 Methods

This update was developed based on the process and methods described in the guidelines manual 2014. For details specific to the evidence review for each question, see Sections 2.1.3 and 2.2.3.

2 Evidence review and recommendations

2.1 Review question 1

The NICE guideline on attention deficit hyperactivity disorder (ADHD) was reviewed in 2015, and new evidence on the effectiveness of elimination and restriction diets on ADHD was found. The aim of the review is to evaluate the effectiveness of elimination and restriction diets on children and young people with ADHD.

2.1.1 Review question

What is the clinical and cost-effectiveness of elimination/restriction diets in children and young people with ADHD?

2.1.2 Clinical evidence review

2.1.3 Methods

A systematic review of the literature was conducted, as specified in the review protocol in Appendix C. The protocol was developed in consultation with the topic expert members, and then reviewed by the core Committee members, before the review was carried out. The following outcomes were considered important for decision making: ADHD symptom severity (rated by the parent, teacher or self-rated), academic performance, functional status, side effects (limited to: gastrointestinal symptoms, change in weight/height, change in appetite, change in sleep pattern, headache), number of participants and quality of life.

A systematic search was conducted (see appendix D). The titles and abstracts were screened and full-text version of articles that were identified as potentially relevant were obtained and reviewed against the criteria specified in the review protocol (appendix C).

Many of the outcomes for the review were reported as change measures from baseline (for example, change in ADHD symptom severity). Some studies did not report this measure directly, but instead reported the measure at baseline and at follow up for each group. In these situations the reviewer calculated the mean change from baseline and imputed the standard deviation for this measure using the following equation:

$$SD(change)=\sqrt{(〖SD(baseline)〗^2+〖SD(followup)〗^2-(2\times\rho\times SD(baseline)\times SD(followup))}$$

Where SD is the standard deviation and ρ is the correlation between baseline and follow up measurements across participants. This correlation can be estimated from studies that report both baseline and follow-up measurements as well as change scores. However, such studies were not available for all outcomes in this review, and so a conservative value of 0.5 was used, as is recommended when reliable correlation coefficients for the outcomes and populations of interest are not available (Follman et al., 1992; Fu et al., 2013).

When more than one study assessed an outcome for a given comparison, data were combined using pair-wise meta-analyses. The Mantel-Haenszel and inverse variance methods were used for dichotomous and continuous outcomes, respectively. A random effects model was chosen because the treatment effects were unlikely to be identical across studies due to differences in baseline ADHD severity and the heterogeneity in interventions across studies. The I^2, chi^2 and tau^2 statistics were calculated to assess heterogeneity. Forest plots showing the outcome of these meta-analyses are shown in appendix I.

Data were not available to assess any of the subgroup effects specified in the review protocol (age, comorbid learning disability, neurological or behavioural disorder, ADHD severity).

The quality of evidence for each outcome for each comparison was appraised using the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (for full GRADE profiles, see appendix H). All included studies were randomised controlled trials. Both included studies were unblinded; parents, teachers and clinicians were aware of group allocation. This was considered a very serious risk of bias for subjective outcomes rated by an unblinded observer (e.g. ADHD symptom severity) and a serious risk of bias for outcomes that could be objectively measured (e.g. number of participants leaving the study early). Inconsistency (the variability in the results from different trials) was only assessed when data were combined in a meta-analysis. The degree of heterogeneity was assessed, and 95% confidence intervals were examined to determine whether serious inconsistency was present, using the methods described by the GRADE working group. Indirectness was assessed by noting whether the evidence directly applied to the review question; the outcome 'number of participants leaving the study early' was judged to have serious indirectness because it was a surrogate measure for treatment acceptability. Imprecision was assessed by determining whether 95% confidence intervals incorporated clinically important harm, no effect and clinically important benefit. If all three were incorporated in the confidence interval, imprecision was judged very serious. If two of the three were incorporated, imprecision was considered serious. Other factors such as publication bias were also considered, but none gave rise to serious uncertainty.

The GRADE default minimally important differences were used (0.75 and 1.25 for dichotomous outcomes, and -0.5 and 0.5 standardised mean differences for continuous outcomes). Published minimally important differences were sought for all outcomes via an internet search and through consulting the topic expert members, but none were found.

2.1.4 Results

The systematic search identified 2364 articles. The titles and abstracts were screened and 34 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 32 were excluded as they did not meet the criteria and 2 met the criteria and were included.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

For a summary of included studies see Table 1(for the full evidence tables and full GRADE profiles please see appendices G and H).

Table 1: Summary of included studies

Study id	Population	Intervention & comparator	Location and setting	Outcomes reported
Pelsser 2009	Children with ADHD (age 3.8 to 8.5)	'Few food' diet vs control (no treatment)	The Netherlands, research setting	ADHD symptoms (parent reported), ADHD symptoms (teacher reported), Number leaving study early
Pelsser 2011	Children with ADHD (age 4 to 8)	'Few food' diet vs control (no treatment)	The Netherlands, research setting	ADHD symptoms (parent reported), ADHD symptoms (teacher reported), Functional status (parent reported), Functional status (teacher reported) Number leaving study early

2.1.5 Health economic evidence review

2.1.5.1 Methods

Evidence of cost effectiveness

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits rather than the total implementation cost.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought. The health economist undertook a systematic review of the published economic literature.

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to both review questions. The evidence was identified by conducting a broad search relating to restriction diets, elimination diets, and dietary supplements (polyunsaturated fatty acids) in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). The search also included Medline and Embase databases based on the review protocol using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 2 July 2015. The health economic search strategies are detailed in appendix J.

The health economist also sought out relevant studies identified by the surveillance review or Committee members.

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

In the absence of economic evidence

When no relevant economic studies were found from the economic literature review, and de novo modelling was not feasible or prioritised, the Committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the Committee and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication. However, we have no reason to believe they have been changed substantially.

2.1.5.2 Results of the economic literature review

590 articles were identified by the search. All articles were excluded based on title and abstract. No studies were included in the economic literature review for both review questions. The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in appendix K. No full-text versions of the articles were obtained so there is no excluded economic studies list provided in the appendices.

2.1.5.3 Unit costs

Specific unit costs for the 'few food' diet were not considered because insufficient evidence on long-term effectiveness was identified to support a recommendation.

2.1.6 Evidence statements

2.1.6.1 Clinical evidence statements

Two studies compared a 'few food' diet (rice, meat, vegetables, pears and water, supplemented by specific foods according to the behavioural response of each child) with no treatment for children aged 4 to 8 with ADHD. Overall, the evidence favoured the 'few –food' diet, although the evidence was generally of low quality with major limitations. There was low-quality evidence of a reduction in both parent and teacher-reported ADHD symptoms favouring the 'few food' diet (standardised mean difference of -1.92 [95%CI -2.34 to -1.49] and -2.35 [95%CI -2.87 to -1.82], respectively). There was also low to very-low-quality evidence on parent and teacher-reported functional status favouring the 'few food' diet (although evidence on teacher-reported functional status was associated with considerable uncertainty). There was very low quality and inconclusive evidence on the number of participants leaving the study early.

2.1.6.2 Health economic evidence statements

No studies were included in the economic evidence review.

2.1.7 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The Committee valued 'ADHD symptoms' highly as an outcome, because it gives a direct measure of the severity of ADHD and its impact. The Committee also valued academic performance because ADHD often has a large impact in this area, and academic achievement can have a large effect on future prospects in adult life. The Committee also noted that functional status and quality of life were important outcomes that could add useful additional information on the impact of ADHD on everyday life that was separate from ADHD symptoms.
Quality of evidence	Evidence was rated as low to very low quality. Evidence was from two studies conducted by the same research group, and the Committee were concerned that the findings may not be replicated in a different setting or for different population groups (planned subgroup analyses were not possible as data was not available, and this may limit the applicability of the evidence to some groups). Another concern was that the trials were unblinded. The Committee considered this a serious limitation which may bias studies in favour of the 'few food' diet, particularly for subjective outcomes such as ADHD symptoms and functional status. The Committee discussed the difficulties in producing high-quality randomised controlled trials for the effectiveness of dietary interventions, and acknowledged that double blinding was not usually possible (although blinding of outcome assessors would be feasible, but not done in the reviewed evidence). The Committee were also concerned that the studies were only 5 weeks in duration and there was no evidence on longer-term effects. This was a particular concern for potential long-term side effects such as a change in weight or height, which might be expected to be affected by a very restrictive diet.
Trade-off between benefits and harms	The Committee agreed that overall the evidence favoured the 'few food' diet over no intervention. No harms were identified in the evidence review, although there were no included studies that reported the side effects specified in the review protocol. The topic expert Committee members advised that following a restrictive diet could be potentially harmful,

	Committee discussions
	especially if followed without the supervision of a dietician and over a long period of time. Dietary supplements would be required to ensure adequate intake of vitamins and minerals. The Committee noted that following a restrictive diet such as the 'few food' diet would also have a large impact on families and schools, because of the time needed to prepare separate foods and ensuring compliance with the diet. Therefore the Committee agreed that although there is evidence that the 'few food' diet may be beneficial, there was insufficient evidence on long-term effectiveness and potential harms to support a recommendation. No evidence was found on the effectiveness of the elimination of artificial colours and preservatives for the management of ADHD in children and young people, despite feedback from stakeholders and topic-expert committee members that this was an important area of clinical uncertainty.
Trade-off between net health benefits and resource use	There were no economic studies that met the criteria for inclusion in the review. The Committee considered that the 'few food' diet was likely to be associated with additional resource use because of costs associated with a referral for dietary advice, and costs associated with providing vitamin and mineral supplements that are required when following a 'few food' diet. The topic expert committee members also noted that resources for routine dietary advice were currently not often available and that it would not be advisable to follow a 'few food' diet without advice from a dietician, because the restrictive nature of the diet could lead to malnutrition if not properly supervised. The Committee concluded that there was insufficient evidence of long-term clinical benefit to justify the additional resource use.
Other considerations	The Committee discussed the feasibility of implementing a 'few food' diet. Topic expert committee members indicated that a very restrictive diet such as the 'few food' diet would be difficult to implement in practice as compliance is likely to be low. Ensuring compliance with a restrictive diet is particularly challenging for school age children, as food items are often swapped with peers, and children eat in a number of different settings. The topic expert members were also concerned that a very restrictive diet could be seem as a punishment, especially if used in the long term, and therefore could be counterproductive. The Committee concluded that there was insufficient evidence that the benefits of a 'few food' diet outweighed potential harms and resource use in the long term. However, the evidence reviewed suggested that a 'few food' diet may be a useful intervention in the management of ADHD and warranted further investigation. Therefore, the Committee made a research recommendation, recommending a longer-term trial of the 'few food' diet for children and young people with ADHD. The original NICE guideline on ADHD recommended that artificial colouring and additives should not be routinely eliminated for the management of ADHD in children and young people. There was no evidence in the current review to counter this recommendation, and therefore the recommendation stands (with editorial changes to bring it up to date with current NICE style). However, the Committee made a new research recommendation recommending a randomised controlled trial in this area as it was considered an important area of clinical uncertainty. Recommendation 2, which recommends referral to a dietician if a clear link to a particular food or drink is established was also made by the previous guideline development group. The Committee thought that this recommendation should stand as no new evidence has been found to contradict this advice.

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2.1.8 Recommendations

1. **Do not advise elimination of artificial colouring and additives from the diet as a generally applicable treatment for children and young people with ADHD. [2016]**

2. **Ask about foods or drinks that appear to influence hyperactive behaviour as part of the clinical assessment of ADHD in children and young people, and:**
   - if there is a clear link, advise parents or carers to keep a diary of food and drinks taken and ADHD behaviour
   - if the diary supports a relationship between specific foods and drinks and behaviour, offer referral to a dietitian
   - ensure that further management (for example, specific dietary elimination) is jointly undertaken by the dietitian, mental health specialist or paediatrician, and the parent or carer and child or young person. [2016]

3. **Advise the family members or carers of children with ADHD that there is no evidence about the long-term effectiveness or potential harms of a 'few food' diet for children with ADHD, and only limited evidence of short-term benefits. [new 2016]**

2.1.9 Research recommendations

1. **What is the long-term clinical and cost effectiveness of 'few food' diets, with managed reintroduction of restricted foods, in the management of ADHD in children and young people?**

Why is this important?

The Committee reviewed evidence on 'few food' diets in the management of ADHD in children and young people. The Committee decided that although such an intervention may result in a reduction in ADHD symptoms in the short term for children aged 4–8 years, the evidence of a positive effect was not strong enough to recommend this very restrictive diet, given the potential for nutritional harm and the additional costs of the dietary support that would be necessary to implement this diet safely. A randomised controlled trial is needed to investigate the long-term clinical effectiveness, cost effectiveness and feasibility of this type of dietary intervention. Outcomes should be assessed by an assessor blinded to treatment allocation.

Table 2: Criteria for selecting high-priority research recommendations

PICO	**Population:** Children and young people (aged 3 to 18) with ADHD. **Intervention:** 'Few food' diet with managed reintroduction of restricted foods. The Committee suggested that a strict 'few food' diet was unlikely to be acceptable to children and young people with ADHD and their parents and carers in the long term, but that a managed reintroduction of restricted foods (with withdrawal if associated with behavioural deterioration) could make the diet more acceptable in the long term. **Comparison:** Waiting list control or a control dietary intervention.

	Outcomes: ADHD symptoms, functional status, quality of life, treatment costs, adherence to treatment.
Current evidence base	Two randomised controlled trials of 5 weeks duration were identified by the systematic literature review. Both studies were carried out in the same research centre. Participants were children between the ages of 4 and 8. The studies showed large beneficial effects of a 'few food' diet on ADHD symptoms and functional status, but did not assess the longer-term effects of the diet. Parents, teachers and children were not blinded to treatment allocation.
Study design	Randomised controlled trial.
Other comments	The Committee acknowledged that double blinding would not be feasible, due to the nature of the intervention. However, the trial should include outcomes assessed by an assessor blind to treatment allocation. The trial should also include an assessment of cost effectiveness.

2. What is the long-term effectiveness of dietary restriction of artificial colouring and preservatives in the management of ADHD in children and young people?

Why is this important?

We searched for evidence on restriction or elimination diets in the management of ADHD in children and young people. No studies were found on eliminating artificial colouring or preservatives, despite a recommendation in the original guideline that elimination of artificial colouring or additives should not be advised for children or young people with ADHD. However, feedback from stakeholders and topic expert committee members indicated that this is an important clinical question, and that evidence suggests that artificial colouring and preservatives may contribute to hyperactive behaviour in other population groups. A randomised controlled trial is needed to investigate the long-term clinical and cost effectiveness and feasibility of this type of dietary intervention. Outcomes should be assessed by an assessor blind to treatment allocation.

Table 3: Criteria for selecting high-priority research recommendations

PICO	**Population:** Children and young people (aged 3 to 18) with ADHD. **Intervention:** Dietary elimination of artificial colours or preservatives. **Comparison:** Waiting list control or a control dietary intervention. **Outcomes:** ADHD symptoms, functional status, quality of life, treatment costs, adherence to treatment
Current evidence base	No studies met the criteria specified in the review protocol. However, feedback from stakeholders and topic expert Committee members indicated that evidence suggests that artificial colourings and preservatives may contribute to hyperactive behaviour in other population groups.
Study design	Randomised controlled trial.
Other comments	The Committee acknowledged that double blinding would not be feasible, due to the nature of the intervention. However, the trial should include outcomes assessed by an assessor blind to treatment allocation.

2.2 Review question 2

The NICE guideline on attention deficit hyperactivity disorder (ADHD) was reviewed in 2015, and new evidence on the effectiveness on dietary supplementation with polyunsaturated fatty acids (PUFAs) on ADHD was found that may impact current recommendations. The aim of the review is to evaluate the effectiveness of dietary supplements with PUFAs on children and young people with ADHD.

2.2.1 Review question

What is the clinical and cost-effectiveness of dietary supplementation with polyunsaturated fatty acids, (PUFAs) in children and young people with ADHD?

2.2.2 Clinical evidence review

2.2.3 Methods

A systematic review of the literature was conducted, as specified in the review protocol in Appendix C. The protocol was developed in consultation with the topic expert members, and then reviewed by the core Committee members, before the review was carried out. The following outcomes were considered important for decision making: ADHD symptom severity (rated by the parent, teacher or self-rated), academic performance, functional status, side effects (limited to: gastrointestinal symptoms, change in weight/height, change in appetite, change in sleep pattern, headache), number of participants and quality of life.

A systematic search was conducted (see appendix D). The titles and abstracts were screened and full-text version of articles that were identified as potentially relevant were obtained and reviewed against the criteria specified in the review protocol (appendix C).

Many of the outcomes for the review were reported as change measures from baseline (for example, change in ADHD symptom severity). Some studies did not report this measure directly, but instead reported the measure at baseline and at follow up for each group. In these situations the reviewer calculated the mean change from baseline and imputed the standard deviation for this measure using the following equation:

$$SD(change)=\sqrt{(〖SD(baseline)〗^2+〖SD(followup)〗^2-(2\times\rho\times SD(baseline)\times SD(followup))}$$

Where SD is the standard deviation and ρ is the correlation between baseline and follow up measurements across participants. This correlation can be estimated from studies that report both baseline and follow-up measurements as well as change scores. However, such studies were not available for all outcomes in this review, and so a conservative value of 0.5 was used, as is recommended when reliable correlation coefficients for the outcomes and populations of interest are not available (Follman et al., 1992; Fu et al., 2013).

When more than one study assessed an outcome for a given comparison, data were combined using pair-wise meta-analyses. The Mantel-Haenszel and inverse variance methods were used for dichotomous and continuous outcomes, respectively. A random effects model was chosen because the treatment effects were unlikely to be identical across studies due to differences in baseline ADHD severity and the heterogeneity in interventions across studies. The I^2, chi^2 and tau^2 statistics were calculated to assess heterogeneity. Forest plots showing the outcome of these meta-analyses are shown in appendix I.

Data were not available to assess any of the subgroup effects specified in the review protocol. However, the included studies consisted of a mixture of studies assessing the effectiveness of a combination of omega 3 and 6 polyunsaturated fatty acids (PUFAs) and studies assessing the effectiveness of omega 3 PUFAs alone. These groups of studies were

considered as separate subgroups in the meta-analyses and tests for subgroup differences were used to assess the evidence for the presence of a subgroup effect. The tests for subgroup differences were not significant in any case. Therefore the overall effect was reported in the results of the analyses.

Different studies used different doses of PUFAs. Initially we planned to perform subgroup analyses for studies using different doses. However, the composition and doses of PUFAs used differed markedly across all studies and so this approach was not possible. Instead, the studies were ordered in the forest plots showing the results of the meta-analyses according to omega 3 dose from low to high, and the dose for each study is indicated in order to give a qualitative indication of the effect of dose on each outcome.

The quality of evidence for each outcome for each comparison was appraised using the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (for full GRADE profiles, see appendix H). All included studies were randomised controlled trials. Reasons for downgrading for risk of bias typically included a lack of blinding of participants, parents or outcome assessors. This was considered a very serious risk of bias for subjective outcomes rated by an unblinded observer (e.g. ADHD symptom severity) and a serious risk of bias for outcomes that could be objectively measured (e.g. number of participants leaving the study early) or when only some of the studies contributing to an outcome were affected. Randomisation methods and allocation concealment was assessed across studies. Many studies had unclear randomisation methods and methods for ensuring allocation concealment, but this was not judged sufficient to warrant downgrading for risk of bias. Similarly, some studies had moderate dropout rates and did not perform an intention to treat analysis, but as drop-out rates were similar across groups in all cases, this was not considered a serious risk of bias. Inconsistency (the variability in the results from different trials) was only assessed when data were combined in a meta-analysis.

The degree of heterogeneity was assessed, and 95% confidence intervals were examined to determine whether serious inconsistency was present, using the methods described by the GRADE working group. Indirectness was assessed by noting whether the evidence directly applied to the review question; the outcome 'number of participants leaving the study early' was judged to have serious indirectness because it was a surrogate measure for treatment acceptability. Imprecision was assessed by determining whether 95% confidence intervals incorporated clinically important harm, no effect and clinically important benefit. If all three were incorporated in the confidence interval, imprecision was judged very serious. If two of the three were incorporated, imprecision was considered serious. Other factors such as publication bias were also considered, but none gave rise to serious uncertainty.

The GRADE default minimally important differences were used (0.75 and 1.25 for dichotomous outcomes, and -0.5 and 0.5 standardised mean differences for continuous outcomes). Published minimally important differences were sought for all outcomes via an internet search and through consulting the topic expert members, but none were found.

2.2.41 Results

The systematic search identified 1184 articles. The titles and abstracts were screened and 56 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 41 were excluded as they did not meet the criteria and 15 met the criteria and were included.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

For a summary of included studies see Table 4 (for the full evidence tables and full GRADE profiles please see appendices G and H).

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Table 4: Summary of included studies

Study id	Population	Intervention & comparator	Location and setting	Study duration	Outcomes reported
Assareh 2012	Children with ADHD (aged 6 to 12)	Omega 3/6 +methylphenidate vs Placebo + methylphenidate	Iran, secondary care setting	10 weeks	ADHD symptoms (parent reported)
Barragan 2014	Children with ADHD (aged 6 to 12)	Omega 3/6 +methylphenidate vs Placebo + methylphenidate	Mexico, secondary care setting	12 months	ADHD symptoms (parent reported), Functional status (clinician reported), Side effects (Headache, nausea, dyspepsia, diarrhoea) Number leaving study early
Behdani 2013	Children and young people with ADHD (aged 7 to 15)	Omega 3 +methylphenidate vs Placebo + methylphenidate	Iran, secondary care setting	8 weeks	ADHD symptoms (parent reported), ADHD symptoms (teacher reported), Number leaving study early
Bélanger 2009	Children (aged 6 to 11)	Omega 3 vs Placebo	Canada, secondary care setting	8 weeks	Number leaving study early
Bos 2015	Children and young people with ADHD (aged 8 to 14)	Omega 3 vs Placebo	The Netherlands, secondary care setting	16 weeks	ADHD symptoms (parent reported), Number leaving study early
Dubnov-Raz 2014	Children and young people with ADHD (aged 6 to 16)	Omega 3/6 vs Placebo	Israel, secondary care setting	8 weeks	ADHD symptoms (parent reported), Number leaving study early
Gustafsson 2010	Children with ADHD (aged 7 to 12)	Omega 3 vs Placebo	Sweden, secondary care setting	15 weeks	ADHD symptoms (parent reported), ADHD symptoms (teacher reported), Adverse events (nausea, diarrhoea), Number leaving study early
Hariri 2012	Children with ADHD (aged 6 to 11)	Omega 3 vs Placebo	Iran, secondary care	8 weeks	ADHD symptoms (parent reported), Number leaving study early
Johnson 2009	Children and young people with ADHD	Omega 3/6 vs Placebo	Sweden, secondary care setting	12 weeks	ADHD symptoms (parent reported), Functional status (clinician rated),

Study id	Population	Intervention & comparator	Location and setting	Study duration	Outcomes reported
	(aged 8 to 18)				Number leaving study early
Manor 2012	Children and young people with ADHD (aged 6 to 13)	Omega 3 vs Placebo	Israel, research setting	15 weeks	ADHD symptoms (parent reported), ADHD symptoms (teacher reported), Side effects (decreased appetite), headaches, stomach ache), Number leaving study early
Perera 2012	Children with ADHD (aged 6 to 12)	Omega 3/6 vs Placebo	Sri Lanka, secondary care setting	6 months	Number leaving study early
Stevens 2003	Children and young people with ADHD (aged 6 to 13)	Omega 3/6 vs Placebo	USA, research setting	4 months	ADHD symptoms (parent reported), ADHD symptoms (teacher reported), Number leaving study early
Vaisman 2008	Children and young people with ADHD (aged 8 to 13)	Omega 3 vs Placebo	Israel, secondary care setting	3 months	ADHD symptoms (parent reported), Number leaving study early
Voigt 2001	Children and young people with ADHD (mean age 9.3)	Omega 3 vs Placebo	US, research setting	4 months	Number leaving study early
Widenhorn-Muller 2014	Children with ADHD (mean age 8.9)	Omega 3 vs Placebo	Germany, secondary care setting	16 weeks	ADHD symptoms (parent reported), ADHD symptoms (teacher reported), Academic performance (working memory), Number leaving study early

2.2.51 Health economic evidence review

2.2.5.12 Methods

A single economic search was conducted for both review questions. Please refer to section 2.1.5.1 for the methods used for this literature review.

2.2.5.25 Results of the economic literature review

590 articles were identified by the search. All articles were excluded based on title and abstract. No studies were included in the economic literature review. The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in appendix K. No full-text versions of the articles were obtained so there is no excluded economic studies list provided in the appendices.

2.2.5.31 Unit costs

As a prescribed supplement (as opposed to bought over the counter), the cost of two omega-3 fatty acid compounds was calculated from the BNF for the following indications: adjunct to diet and statin in type IIb or III hypertriglyceridaemia; adjunct to diet in type IV hypertriglyceridaemia; adjunct in secondary prevention in those who have had a myocardial infarction in the preceding 3 months. Pricing is sourced from the Drug Tariff unless they do not appear there in which case the BNF is used.

Table 5: Unit cost of omega-3-acid fatty acid compounds

Medicine	Price per pack	Content per pack	Cost per dose[1]	Cost per month[1]	Cost per year[1]	Source
Omacor, 28 cap pack 1 g of omega-3-acid ethyl esters 90 containing eicosapentaenoic acid 460 mg and docosahexaenoic acid 380 mg	14.24	28	0.51	6.10	185.63	Drug Tariff
Omacor, 100 cap pack 1 g of omega-3-acid ethyl esters 90 containing eicosapentaenoic acid 460 mg and docosahexaenoic acid 380 mg	50.84	100	0.51	6.10	185.57	BNF
Prestylon, 28 cap pack 1 g of omega-3-acid ethyl esters 90 containing eicosapentaenoic acid 460 mg and docosahexaenoic acid 380 mg	10.68	28	0.38	4.58	139.22	BNF

Medicine	Price per pack	Content per pack	Cost per dose[1]	Cost per month[1]	Cost per year[1]	Source
Prestylon, 100 cap pack 1 g of omega-3-acid ethyl esters 90 containing eicosapentaenoic acid 460 mg and docosahexaenoic acid 380 mg	38.13	100	0.38	4.58	139.17	BNF

1: Based on 1 capsule per day. This is the dose specified by the BNF for secondary prevention after myocardial infarction. If omega-3 fatty acid compounds were recommended for the treatment of ADHD, the doses prescribed may be different.

2.2.6 Evidence statements

2.2.6.1 Clinical evidence statements

Fifteen studies compared polyunsaturated fatty acids (PUFAs) with a control intervention (placebo or no treatment). There was high to very-low quality evidence suggesting no clinically important difference in ADHD symptoms in the short (0 to 3 months of treatment), medium (3 to 6 months) or long term (over 6 months) and low quality evidence suggesting no difference in academic performance across groups. There was low to very low quality evidence favouring PUFAs over control in terms of functional status in the short and medium term, but very low quality evidence of no difference between groups for treatment in the long term. There was very low quality and inconclusive evidence on the number of participants leaving the studies early.

2.2.6.2 Health economic evidence statements

No studies were included in the economic evidence review.

2.2.7 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The Committee valued outcomes in the same way as for question 1 (as discussed in section 2.1.7).
Quality of evidence	The majority of studies in the review were blinded (including the outcome assessment) and free from other serious sources of bias. One trial, which provided the majority of evidence on functional status, and the only evidence on outcomes at over 6 months duration was not blinded and had other serious sources of bias. Consequently, the committee attributed less weight to this evidence. The number leaving the study early was widely reported across trials, but was associated with high uncertainty due to small numbers of events in both groups, and was an indirect measure of treatment acceptability; the Committee therefore could not draw conclusions from this evidence. Planned subgroup analyses were not possible as data were not available. This may limit the applicability of the evidence to some groups.
Trade-off between benefits and harms	The Committee concluded that there was evidence of no clinically important difference between polyunsaturated fatty acids (PUFAs) and control in terms of ADHD symptoms and academic performance. There was evidence of a statistically significant difference favouring PUFAs for ADHD symptoms for treatment of 3 to 6 months duration, but not other time periods, and the difference between groups was small and unlikely to be clinically important. There was some evidence suggesting an improvement

	Committee discussions
	in functional status favouring PUFAs, but the evidence was of low to very low quality, and the Committee considered that this was insufficient evidence to warrant a recommendation favouring PUFAs. The evidence review did not identify any harms of PUFAs, although no evidence on side effects were available, so harms could not be excluded. The Committee concluded that evidence suggested no clinically important benefits of PUFAs for ADHD, and harms could not be excluded.
Trade-off between net health benefits and resource use	There were no economic studies that met the criteria for inclusion in the review. The Committee considered the resources that would be used if PUFAs were recommended for the treatment of ADHD. The main cost would be the cost of PUFAs, which would either be borne by the family of the child or young person (as PUFAs are widely available as a food product), or by the NHS (if PUFAs were prescribed). Unit costs for PUFAs were considered. The Committee decided that given the clinical evidence did not show a clear clinically important benefit of PUFAs for ADHD in children and young people, net benefits did not outweigh any additional resource use and PUFAs should not be offered, nor should patients be advised to purchase supplements over the counter.
Other considerations	None.

2.2.82 Recommendations

4. Do not advise or offer dietary fatty acid supplementation for treating ADHD in children and young people. [2016]

31 References

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4 Glossary and abbreviations

Please refer to the NICE glossary.

Additional terms used in this document are listed below:

ADHD: Attention deficit hyperactivity disorder.

'Few food' diet: A type of restriction/elimination diet, where certain foods are either restricted, or removed from the diet completely. When following a 'few food' diet, a diet is limited to 1 or a small number of foods from each food group; for example a diet could be restricted to rice, meat, vegetables, pears and water.

PUFA: Polyunsaturated fatty acids.

Omega 3 PUFA: A type of PUFA with a double bond at the third carbon atom from the end of the carbon chain. Examples include docosahexaenoic acid, eicosapentaenoic acid and alpha-linolenic acid.

Omega 6 PUFA: A type of PUFA with a double bond at the sixth carbon atom from the end of the carbon chain. Examples include linoleic acid, gamma-linolenic acid and arachidonic acid.

1 Appendices

2 Appendix A: Standing Committee 3 members and NICE teams

A.1 4 Core members

Name	Role
Susan Bewley (Chair)	Professor of Complex Obstetrics, Kings College London
Gita Bhutani	Clinical Psychologist, Lancashire Care NHS Foundation Trust
Simon Corbett	Cardiologist, University Hospital Southampton NHS Foundation Trust
Gail Fortes Mayer	Commissioner
John Graham	Consultant Oncologist & Trust Cancer Lead Clinician, Taunton & Somerset Hospital
Peter Hoskin	Consultant in Clinical Oncology, Mount Vernon Hospital
Roberta James	Programme Lead, Scottish Intercollegiate Guidelines Network (SIGN)
Jo Josh	Lay member
Asma Khalil	Obstetrician, St George's Hospital University London
Manoj Mistry	Lay member
Amaka Offiah	Reader in Paediatric Musculoskeletal Imaging and Honorary Consultant Paediatric Radiologist, University of Sheffield
Mark Rodgers	Research Fellow, University of York
Nicholas Steel	Clinical Senior Lecturer in Primary Care, Norwich Medical School
Sietse Wieringa	General Practitioner, Barts & the London School of Medicine & Dentistry

A.2 5 Topic expert Committee members

Name	Role
Bernadette Ashton	Lay Member
David Edwards	GP
Nicole Horwitz	Community Paediatrician
Paul McArdle	Child and Adolescent Psychiatrist
Sarah Owen	Dietician
Noreen Ryan	Nurse

A.3 6 NICE project team

Name	Role
Martin Allaby	Clinical Adviser
Jessica Fielding	Public Involvement Adviser
Lyn Knott	Senior Medical Editor
Bhash Naidoo	Technical Lead (Health Economics)
Louise Shires	Guideline Commissioning Manager
Sharon Summers-Ma	Guideline Lead
Judith Thornton	Technical Lead
Trudie Willingham	Guideline Co-ordinator

7

A.41 Clinical guidelines update team

Name	Role
Phil Alderson	Clinical Adviser
Emma Banks	Co-ordinator
Elizabeth Barrett	Information Specialist
Jane Birch	Project Manager
Paul Crosland	Health Economist
Kathryn Hopkins	Technical Analyst
Nick Lowe	Administrator
Susannah Moon	Programme Manager
Toni Tan	Technical Adviser
Lorraine Taylor	Associate Director

2

1 Appendix B: Declarations of interest

Member name	Interest declared	Type of interest	Decision
Susan Bewley	Self-employed academic and obstetric expert.	Personal financial, non-specific	Declare and participate
Susan Bewley	100 hour per annum teaching contract with Kings College London.	Personal financial, non-specific	Declare and participate
Susan Bewley	Received income/fee for Teaching (BSc law and ethics tutor at KCL, occasional fees for lectures on obstetrics)	Personal financial, non-specific	Declare and participate
Susan Bewley	Received income/fee for Medico-legal reports (approx. 2/year) and Medical Defence Union cases committee and council	Personal financial, non-specific	Declare and participate
Susan Bewley	Received income/fee for external reviews for NHS organisations related to my obstetric expertise (serious incident and maternal mortality investigations, RCOG review)	Personal financial, non-specific	Declare and participate
Susan Bewley	Received royalties from edited books	Personal financial, non-specific	Declare and participate
Susan Bewley	Expressed views in publications about obstetric matters, largely based on evidence.	Personal non-financial, non-specific	Declare and participate
Susan Bewley	A trustee and committee member of Healthwatch (a charity devoted to evidence and “for treatments that work”) and a trustee of Sophia (a charity devoted to women with HIV and the UK arm of the Global Coalition for Women and AIDS).	Personal non-financial, non-specific	Declare and participate
Susan Bewley	Member of the following editorial boards: Medical Law Review, International Journal of Childbirth, Journal Article Summary Service; Member All-Parliamentary Party Group on Maternity; Trustee of Maternity Action (a charity which aims to end inequality and improve the health and well-being of pregnant women, partners and young children), one of seven members of the Women’s Health and Equality Consortium which is a Strategic Partner of the Department of Health.	Personal non-financial, non-specific	Declare and participate
Susan Bewley	Part-time on call sexual offences examiner (forensic medical examinations) working at the Haven Camberwell Sexual Assault Referral Centre (Kings College Hospital)	Personal financial, non-specific	Declare and participate
Susan Bewley	Received income/fee as Consultant for the World Health Organisation (five days approx), for their updated guideline on Reproductive and Sexual Health and Human Rights for Women living with HIV	Personal financial, non-specific	Declare and participate
Susan Bewley	Received fee as Chair of NICE Fertility	Personal	Declare and

Member name	Interest declared	Type of interest	Decision
	Evidence Update	financial, non-specific	participate
Susan Bewley	Received income/fee as External examiner obstetrics and gynaecology, University College Dublin	Personal financial, non-specific	
Susan Bewley	Expert fee (one off piece of work) for maternal mortality investigation	Personal financial, non-specific	Declare and participate
Susan Bewley	Expert fee (one off piece of work) for RCOG service review Independent Review panel	Personal financial, non-specific	Declare and participate
Susan Bewley	Expert fee (one off piece of work) for medicolegal criminal case	Personal financial, non-specific	Declare and participate
Susan Bewley	Expert fee (one off piece of work) for obstetric and managerial advice (overseas not- hospital)	Personal financial, non-specific	Declare and participate
Susan Bewley	Received fee for attending NICE GRADE training development	Personal financial, non-specific	Declare and participate
Susan Bewley	Received fee for lecture at Royal Society of Medicine Retired Fellows Modern Reproduction: blood, guts, loss and King Midas	Personal financial, non-specific	Declare and participate
Susan Bewley	Expenses paid to lecture at the National RCOG trainees annual conference	Personal financial, non-specific	Declare and participate
Susan Bewley	Expenses only lecture at the Royal Society of Medicine	Personal non-financial, non-specific	Declare and participate
Susan Bewley	Expenses only lecture at the GLADD Annual conference	Personal non-financial, non-specific	Declare and participate
Susan Bewley	Expenses only lecture at the FIL Annual conference	Personal non-financial, non-specific	Declare and participate
Susan Bewley	Expenses only lecture at the RCOG Review training	Personal financial, non-specific	Declare and participate
Susan Bewley	Expenses only lecture at the BPAS Annual Meeting Clinical Forum	Personal financial, non-specific	Declare and participate
Susan Bewley	Expenses only lecture at the WOW Festival	Personal financial, non-specific	Declare and participate
Susan Bewley	Expenses only lectures relating to publicising NICE intrapartum guidelines	Personal financial, non-specific	Declare and participate
Susan Bewley	Lecture fee, at ‘safe hands conference’ Bolton	Personal financial, non-specific	Declare and participate
Susan Bewley	Unpaid (but travel, hotel and subsistence) trip to two not-for-profit maternity hospitals in return for four days teaching/ expert	Personal financial, non-specific	Declare and participate

Member name	Interest declared	Type of interest	Decision
	advice, India		
Susan Bewley	Al Jazeera: studio fee for commenting as an obstetric expert about egg freezing	Personal financial, non-specific	Declare and participate
Susan Bewley	PRP: fee for review of NIHR policy research programme domestic violence report	Personal financial, non-specific	Declare and participate
Susan Bewley	Birmingham University: fee for assisting NICE training tool development	Personal financial, non-specific	Declare and participate
Susan Bewley	Choitham Hospitals, India: fee for maternity services advice	Personal financial, non-specific	Declare and participate
Susan Bewley	NICE: fee for chairing Evidence Update Fertility Group	Non-personal financial, non-specific	Declare and participate
Susan Bewley	Fee for lecture on egg freezing (debate at British Fertility Society, January 2016)	Personal financial, non-specific	Declare and participate
Susan Bewley	Fee for lecture on domestic violence (Faculty of Sexual and Reproductive Healthcare, RCOG)	Personal financial, non-specific	Declare and participate
Susan Bewley	Fee for lecture on reproductive health as public health issue (European society for human reproduction and embryology)	Personal financial, non-specific	Declare and participate
Susan Bewley	Fee for lecture on female genital mutilation (Liverpool medical society)	Personal financial, non-specific	Declare and participate
Gita Bhutani	Chair of Psychological Professions Network North West	Personal non-financial, non-specific	Declare and participate
Gita Bhutani	Member of British Psychological Society; Division of Clinical Psychology; Faculty of Leadership and Management Committee Member	Personal non-financial, non-specific	Declare and participate
Gita Bhuitani	Project lead on BPS Division of Clinical Psychology project on 'Comprehensively representing the complexity of psychological services'	Personal non-financial, non-specific	Declare and participate
Gita Bhutani	Analytical support in partnership with Liverpool University on Liverpool Health Partners project on Patient Quality and Safety	Personal non-financial, non-specific	Declare and participate
Gita Bhutani	Joint project lead on Health Education North West funded project on Schwartz Rounds	Personal non-financial, non-specific	Declare and participate
Simon Corbett	Network Service Adviser for the British Cardiovascular Society. This role incorporates the regional specialty adviser role for the Royal College of Physicians.	Personal non-financial, non-specific	Declare and participate
Simon Corbett	Director for Clinical Effectiveness for employer (University Hospital Southampton NHS Foundation Trust). Part of this role involves the dissemination and	Personal non-financial, non-specfic	Declare and participate

Member name	Interest declared	Type of interest	Decision
	implementation of NICE guidance in the Trust.		
Simon Corbett	Independent cardiologist on the Trial Steering Committee of the randomised controlled AVATAR trial, a randomised trial of medical therapy vs ablation in patients with atrial fibrillation. The study is sponsored by Imperial College London and is part funded by Medtronic. Travel expenses are paid by Imperial.	Personal non-financial, non-specific	Declare and participate
Gail Fortes Mayer	None	No action	Declare and participate
John Graham	Director of National Collaborating Centre for Cancer – this post is funded through a contract with NICE to produce NICE's clinical guidelines.	Non-personal financial, non-specific	Declare and participate
John Graham	Principal investigator for On-going clinical trials in prostate cancer: 1) With Custirsen funded by OncoGenex Technologies Inc and Teva Pharmaceutical Industries Ltd. 2) Orteronel Affinity Trial funded by Millenium Pharmaceuticals Inc 3) Principal investigator for a study of radium-223 in prostate cancer that is funded by Bayer Pharmaceuticals 4) Principal investigator in 2 trials of radium-223 in breast cancer funded by Bayer Pharmaceuticals.	Non-personal financial, non-specific	Declare and participate
John Graham	Principal investigator for 8 On-going clinical trials in breast and prostate cancer run via the National Cancer Research Network (not pharmaceutical industry funded)	Non-personal financial, non-specific	Declare and participate
John Graham	Member of the trial management groups for 2 prostate cancer trials: RT01 and CHHIP. Both are closed to recruitment but continuing to report trial results.	Personal non-financial, non-specific	Declare and participate
John Graham	Council member of the South-West England Clinical Senate	Personal non-financial, non-specific	Declare and participate
Peter Hoskin	Investigator in research studies sponsored by various companies with payment for expenses to NHS Trust and department which fund research staff. Recent studies have been on behalf of Millenium, Astellas, Ipsen and Amgen.	Non-personal financial, non-specific	Declare and participate
Peter Hoskin	Fellow of the Royal College of Radiologists and member of Faculty Board, Specialist Training Board and Chair of Exam Board.	Personal non-financial, non-specific	Declare and participate
Peter Hoskin	Consultant to the IAEA; Undertake by invitation lectures and working group meetings for which expenses may be paid.	Personal financial, non-specific	Declare and participate
Peter Hoskin	Department reimbursed for studies on alpharadin by Astellas.	Non-personal financial, non-specific	Declare and participate

Member name	Interest declared	Type of interest	Decision
Peter Hoskin	Department reimbursed for studies on MDV 3100 by Medivation. and Astellas	Non-personal financial, non-specific	Declare and participate
Peter Hoskin	Department receives grants from Astellas for trials in prostate cancer.	Non-personal financial, non-specific	Declare and participate
Peter Hoskin	Department receives grants from Bayer for trials in prostate cancer.	Non-personal financial, non-specific	Declare and participate
Peter Hoskin	Department received grants from Millennium for trials in prostate cancer.	Non-personal financial, non-specific	Declare and participate
Peter Hoskin	Trustee for funding research within the unit/department. Funded by Donations/Legacies.	Personal non-financial, non-specific	Declare and participate
Peter Hoskin	Member of the Steering Group for National Cancer Intelligence Network (NCIN)	Personal non-financial, non-specific	Declare and participate
Peter Hoskin	Member of the faculty board of the Royal College of Radiologists.	Personal non-financial, non-specific	Declare and participate
Peter Hoskin	Member of the specialist training committee for the Royal College of Radiologists.	Personal non-financial, non-specific	Declare and participate
Peter Hoskin	Editorial board member for the Journal of Contemporary Brachytherapy.	Personal non-financial, non-specific	Declare and participate
Peter Hoskin	Member of the East of England senate.	Personal non-financial, non-specific	Declare and participate
Peter Hoskin	Member of the NICE standing committee for rapid updates / and non-Hodgkin's lymphoma GDG.	Personal non-financial, non-specific	Declare and participate
Peter Hoskin	Member European Society for Radiotherapy and Oncology (ESTRO) Board	Personal non-financial, non-specific	Declare and participate
Peter Hoskin	Member HTA Clinical Evaluation and Trials Board	Personal non-financial, non-specific	Declare and participate
Peter Hoskin	Clinical Editor, radiotherapy and Oncology	Personal non-financial , non-specific	Declare and participate
Roberta James	Programme Lead at Scottish Intercollegiate Guidelines Network	Personal financial, non-specific	Declare and participate
Roberta James	Member of Guideline Implementability Research and Application Network	Personal non-financial, non-specific	Declare and participate
Roberta James	Expert group member of Project on a Framework for Rating Evidence in Public Health	Personal non-financial, non-specific	Declare and participate
Asma Khalil	Member of the National Clinical Reference Group for Fetal Medicine	Personal non-financial, non-	Declare and participate

Member name	Interest declared	Type of interest	Decision
		specific	
Asma Khalil	Co-chair of the “Improving Outcomes” working group, South West London Maternity Network	Personal non-financial, non-specific	Declare and participate
Asma Khalil	Associate Editor for the journal Biomedical Central Pregnancy and Childbirth	Personal non-financial, non-specific	Declare and participate
Asma Khalil	Member of the Maternal and Fetal Medicine National Clinical Study Group	Personal non-financial, non-specific	Declare and participate
Asma Khalil	Assistant Convenor for the MRCOG Part1 course, RCOG	Personal non-financial, non-specific	Declare and participate
Asma Khalil	Principal Investigator at St George’s Hospital for several NIHR funded studies, e.g. Non-invasive Prenatal Testing	Non-personal financial, non-specific	Declare and participate
Asma Khalil	Chief Investigator for Cardiovascular changes in Pregnancy study and Quantitative fetal fibronectin, Cervical length and ActimPartus® for the prediction of Preterm birth in Symptomatic women (QFCAPS)	Non-personal financial, non-specific	Declare and participate
Asma Khalil	Collaboration with commercial companies, such as USCOM®, Roche Diagnostics®, Alere Diagnostics® and proact medical Ltd® (research equipment and/or consumables)	Non-personal financial, non-specific	Declare and participate
Asma Khalil	Reviewer for the National Maternal Near-miss Surveillance Programme	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	Public member of Pennine Care NHS FT in the capacity as a carer	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	PPI representative for the Health Research Authority, London	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	PPI representative for the Health Quality Improvement Partnership, London	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	PPI representative for the Primary Care Research in Manchester Engagement Resource group at the University of Manchester.	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	Carer representative on NICE Guideline Development Group: ‘Transition between inpatient hospital settings and community or care home settings for adults with social care needs.’	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	Lay representative for the MSc Clinical Bioinformatics at the University of Manchester	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	Lay Educational Visitor with the Health and Care Professions Council, London	Personal non-financial, non-	Declare and participate

Member name	Interest declared	Type of interest	Decision
		specific	
Manoj Mistry	Lay representative at the Clinical Research Facility (collaboration between Central Manchester University Hospital NHS FT/University of Manchester)	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	Public Representative Interviewer at the Medical School, Lancaster University	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	Public Member of NIHRs 'Research for Patient Benefit Programme Committee' (North West region)	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	Member of the Patient Panel at NIHRs 'The Collaboration for Leadership in Applied Health Research and Care' Greater Manchester	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	Member of the Patient and Public Involvement Group, Liverpool Clinical Trials Unit, University of Liverpool	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	PPI panel assisting research into Information Systems: Dashboard: Monitoring and Managing from Ward to Board at the University of Leeds	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	Member of the Study Steering Committee for the research project: ''Comprehensive Longitudinal Assessment of Salford Integrated Care (CLASSIC): a study of the implementation and effectiveness of a new model of care for long term conditions ''(University of Manchester/ Salford Royal).	Personal non-financial, non-specific	Declare and participate
Manoj Mistry	appointed Patient-Public Representative for the new postgraduate 'Advanced Clinical Skills' course at Manchester Pharmacy School, The University of Manchester, England, UK	Personal non-financial, non-specific	Declare and participate
Amaka Offiah	Provision of expert advice to Her Majesty's Courts in cases of suspected child abuse.	Personal financial, non-specific	Declare and participate
Amaka Offiah	Recipient of honoraria and/or expenses for lectures and/or guidelines development from BioMarin, InfoMed and Alexion.	Personal financial, non-specific	Declare and participate
Amaka Offiah	Chairperson Skeletal Dysplasia Group for Teaching and Research	Personal non-financial, non-specific	Declare and participate
Amaka Offiah	Chairperson Child Abuse Taskforce of the European Society of Paediatric Radiology.	Personal non-financial, non-specific	Declare and participate
Amaka Offiah	Member Joint RCR/RCPCH NAI Working Party for Guideline Update - Imaging in Suspected Non-Accidental Injury.	Personal non-financial, non-specific	Declare and participate
Amaka Offiah	Member of the Royal College of Radiology Academic Committee.	Personal non-financial, non-specific	Declare and participate
Amaka Offiah	Committee member of the International Consortium for Vertebral Anomalies and	Personal non-financial, non-	Declare and participate

Member name	Interest declared	Type of interest	Decision
	Scoliosis.	specific	
Amaka Offiah	Vice Chair of South Yorkshire (Sheffield) Research Ethics Committee.	Personal non-financial, non-specific	Declare and participate
Amaka Offiah	Medical Academic Staff Committee Representative of the Yorkshire Regional Council of the BMA	Personal non-financial, non-specific	Declare and participate
Amaka Offiah	Partner Governor of the Sheffield Children's NHS Foundation Trust (representing the University of Sheffield)	Personal non-financial, non-specific	Declare and participate
Amaka Offiah	Editorial Committee Member of the journal Paediatric Radiology	Personal non-financial, non-specific	Declare and participate
Amaka Offiah	Recipient of research funding from NIHR, ARUK, The Sheffield Children's Charity, Skeletal Dysplasia Group for Teaching and Research	Non-personal financial, non-specific	Declare and participate
Amaka Offiah	Member of the Sheffield Children's Hospital Research and Innovations Committee	Personal non-financial, non-specific	Declare and participate
Mark Rodgers	Associate editor of the journal Systematic Reviews that publishes research on health and social care.	Personal non-financial, non-specific	Declare and participate
Mark Rodgers	Research fellow in health services research; has provided independent academic reviews of clinical effectiveness and diagnostic accuracy evidence for funders including NIHR and NICE.	Non-personal financial, non-specific	Declare and participate
Mark Rodgers	Employee of the Centre for Reviews and Dissemination (University of York) which provides Evidence Review Group reports and Technology Assessment Reports as part of the NICE technology appraisals process.	Non-personal financial, non-specific	Declare and participate
Nicholas Steel	Work as the principal investigator on a National Institute of Health Research funded project on: 'Are NICE clinical guidelines for primary care based on evidence from primary care?'	Non-personal financial, non-specific	Declare and participate
Nicholas Steel	National Institute for Health Research Health Services & Delivery Research Programme Healthcare Delivery Research Panel member	Personal non-financial, non-specific	Declare and participate
Nicholas Steel	NIHR Regional Advisory Committee for the Research for Patient Benefit Programme East of England region	Personal non-financial, non-specific	Declare and participate
Nicholas Steel	Norfolk & Suffolk Primary & Community Care Research Steering Group	Personal non-financial, non-specific	Declare and participate
Nicholas Steel	Advisory Committee on Clinical Excellence Awards East of England	Personal non-financial, non-specific	Declare and participate
Nicholas Steel	'Implementation Science' Editorial Board member	Personal non-financial, non-	Declare and participate

Member name	Interest declared	Type of interest	Decision
		specific	
Nicholas Steel	'Quality in Primary Care' Editorial Board member	Personal non-financial, non-specific	Declare and participate
Nicholas Steel	Faculty of Public Health Part A MFPH Examiner	Personal non-financial, non-specific	Declare and participate
Nicholas Steel	Faculty of Public Health Part A MFPH Development Committee	Personal non-financial, non-specific	Declare and participate
Nicholas Steel	Honorary Public Health Academic Consultant, Public Health England	Personal non-financial, non-specific	Declare and participate
Nicholas Steel	Publication in press: Steel N, Abdelhamid A, Stokes T, Edwards H, Fleetcroft R, Howe A, Qureshi N. Publications cited in national clinical guidelines for primary care were of uncertain relevance: literature review. In Press Journal of Clinical Epidemiology	Personal non-financial, non-specific	Declare and participate
Sietse Wieringa	At the Centre for Primary care & Public Health at Barts & The London School of Medicine & Dentistry/Queen Mary University I am working on a literature review of 'mindlines' (related to communities of practice) and a qualitative study of a large group of GPs on a virtual social network sharing medical knowledge. I was funded for this via an NIHR In practice fellowship.	Personal financial, non-specific	Declare and participate
Sietse Wieringa	I co-own a small social enterprise called ZorgIdee that develops ideas to help GPs to collaborate. There are no current funders.	Personal financial, non-specific	Declare and participate
Sietse Wieringa	Board member of the Platform of Medical Leadership in the Netherlands, via which I am involved in a mixed methods study for the development of a medical leadership competency framework. The study group receives funds from KNMG (Royal Dutch College of Medicine) and SBOH which receives its funds from the Dutch Ministry of Health.	Non-personal financial, non-specific	Declare and participate
Sietse Wieringa	Member of Generation Next, a think tank and network of young GPs. It's indirectly funded by the Ministry of Health.	Personal non-financial, non-specific	Declare and participate
Sietse Wieringa	Member of NHG (Dutch GP Society), which produces guidelines and I worked for this organisation in the past.	Personal non-financial, non-specific	Declare and participate
Topic expert	Interest declared	Type of interest	Decision
Noreen Ryan	On Advisory Board for SANDOZ UK	Personal financial non-specific	Declare and participate
Nicole Horwitz	None	No action	Declare and participate
Paul McArdle	None	No action	Declare and

Member name	Interest declared	Type of interest	Decision
			participate
Bernadette Ashton	None	No action	Declare and participate
David Edwards	None	No action	Declare and participate
Sarah Owen	None	No action	Declare and participate

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1 Appendix C: Review protocol

C.1 2 Question 1

Components	Details
Review question	What is the clinical and cost-effectiveness of elimination/restriction diets in children and young people with ADHD?
Background/objectives	The NICE guideline on ADHD was reviewed in 2015, and new evidence on the effectiveness of elimination and restriction diets on ADHD was found. The aim of the review is to evaluate the effectiveness of elimination and restriction diets on children and young people with ADHD.
Types of study to be included	Randomised controlled trials (including crossover trials), systematic reviews of randomised controlled trials.
Language	English (original English version or existing full text English translation)
Status	Published papers (full text only)
Population	Children and young people (aged 3 to 18*) diagnosed with ADHD or hyperkinetic disorder. Diagnosis must be made using validated diagnostic criteria such as those specified for ADHD in the diagnostic and statistical manual (DSM IV or DSM 5) or the hyperkinetic syndrome in the international classification of diseases (ICD 9 or 10). *A study will not be excluded if the majority of participants fall within this age range
Intervention	Diet which eliminates or restricts a food or group of foods. The food to be eliminated may be the same across all participants allocated to the intervention group, or identified individually for each child during a baseline period.
Comparator	No treatment, waiting list, usual care, 'placebo' dietary intervention. Other concurrent treatments (for example medication, psychological therapy, parenting interventions) will be permitted, provided that they are the same for both intervention and control groups. Comparison between dietary and pharmacological or psychological interventions will not be included.
Outcomes	ADHD symptom severity – self reported (measured using Connors' rating scale, ADHD-RS score, SKAMP test score, SNAP rating scale or other validated rating scale) ADHD symptom severity – parent reported (measured using Connors' rating scale, ADHD-RS score, SKAMP test score, SNAP rating scale or other validated rating scale) ADHD symptom severity – teacher reported (measured using Connors' rating scale, ADHD-RS score, SKAMP test score, SNAP rating scale or other validated rating scale) Academic performance (including verbal memory, reading, spelling, executive function) Functional status (measured using the global assessment of functioning questionnaire, children's global assessment

Components	Details
	of function, strengths and difficulties questionnaire or other validated tool for measuring functional status) Side effects (limited to: gastrointestinal symptoms, change in weight/height, change in appetite, change in sleep pattern, headache) Number of participants leaving the study early (as a surrogate measure for treatment acceptability) Quality of life
Any other information or criteria for inclusion/exclusion	Treatment duration must be at least 2 weeks. Cross over trials must have a washout period of 2 weeks to mitigate potential carryover effects. Continuous outcome measures will only be extracted if appropriate measures of variability (such as standard deviations) are reported or calculable from other reported values. **Selection of papers:** i) Selection based on titles and abstracts Full double-sifting of titles and abstracts will not be conducted due to the straightforward nature of the review question (intervention question with clearly defined interventions and comparators). ii) Selection based on full papers A full double-selecting of full papers for inclusion/exclusion will not be conducted due to the nature of the review question (as mentioned above). Other mechanisms will be in place for quality assurance: • Internal quality assurance by CGUT technical adviser on the reasons for inclusion and exclusion. • As an additional check the Committee will be sent the list of included and excluded studies prior to the committee meeting, and the Committee will be requested to cross check whether any studies have been excluded inappropriately, and (in the case of topic expert members) whether there are any relevant studies they have known of which have not been identified by the searches.
Analysis of subgroups or subsets	People with a comorbid learning disability People with a comorbid specific neurological or behavioural disorder Children (3 to 11) and young people (12 to 18) ADHD severity (mild/moderate vs severe)
Data extraction and quality assessment	Key features of included studies and reported outcomes will be extracted into evidence tables. The quality of evidence for each outcome will be assessed using the approach for intervention questions outlined by the GRADE working group. **Reliability of quality assessment:** A full double-scoring quality assessment will not be conducted due to the nature of the review question (as mentioned above) and the studies that are likely to be included. Other quality assurance mechanisms will be in

Components	Details
	place as the following: • Internal quality assurance by CGUT technical adviser on the quality assessment that is being conducted. • As an additional check, the Committee will be sent the evidence synthesis prior to the committee meeting and the Committee will be requested to comment on the quality assessment (GRADE profiles), which will serve as another quality assurance function.
Strategy for data synthesis	Data for each outcome from different studies will be synthesised using pairwise meta-analysis where possible. Data will be pooled across the following time points: short term (up to 3 months), medium term (3 to 6 months), long term (over 6 months) Where synthesis by meta-analysis is not possible, data will be presented for individual studies.
Searches	Databases to be searched: Clinical searches - Medline, Medline in Process, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA, CINAHL and PsycInfo. Economic searches - Medline, Medline in Process, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. Supplementary search techniques: None identified Limits: Studies reported in English Study design RCT and Systematic Review Animal studies will be excluded from the search results Conference abstracts will be excluded from the search results No date limit will be set.

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C.22 Question 2

Components	Details
Review question	What is the clinical and cost-effectiveness of dietary supplementation with polyunsaturated fatty acids, (PUFAs) in children with ADHD?
Background/objectives	The NICE guideline on ADHD was reviewed in 2015, and new evidence on the effectiveness on dietary supplementation with fatty acids ADHD was found that may impact current recommendations. The aim of the review is to evaluate the effectiveness of dietary supplements on children with ADHD.
Types of study to be included	Randomised controlled trials (excluding crossover trials), systematic reviews of randomised controlled trials.
Language	English (original English version or existing full text English translation)
Status	Published papers (full text only)
Population	Children and young people (aged 3 to 18*) diagnosed with ADHD or hyperkinetic disorder.

Components	Details
	Diagnosis must be made using validated diagnostic criteria such as those specified for ADHD in the diagnostic and statistical manual (DSM IV or DSM 5) or the hyperkinetic syndrome in the international classification of diseases (ICD 9 or 10). *A study will not be excluded if the majority of participants fall within this age range
Intervention	Dietary supplementation with polyunsaturated fatty acids.
Comparator	No treatment, waiting list, usual care, 'placebo' dietary intervention. Other concurrent treatments (for example medication, psychological therapy, parenting interventions) will be permitted, provided that they are the same for both intervention and control groups. Comparison between dietary and pharmacological or psychological interventions will not be included.
Outcomes	ADHD symptom severity – self reported (measured using Connors' rating scale, ADHD-RS score, SKAMP test score, SNAP rating scale or other validated rating scale) ADHD symptom severity – parent reported (measured using Connors' rating scale, ADHD-RS score, SKAMP test score, SNAP rating scale or other validated rating scale) ADHD symptom severity – teacher reported (measured using Connors' rating scale, ADHD-RS score, SKAMP test score, SNAP rating scale or other validated rating scale) Academic performance (including verbal memory, reading, spelling, executive function) Functional status (measured using the global assessment of functioning questionnaire, children's global assessment of function, strengths and difficulties questionnaire or other validated tool for measuring functional status) Side effects (limited to: gastrointestinal symptoms, change in weight, change in appetite, change in sleep pattern, headache) Number of participants leaving the study early (as a surrogate measure for treatment acceptability) Quality of life
Any other information or criteria for inclusion/exclusion	Treatment duration must be at least 8 weeks. Cross over trials will be excluded. Continuous outcome measures will only be extracted if appropriate measures of variability (such as standard deviations) are reported or calculable from other reported values. **Selection of papers:** i) Selection based on titles and abstracts Full double-sifting of titles and abstracts will not be conducted due to the straightforward nature of the review question (intervention question with clearly defined interventions and comparators). ii) Selection based on full papers A full double-selecting of full papers for inclusion/exclusion

Components	Details
	will not be conducted due to the nature of the review question (as mentioned above). Other mechanisms will be in place for quality assurance: • Internal quality assurance by CGUT technical adviser on the reasons for inclusion and exclusion. • As an additional check the Committee will be sent the list of included and excluded studies prior to the committee meeting, and the Committee will be requested to cross check whether any studies have been excluded inappropriately, and (in the case of topic expert members) whether there are any relevant studies they have known of which have not been identified by the searches.
Analysis of subgroups or subsets	People with a comorbid learning disability People with a comorbid specific neurological or behavioural disorder Children (3 to 11) and young people (12 to 18) ADHD severity (mild/moderate vs severe) Participants with a deficiency in the PUFA to be supplemented in the study at enrolment. Subgroup analysis by dose (below recommended dose, within recommended dose range, above recommended dose.
Data extraction and quality assessment	Key features of included studies and reported outcomes will be extracted into evidence tables. The quality of evidence for each outcome will be assessed using the approach for intervention questions outlined by the GRADE working group. **Reliability of quality assessment:** A full double-scoring quality assessment will not be conducted due to the nature of the review question (as mentioned above) and the studies that are likely to be included. Other quality assurance mechanisms will be in place as the following: • Internal quality assurance by CGUT technical adviser on the quality assessment that is being conducted. • As an additional check, the Committee will be sent the evidence synthesis prior to the committee meeting and the Committee will be requested to comment on the quality assessment (GRADE profiles), which will serve as another quality assurance function.
Strategy for data synthesis	Data for each outcome from different studies will be synthesised using pairwise meta-analysis where possible. Data will be pooled across the following time points: short term (up to 3 months), medium term (3 to 6 months), long term (over 6 months) Where synthesis by meta-analysis is not possible, data will be presented for individual studies.
Searches	Databases to be searched: Clinical searches - Medline, Medline in Process, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA, CINAHL and PsycInfo. Economic searches - Medline, Medline in Process, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. Supplementary search techniques:

Components	Details
	None identified Limits: Studies reported in English Study design RCT and Systematic Review Animal studies will be excluded from the search results Conference abstracts will be excluded from the search results No date limit will be set.

1

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Appendix D: Search strategy

D.1 Question 1

Sources searched to identify the clinical evidence:

Database	Date searched	Version/files
Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)	19/06/2015	5 of 12 May 2015
Cochrane Database of Systematic Reviews (CDSR) (Wiley)	19/06/2015	6 of 12 June 2015
Cumulated Index to Nursing and Allied Health Literature (CINAHL) (EBSCO)	19/06/2015	
Database of Abstracts of Reviews of Effectiveness (DARE) (Wiley)	19/06/2015	2 of 4 April 2015
Embase (Ovid)	19/06/2015	1974 to 2015 June 18
MEDLINE (Ovid)	19/06/2015	1946 to June wk 2 2015
MEDLINE In-Process (Ovid)	19/06/2015	June 18
PubMed	24/06/2015	
PsycINFO (Ovid)	19/06/2015	1806 to June wk 3 2015

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. The aim of the search was to identify evidence for the clinical question being asked.

The Pubmed translation consisted of an abbreviated strategy run at the end of the process designed to capture references that had not yet appeared in the Medline in Process database. Randomised Controlled Trial and Systematic Review filters were used to identify the study designs specified in the Review Protocol.

Database: Ovid Medlne
1. (attenti$ or disrupt$ or impulsiv$ or inattenti$).sh.
2. Attention Deficit Disorder with Hyperactivity/
3. "attention deficit and disruptive behavior disorders"/
4. ((attenti* or disrupt*) adj3 (adolescen* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).tw.
5. (disruptive* or impulsiv* or inattentiv*).tw.
6. (adhd or addh or ad hd or ad??hd).tw.
7. (attenti* adj3 deficit*).tw.
8. Hyperkinesis/
9. (hyperkin* or hyperactiv*).tw.
10. (hyper adj1 (activ* or kin*)).tw.
11. hkd.tw.
12. (minimal adj1 brain).tw.

Database: Ovid Medlne

13. overactiv*.tw. not overactive bladder*.ti.
14. (over adj1 activ*).tw. not overactive bladder*.ti.
15. or/1-14
16. Diet/
17. ((eliminat* or restrict*) adj4 (diet* or food* or nutriti*)).tw.
18. exp Flavoring Agents/
19. (flavo* adj4 (food* or agent*)).tw.
20. (flavo* adj1 (aroma or compound)).tw.
21. (sweeten* or sugar* or candy).tw.
22. (acesulfam* or acetosulfam or sunette or alitame or aspart* or apm or canderel or hermesetas or equa or fliks or "mini d" or nutrasweet or sucrandel or "tri sweet" or milisucre or nozucar or (syrup adj1 (maize or corn)) or cyclamate* or "cyclamic acid" or ibiosuc or sucaryl or sukriso or fructose or dextrofructose or diabetin or laevoral or laevoran or laevosan or laevulose or levugen or levulos* or hernandulcin or calarose or insubeta or inversol or invertosteril or nulomoline or solinvert or travert or isomalt or palatinit or leucrose or maltitol or malbit or mannitol or cytal or sorbit*or monellin or neotame or saccharin* or goldswite or "benzoic sulfimide" or benzosulfimide or benzosulphimide or garantose or glu?id* or "ortho sulfobenzimide" or "ortho sulfobenzoic acid" or saccharod or saccharol or "sweet n low" or sweeta or sweetex or sweetnin or sykose or willosetten or cr?stallose or dagutan or kristallose or saxin or glucitol or glucohexitol or diakarman or glycitol or gulitole or karion or neosorb or sorbo* or stevia* or steviosi* or stevoside or sucralose or splenda or sucrose or microtal or saccharose or "saccharum album" or tabfine or (sweet adj2 protein) or thaumatin or xylit* or zerocal or sukrana or sucraplus or canys or cukren or nevella or glucose or isoglucose or lactose or maltose or osmitrol or osmofundin or molasse* or yal or sorbilax or medivac or sweetleaf* or ((rebaudianum adj1 eupatorium) or asugrin or saccharoid or nivitin or sionon or sorbelite)).tw.
23. Caseins/
24. (casein* or phosphocasein).tw.
25. exp Glutens/
26. (glute* or secalin* or hordein*).tw.
27. exp Food additives/
28. ((food adj4 (additive* or preservative*)) or AFCE).tw.
29. ((food or agent*) adj4 (colour* or color* or dye*)).tw.
30. Tartrazine/
31. (alkann* or anchus* or shikalkin or "allura red" or canthaxanthin* or orobronze or carmine or "carminic acid" or carmoisine or curcumin* or nanocurc or turmeric or demethoxycurcumin* or didemethoxycurcumin or bisdemethoxycurcumin or shikonin or tartrazine or "hydrazine yellow" or erioglaucine or alphazurine or indigotine).tw.
32. Sodium Benzoate/
33. (benzoate or benzoylate or carboxybenzene or "dracylic acid" or "phenylformic acid" or "benzoic acid").tw.
34. exp Salicylates/
35. (salicylate* or salicylic).tw.
36. exp Nitrites/
37. (nitrite* or "nitrous acid").tw.
38. (((monosodium or sodium) adj2 (glutamate or monoglutamate)) or monosodiumglutamate or "glutamic acid" or "glutaminate sodium" or glutavene or sodiumglutamate or msg or vestin or accent).tw.
39. exp Caffeine/
40. (caffein* or animine or cafein or coffe* or guaranine or guarin or methyltheobromine or "no doz" or nodoz or "pac compound" or thein or trimethylxanthine or vivarin or percoffedrinol or percutafeine or caffedrine or durvitan or dexitac or (quick adj1 pep)).tw.
41. oligoantigenic.tw.
42. or/16-41
43. 15 and 42
44. Meta-Analysis.pt.

Database: Ovid Medlne
45. Meta-Analysis as Topic/
46. Review.pt.
47. exp Review Literature as Topic/
48. (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
49. (review$ or overview$).ti.
50. (systematic$ adj5 (review$ or overview$)).tw.
51. ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
52. ((studies or trial$) adj2 (review$ or overview$)).tw.
53. (integrat$ adj3 (research or review$ or literature)).tw.
54. (pool$ adj2 (analy$ or data)).tw.
55. (handsearch$ or (hand adj3 search$)).tw.
56. (manual$ adj3 search$).tw.
57. or/44-56
58. animals/ not humans/
59. 57 not 58
60. Randomized Controlled Trial.pt.
61. Controlled Clinical Trial.pt.
62. Clinical Trial.pt.
63. exp Clinical Trials as Topic/
64. Placebos/
65. Random Allocation/
66. Double-Blind Method/
67. Single-Blind Method/
68. Cross-Over Studies/
69. ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
70. (random$ adj3 allocat$).tw.
71. placebo$.tw.
72. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
73. (crossover$ or (cross adj over$)).tw.
74. or/60-73
75. animals/ not humans/
76. 74 not 75
77. 59 or 76
78. 43 and 77
79. limit 78 to english language

1

D.2 2 Question 2

3 Sources searched to identify the clinical evidence:

Database	Date searched	Version/files
Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)	30/06/2015	6 of 12 June 2015
Cochrane Database of Systematic Reviews (CDSR) (Wiley)	30/06/2015	6 of 12 June 2015
Cumulated Index to Nursing and Allied Health Literature (CINAHL) (EBSCO)	30/06/2015	

Database	Date searched	Version/files
Database of Abstracts of Reviews of Effect (DARE) (Wiley)	30/06/2015	2 of 4 April 2015
Embase (Ovid)	30/06/2015	1974 to 2015 June 29
MEDLINE (Ovid)	30/06/2015	1946 to June wk 3
MEDLINE In-Process (Ovid)	30/06/2015	June 29 2015
PubMed	30/06/2015	
PsycINFO (Ovid)	30/06/2015	1806 to June wk 4
Health Technology Assessment (HTA Database) (Wiley)	30/06/2015	

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. The aim of the search was to identify evidence for the clinical question being asked.

The Pubmed translation consisted of an abbreviated strategy run at the end of the process designed to capture references that had not yet appeared in the Medline in Process database. Randomised Controlled Trial and Systematic Review filters were used to identify the study designs specified in the Review Protocol.

Database: Ovid Medlne
1. (attenti$ or disrupt$ or impulsiv$ or inattenti$).sh.
2. Attention Deficit Disorder with Hyperactivity/
3. "attention deficit and disruptive behavior disorders"/
4. ((attenti* or disrupt*) adj3 (adolescen* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).tw.
5. (disruptive* or impulsiv* or inattentiv*).tw.
6. (adhd or addh or ad hd or ad??hd).tw.
7. (attenti* adj3 deficit*).tw.
8. Hyperkinesis/
9. (hyperkin* or hyperactiv*).tw.
10. (hyper adj1 (activ* or kin*)).tw.
11. hkd.tw.
12. (minimal adj1 brain).tw.
13. overactiv*.tw. not overactive bladder*.ti.
14. (over adj1 activ*).tw. not overactive bladder*.ti.
15. or/1-14
16. exp Fatty Acids/
17. (fatty adj4 acid*).tw.
18. (((polyunsaturated or unsaturated) adj4 (fat* or lipid*)) or (ufa* or pufa*)).tw.
19. aliphatic acid*.tw.
20. ((omega or n) adj4 fatty).tw.
21. ("omega 3" or "omega forte" or "bilantin omega" or "conchol 36" or "eicosa e" or eicosapen or epaisidin or epanova or sakana).tw.
22. (((docosahexaenoic or docosahexenoic) adj1 acid*) or docosahexaenoate or dhasco).tw.
23. (((linolenic or octadecatrienoic) adj1 acid*) or linolenate).tw.
24. (((eicosapentaenoic or eicosapentanoic or timnodonic or icosapentaenoic) adj1 acid*) or eicosapentaeonate or icosapentaenoate).tw.

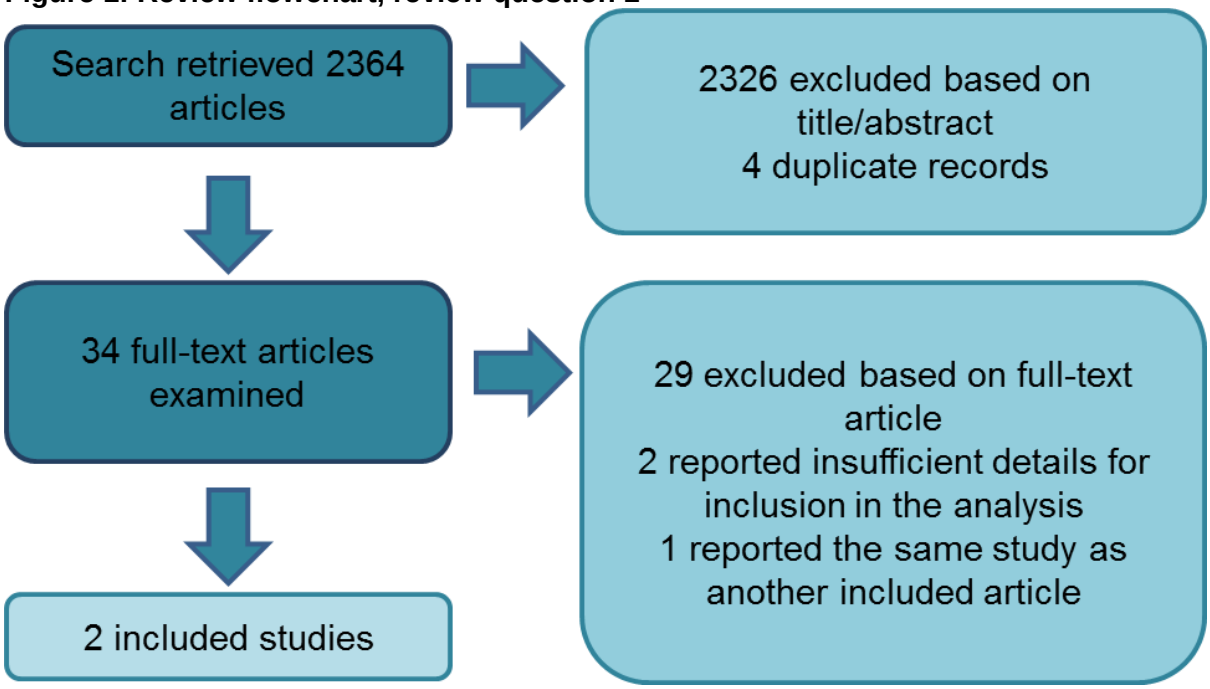
Database: Ovid Medlne

25. ((hexadecatrienoic or stearidonic) adj1 acid*).tw.
26. (((eicosatrienoic or icosatrienoic) adj1 acid*) or eicosatrieonate or icosatrieonate).tw.
27. (((eicosatetraenoic or arachidonic or icosatetraenoic) adj1 acid*) or eicosatetraenoate).tw.
28. ((heneicosapentaenoic or docosapentaenoic or tetracosapentaenoic or nisinic) adj1 acid*).tw.
29. "omega 6".tw.
30. (((linoleic or octadecadienoic or linolelaidic or linoelaidic or linoic or linolic or dienoic) adj1 acid*) or linoleate or linolate).tw.
31. ((linolenic or gamolenic) adj1 acid*).tw.
32. ((calendic or eicosadienoic) adj1 acid*).tw.
33. ((gamma adj1 linolenic) or dhla or dihomogammalinolenic).tw.
34. ((tetraenoic adj1 acid*) or arachidonate or "vitamin f").tw.
35. ((docosadienoic or docosapentaenoic or tetracosatetraenoic) adj1 acid*).tw.
36. or/16-35
37. 15 and 36
38. Meta-Analysis.pt.
39. Meta-Analysis as Topic/
40. Review.pt.
41. exp Review Literature as Topic/
42. (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
43. (review$ or overview$).ti.
44. (systematic$ adj5 (review$ or overview$)).tw.
45. ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
46. ((studies or trial$) adj2 (review$ or overview$)).tw.
47. (integrat$ adj3 (research or review$ or literature)).tw.
48. (pool$ adj2 (analy$ or data)).tw.
49. (handsearch$ or (hand adj3 search$)).tw.
50. (manual$ adj3 search$).tw.
51. or/38-50
52. animals/ not humans/
53. 51 not 52
54. Randomized Controlled Trial.pt.
55. Controlled Clinical Trial.pt.
56. Clinical Trial.pt.
57. exp Clinical Trials as Topic/
58. Placebos/
59. Random Allocation/
60. Double-Blind Method/
61. Single-Blind Method/
62. Cross-Over Studies/
63. ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
64. (random$ adj3 allocat$).tw.
65. placebo$.tw.
66. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
67. (crossover$ or (cross adj over$)).tw.
68. or/54-67
69. animals/ not humans/
70. 68 not 69
71. 53 or 70
72. 71 and 37
73. limit 72 to english language

Appendix E: Review flowchart

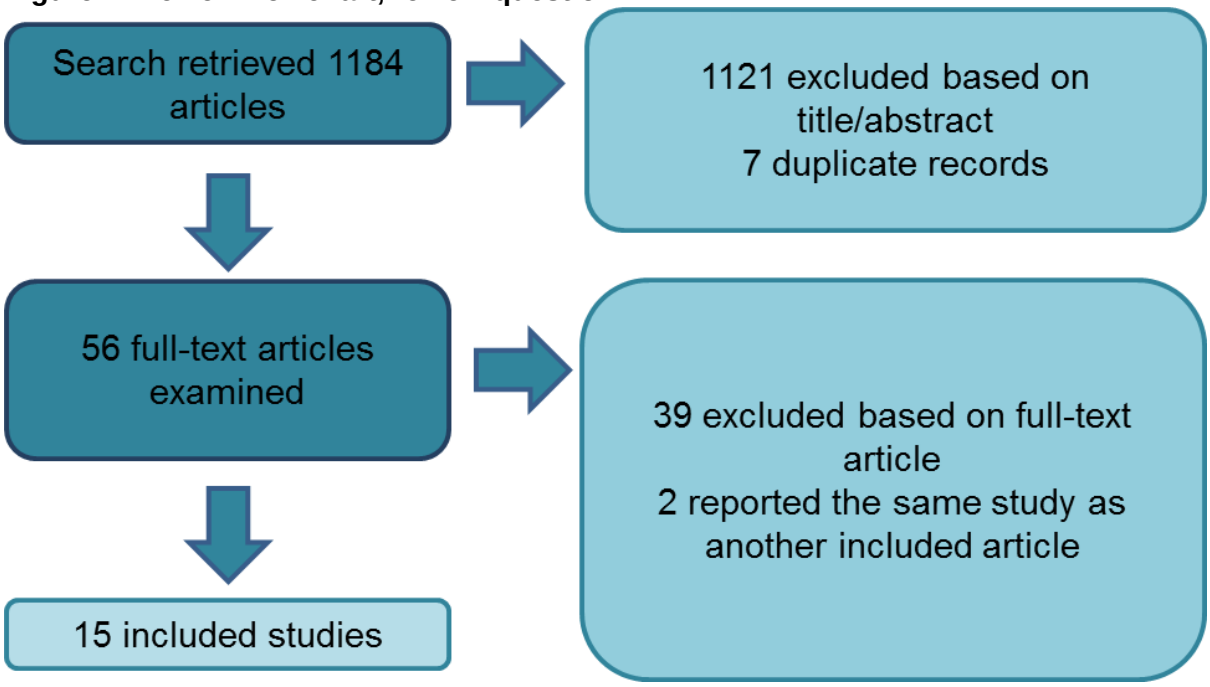
E.1 Question 1

Figure 1: Review flowchart, review question 1



E.2 Question 2

Figure 2: Review flowchart, review question 2



1 Appendix F:Excluded studies

F.1 2 Question 1

Study	Reason for Exclusion
Barling,J., Bullen,G., 19851119, Dietary factors and hyperactivity: a failure to replicate.,Journal of Genetic Psychology, 146, 117-123, 1985	Incorrect study type (observational study assessing diet between hyperactive and control children)
Boris,M., Mandel,F.S., 19940607, Foods and additives are common causes of the attention deficit hyperactive disorder in children. Annals of Allergy, 72, 462-468, 1994	Incorrect study type: non-comparative study.
Carter,C.M., Urbanowicz,M., Hemsley,R., Mantilla,L., Strobel,S., Graham,P.J., Taylor,E., 19940110, Effects of a few food diet in attention deficit disorder, Archives of Disease in Childhood, 69, 564-568, 1993	Treatment duration < 2 weeks (1 week treatment duration in randomised phase)
Conners,C.K., Goyette,C.H., Southwick,D.A., 19760602, Food additives and hyperkinesis: preliminary report of a double-blind crossover experiment, Psychopharmacology Bulletin, 12, 10-11, 1976	Abstract only: no full-text article available.
Egger,J., Carter,C.M., Graham,P.J., Gumley,D., Soothill,J.F., 19850417, Controlled trial of oligoantigenic treatment in the hyperkinetic syndrome, Lancet, 1, 540-545, 1985	Incorrect population: diagnosis of ADHD or hyperkinetic syndrome not required for inclusion.
Ghuman,J.K., 20110317, Restricted elimination diet for ADHD: the INCA study, Lancet, 377, 446-448, 2011	Incorrect study type: commentary
Harley,J.P., Ray,R.S., Tomasi,L., Eichman,P.L., Matthews,C.G., Chun,R., Cleeland,C.S., Traisman,E., 19780929, Hyperkinesis and food additives: testing the Feingold hypothesis, Pediatrics, 61, 818-828, 1978	Incorrect population: ADHD/hyperkinesis diagnosis not required for inclusion
Heilskov Rytter,M.J., Andersen,L.B., Houmann,T., Bilenberg,N., Hvolby,A., Molgaard,C., Michaelsen,K.F., Lauritzen,L., 20150518, Diet in the treatment of ADHD in children - a systematic review of the literature. Nordic Journal of Psychiatry, 69, 1-18, 2015	Systematic review that does not match the review protocol. Relevant sections used for cross checking.
Kaplan,B.J., McNicol,J., Conte,R.A., Moghadam,H.K., 19890203, Dietary replacement in preschool-aged hyperactive boys, Pediatrics, 83, 7-17, 1989	Incorrect study design: Non-randomised crossover trial
Kavale,K.A., Forness,S.R., 19831008, Hyperactivity and diet treatment: a meta-analysis of the Feingold hypothesis, Journal of Learning Disabilities, 16, 324-330, 1983	Incorrect study type: non-systematic review
Levy,F., Dumbrell,S., Hobbes,G., Ryan,M., Wilton,N., Woodhill,J.M.,	Incorrect intervention: challenge study (elimination diet element of the study

Study	Reason for Exclusion
19780715, Hyperkinesis and diet: a double-blind crossover trial with a tartrazine challenge, Medical Journal of Australia, 1, 61-64, 1978	did not have a control comparison and was not randomised)
Levy,F., Hobbes,G., 19790126, Hyperkinesis and diet: a replication study, American Journal of Psychiatry, 135, 1559-1560, 1978	Incorrect intervention: food colouring challenge study.
Lomangino,Kevin, Benefit for elimination diet in ADHD?, Clinical Nutrition Insight, 37, 8-, 2011	Incorrect study design: commentary
Lykogeorgou,M., Karkelis,S., Papadaki-Papandreou,O., Nikita,M., Gluten free diet for children with attention deficit and hyperactivity disorder, Archives of Disease in Childhood, 99, A204-A205, 2014	Abstract only - no full text available
Mattes,J., Gittelman-Klein,R., 19780901, A crossover study of artificial food colorings in a hyperkinetic child, American Journal of Psychiatry, 135, 987-988, 1978	Incorrect study type: narrative review
Mattes,J.A., Gittelman,R., 19810810, Effects of artificial food colorings in children with hyperactive symptoms. A critical review and results of a controlled study, Archives of General Psychiatry, 38, 714-718, 1981	Incorrect intervention: challenge study (elimination diet element of the study did not have a control comparison and was not randomised)
Millichap,J.G., Yee,M.M., 20120327, The diet factor in attention-deficit/hyperactivity disorder, Pediatrics, 129, 330-337, 2012	Incorrect study type (narrative review)
Newmark,S.C., Nutritional Intervention in ADHD, Explore: The Journal of Science and Healing, 5, 171-174, 2009	Incorrect study type: narrative review
Nigg,J.T., Lewis,K., Edinger,T., Falk,M., 20120426, Meta-analysis of attention-deficit/hyperactivity disorder or attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives, Journal of the American Academy of Child & Adolescent Psychiatry, 51, 86-97, 2012	Systematic review that does not match review protocol. Used for cross checking.
Pelsser,L.M., Avoiding specific foods may reduce ADHD: Should we change our prescriptions?, European psychiatry, 27, -, 2012	Incorrect study type: narrative review
Pelsser,L.M., van Steijn,D.J., Frankena,K., Toorman,J., Buitelaar,J.K., Rommelse,N.N., A randomized controlled pilot study into the effects of a restricted elimination diet on family structure in families with ADHD and ODD, Child and Adolescent Mental Health, 18, 39-45, 2013	Incorrect study type: part of a previously reported randomised controlled trial (Pessler 2011) determining whether family environment might explain the trial findings.
Sarantinos,J., Rowe,K.S., Briggs,D.R., Synthetic food colouring and behavioural change in children with attention deficit disorder: a double-blind, placebo controlled, repeated measures study, Proc Nutr Soc Aust, 15, 233-, 1990	Abstract only: no full text article available
Schab,D.W., Trinh,N.H., 20050503, Do artificial food colors promote	Systematic review not meeting criteria specified in review protocol. Used for

Study	Reason for Exclusion
hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials, Journal of Developmental & Behavioral Pediatrics, 25, 423-434, 2004	cross checking.
Schmidt,M.H., Mocks,P., Lay,B., Eisert,H.G., Fojkar,R., Fritz-Sigmund,D., Marcus,A., Musaeus,B., 19970930, Does oligoantigenic diet influence hyperactive/conduct-disordered children--a controlled trial, European Child & Adolescent Psychiatry, 6, 88-95, 1997	Incorrect population: diagnosis of ADHD or hyperkinetic syndrome not required for inclusion.
Schulte-Korne,G., Deimel,W., Gutenbrunner,C., Hennighausen,K., Blank,R., Rieger,C., Remschmidt,H., The influence of an oligoantigenic diet on the behavior of children with attention-deficit hyperactivity disorders, Der Einfluss einer oligoantigenen Diat auf das Verhalten von hyperkinetischen Kindern, Zeitschrift fur Kinder- und Jugendpsychiatrie und Psychotherapie, 24, 176-183, 1996	Article not in English
Sonuga-Barke,E.J., Brandeis,D., Cortese,S., Daley,D., Ferrin,M., Holtmann,M., Stevenson,J., Danckaerts,M., van der Oord,S., Dopfner,M., Dittmann,R.W., Simonoff,E., Zuddas,A., Banaschewski,T., Buitelaar,J., Coghill,D., Hollis,C., Konofal,E., Lecendreux,M., Wong,I.C., Sergeant,J., European ADHD Guidelines Group, 20130415, Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments, American Journal of Psychiatry, 170, 275-289, 2013	Systematic review that does not match review protocol. Used for cross checking.
Stevenson,J., Buitelaar,J., Cortese,S., Ferrin,M., Konofal,E., Lecendreux,M., Simonoff,E., Wong,I.C., Sonuga-Barke,E., 20150302, Research review: the role of diet in the treatment of attention-deficit/hyperactivity disorder--an appraisal of the evidence on efficacy and recommendations on the design of future studies, Journal of Child Psychology & Psychiatry & Allied Disciplines, 55, 416-427, 2014	Incorrect study type: non-systematic review
Varley,C.K., 19840530, Diet and the behavior of children with attention deficit disorder. [Review] [19 refs], Journal of the American Academy of Child Psychiatry, 23, 182-185, 1984	Incorrect study type (narrative review)
Williams,J.I., Cram,D.M., Tausig,F.T., Webster,E., 19780929, Relative effects of drugs and diet on hyperactive behaviors: an experimental study, Pediatrics, 61, 811-817, 1978	Incorrect population: diagnosis of ADHD or hyperkinetic syndrome not required for inclusion.

F.2.1 Question 2

Study	Reason for Exclusion
Aman,M.G., Mitchell,E.A., Turbott,S.H., 19870618, The effects of essential fatty acid supplementation by Efamol in hyperactive children, Journal of Abnormal Child Psychology, 15, 75-90, 1987	Treatment duration < 8 weeks.
Arnold,L.E., Pinkham,S.M., Votolato,N., 20010109, Does zinc moderate essential fatty acid and amphetamine treatment of attention-deficit/hyperactivity disorder?, Journal of Child & Adolescent Psychopharmacology, 10, 111-117, 2000	Treatment duration < 8 weeks (1 month)
Arnold,L.Eugene, Kleykamp,Donald, Votolato,Nicholas, Gibson,Robert A., Horrocks,Lloyd, Potential link between dietary intake of fatty acids and behavior: Pilot exploration of serum lipids in attention-deficit hyperactivity disorder, Journal of Child and Adolescent Psychopharmacology, 4, 171-182, 1994	Treatment duration < 8 weeks (1 month)
Bloch,M.H., Qawasmi,A., 20120208, Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: systematic review and meta-analysis, Journal of the American Academy of Child & Adolescent Psychiatry, 50, 991-1000, 2011	Systematic review that did not match review protocol. Used for cross checking.
Bloch,Michael, Richardson,Alexandra, Review: ¤ë-3 fatty acids produce a small improvement in ADHD symptoms in children compared with placebo, Evidence Based Mental Health, 15, 46-46, 2012	Incorrect study type: commentary
Brue,A.W., Oakland,T.D., Evans,R.A., The use of a dietary supplement combination and an essential fatty acid as an alternative and complementary treatment for children with attention-deficit/hyperactivity disorder, Scientific Review of Alternative Medicine, 5, 187-194, 2001	Incorrect intervention: Combination treatment with several herbal supplements
Busch,B., 20070608, Polyunsaturated fatty acid supplementation for ADHD? Fishy, fascinating, and far from clear, Journal of Developmental & Behavioral Pediatrics, 28, 139-144, 2007	Incorrect study type: narrative review
Calderon-Moore,A., Pizarro-Castellanos,M., Rizzoli-Cordoba,A., Systematic review of the efficacy and safety of omega 3 and omega 6 fatty acid supplementation in developmental neurological disorders, Boletin Medico del Hospital Infantil de Mexico, 69, 265-270, 2012	Article not in English
Dashti,N., Hekmat,H., Soltani,H.R., Rahimdel,A., Javaherchian,M., 20150323, Comparison of therapeutic effects of omega-3 and methylphenidate (ritalin) in treating children with attention deficit hyperactivity disorder, Iranian Journal of Psychiatry & Behavioral Sciences,	Incorrect study type: Although described as a randomised controlled trial, the method of allocation to groups was not truly random, as the allocation depended on time of enrolled (the first patients were allocated to ritalin, later patients to omega 3)

Study	Reason for Exclusion
8, 7-11, 2014	
Gillies,D., Sinn,J.K., Lad,S.S., Leach,M.J., Ross,M.J., 20120921, Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents, Cochrane Database of Systematic Reviews, 7, CD007986-, 2012	Systematic review that does not match review protocol. Use for cross checking.
Grassmann,V., Santos-Galduroz,R.F., Galduroz,J.C., 20130902, Effects of low doses of polyunsaturated Fatty acids on the attention deficit/hyperactivity disorder of children: a systematic review, Current Neuropharmacology, 11, 186-196, 2013	Systematic review that did not match review protocol. Used for cross checking.
Hamazaki,T., Hirayama,S., 20050303, The effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder-a placebo-controlled double-blind study, European Journal of Clinical NutritionEur.J.Clin.Nutr., 58, 838-, 2004	Incorrect study type: letter/comment
Hawkey,E., Nigg,J.T., 20150515, Omega-3 fatty acid and ADHD: blood level analysis and meta-analytic extension of supplementation trials, Clinical Psychology Review, 34, 496-505, 2014	Systematic review that did not match review protocol. Used for cross checking.
Heilskov Rytter,M.J., Andersen,L.B.B., Houmann,T., Bilenberg,N., Hvolby,A., Molgaard,C., Michaelsen,K.F., Lauritzen,L., Diet in the treatment of ADHD in children-A systematic review of the literature, Nordic Journal of Psychiatry, 69, 1-18, 2015	Systematic review that does not match review protocol. Relevant sections used for cross checking.
Hirayama,S., Hamazaki,T., Terasawa,K., 20040629, Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder - a placebo-controlled double-blind study, European Journal of Clinical Nutrition, 58, 467-473, 2004	Incorrect population: ADHD/hyperkinesis diagnosis not needed for inclusion (some participants had 'suspected' ADHD)
Johnson,M., 20130628, Review: little evidence that PUFA supplementation improves symptoms in ADHD, Evidence-Based Mental Health, 16, 12-, 2013	Incorrect study design: commentary
Joshi,K., Lad,S., Kale,M., Patwardhan,B., Mahadik,S.P., Patni,B., Chaudhary,A., Bhave,S., Pandit,A., 20060227, Supplementation with flax oil and vitamin C improves the outcome of Attention Deficit Hyperactivity Disorder (ADHD), Prostaglandins Leukotrienes & Essential Fatty Acids, 74, 17-21, 2006	Incorrect study type: not a randomised controlled trial (participants tested before and after treatment)
Karpouzis,F., Bonello,R., Nutritional complementary and alternative medicine for pediatric attention-deficit/hyperactivity disorder, Ethical Human Psychology and Psychiatry, 14, 41-60, 2012	Incorrect study type: non-systematic review
Lim-Ashworth,N., Ooi,Y.P., Weng,S.J., Lim,C.G., Fung,D.S.S., Glenn,A.,	Abstract only: no full text available

Study	Reason for Exclusion
Ang,R.P., Raine,A., Preliminary Findings on the Effects of Nutritional and Social Skills Intervention among Children with Attention Deficit Hyperactivity Disorder, Annals of the Academy of Medicine Singapore.(S327 pages), 42, S162-, 2013	
Milte,C.M., Parletta,N., Buckley,J.D., Coates,A.M., Young,R.M., Howe,P.R., Increased Erythrocyte Eicosapentaenoic Acid and Docosahexaenoic Acid Are Associated With Improved Attention and Behavior in Children With ADHD in a Randomized Controlled Three-Way Crossover Trial, Journal of Attention Disorders, -, 2013	Incorrect population: ADHD diagnosis not required for inclusion
Milte,C.M., Parletta,N., Buckley,J.D., Coates,A.M., Young,R.M., Howe,P.R., 20120830, Eicosapentaenoic and docosahexaenoic acids, cognition, and behavior in children with attention-deficit/hyperactivity disorder: a randomized controlled trial, Nutrition, 28, 670-677, 2012	Incorrect population: ADHD diagnosis not required for inclusion
Puri,B.K., Martins,J.G., 20141209, Which polyunsaturated fatty acids are active in children with attention-deficit hyperactivity disorder receiving PUFA supplementation? A fatty acid validated meta-regression analysis of randomized controlled trials, Prostaglandins Leukotrienes & Essential Fatty Acids, 90, 179-189, 2014	Systematic review that does not match review protocol. Used for cross checking.
Raz,R., Carasso,R.L., Yehuda,S., 20090724, The influence of short-chain essential fatty acids on children with attention-deficit/hyperactivity disorder: a double-blind placebo-controlled study, Journal of Child & Adolescent Psychopharmacology, 19, 167-177, 2009	Treatment period < 8 weeks (7 weeks)
Raz,R., Gabis,L., Essential fatty acids and attention-deficit-hyperactivity disorder: A systematic review, Developmental Medicine and Child Neurology, 51, 580-592, 2009	Incorrect study type: Although described as a systematic review, no description of systematic search and criteria for inclusion.
Reading,Richard, Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: systematic review and meta-analysis, Child: Care, Health & Development, 39, 150-151, 2013	Incorrect study type: Commentary on systematic review
Richardson,A.J., Puri,B.K., 20020722, A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 26, 233-239, 2002	Incorrect population: ADHD diagnosis not required for inclusion
Richardson,A.J., 20120611, Review: omega-3 fatty acids produce a small improvement in ADHD symptoms in children compared with placebo,	Incorrect study type: commentary

Study	Reason for Exclusion
Evidence-Based Mental Health, 15, 46-, 2012	
Ross,S.M., 20131028, Omega-3 fatty acids, part I: the effects of n-3 polyunsaturated fatty acid in the treatment of attention-deficit hyperactivity disorder in children, Holistic Nursing Practice, 26, 356-359, 2012	Incorrect study type: commentary on trial
Searight,H.R., Robertson,K., Smith,T., Searight,B.K., A qualitative systematic review of complementary and alternative therapies for childhood attention deficit hyperactivity disorder: Botanicals, diet, minerals, and homeopathy, Family Medicine and Primary Care Review, 13, 798-803, 2011	Systematic review that does not match criteria specified in review protocol. Relevant sections used for cross checking.
Sinn,J.K.H., Gillies,D., Ross,M.J., Lad,S.S., Polyunsaturated fatty acids (PUFAs) for attention deficit hyperactivity disorder in children and adolescents, Cochrane Database of Systematic Reviews, -, 2009	Systematic review that has subsequently been updated (Gillies 2012)
Sinn,N., Bryan,J., Wilson,C., 20081014, Cognitive effects of polyunsaturated fatty acids in children with attention deficit hyperactivity disorder symptoms: a randomised controlled trial, Prostaglandins Leukotrienes & Essential Fatty Acids, 78, 311-326, 2008	Incorrect population: diagnosis of ADHD or hyperkinetic syndrome not required for inclusion.
Sinn,N., Bryan,J., 20070608, Effect of supplementation with polyunsaturated fatty acids and micronutrients on learning and behavior problems associated with child ADHD, Journal of Developmental & Behavioral Pediatrics, 28, 82-91, 2007	Incorrect population: diagnosis with ADHD or hyperkinetic disorder not required.
Sinn,N., 20090126, Nutritional and dietary influences on attention deficit hyperactivity disorder, Nutrition Reviews, 66, 558-568, 2008	Incorrect study type: narrative review.
Sonuga-Barke,E.J., Brandeis,D., Cortese,S., Daley,D., Ferrin,M., Holtmann,M., Stevenson,J., Danckaerts,M., van der Oord,S., Dopfner,M., Dittmann,R.W., Simonoff,E., Zuddas,A., Banaschewski,T., Buitelaar,J., Coghill,D., Hollis,C., Konofal,E., Lecendreux,M., Wong,I.C., Sergeant,J., European ADHD Guidelines Group, 20130415, Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments, American Journal of Psychiatry, 170, 275-289, 2013	Systematic review that does not match review protocol. Relevant sections used for cross checking.
Tan,X., Lee,X.Y., Lim,C.G., Fung,D.S.S., Effectiveness of omega-3 fatty acids supplementation on sleep in children and adolescents with attention deficit hyperactivity disorder, Annals of the Academy of Medicine Singapore, 43, S340-, 2014	Abstract only: no full text article available
Transler,C., Eilander,A., Mitchell,S., van de Meer,N., 20110204, The impact of polyunsaturated fatty acids in reducing child attention deficit and hyperactivity disorders, Journal of Attention Disorders, 14, 232-246, 2010	Incorrect study type: narrative review

Study	Reason for Exclusion
Vanasse,M., Ageranioti-Bélanger,S., L'heureux,F., Ghadirian,P., Levy,E., Spahis,S., Lippé,S., Vannase,C.M., A randomized, controlled trial of omega-3 and phospholipids supplementation in children with attention-deficit-hyperactivity disorder, Developmental Medicine & Child Neurology, 48, 48-48, 2006	Abstract only: no full text version available
Yehuda,S., Rabinovitz-Shenkar,S., Carasso,R.L., 20120123, Effects of essential fatty acids in iron deficient and sleep-disturbed attention deficit hyperactivity disorder (ADHD) children, European Journal of Clinical Nutrition, 65, 1167-1169, 2011	Incorrect study design: not a randomised controlled trial (non-comparative study with several participant population groups)
Zaref,J., Kemper,K.J., Does fish oil help with ADHD?, Contemporary Pediatrics, 22, 94-94, 2005	Incorrect study type: commentary

1 Appendix G: Evidence tables

G.1 2 Question 1: Elimination/restriction diets for ADHD

3 **Table 6: Studies meeting inclusion criteria but reporting no outcomes specified in the review protocol**

Bibliographic reference	Outcomes reported but not extracted
Conners, Keith C, And O (1975) Food Additives and Hyperkinesis: A Controlled Double-Blind Experiment. (Includes NIE Staff Critique). Pittsburgh Univ., Pa.Dept.of Psychiatry. 59	Parent and teacher ADHD symptom scores (no measure of variability, such as standard deviation reported or calculable). Other outcomes were not reported separately for the two crossover periods, and there was no washout between phases so the study was not eligible for inclusion as a cross over trial.
Conners CK, Goyette CH, Southwick DA et al. (1976) Food additives and hyperkinesis: a controlled double-blind experiment. Pediatrics 58: 154-66	Parent and teacher ADHD symptom scores (no measure of variability, such as standard deviation reported or calculable). Other outcomes were not reported separately for the two crossover periods, and there was no washout between phases so the study was not eligible for inclusion as a cross over trial.

G.1.1 Included studies

Table 7: Pelsser 2009, Pelsser 2010

<table>
<tr><td>Bibliographic reference</td><td>Pelsser LM, Frankena K, Toorman J et al. (2009) A randomised controlled trial into the effects of food on ADHD. European Child & Adolescent Psychiatry 18: 12-9

Pelsser LM, Frankena K, Buitelaar JK et al. (2010) Effects of food on physical and sleep complaints in children with ADHD: a randomised controlled pilot study. European Journal of Pediatrics 169: 1129-38</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial</td></tr>
<tr><td>Aim</td><td>To assess the efficacy of a restricted elimination diet in reducing symptoms in children with ADHD.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
- Between 3.8 and 8.5 years
- Met criteria specified in DSM-IV for ADHD combined type or predominantly hyperactive impulsive type.
Exclusion criteria:
- Adopted or fostered
- Co-existing neurological diseases
- an IQ below 70
- prematurity or dysmaturity
- use of alcohol
- smoking by mother during pregnancy
- co-existence of other psychiatric disorders, except for oppositional defiant disorder (ODD) and conduct disorder (CD)

Baseline characteristics
<table>
<tr><th></th><th>Elimination diet</th><th>Control</th></tr>
<tr><td>Sex (M/F)</td><td>12/15</td><td>10/12</td></tr>
<tr><td>Age (mean,sd)</td><td>6.3 (1.6)</td><td>6.1 (1.7)</td></tr>
<tr><td>Diagnosis</td><td>ADHD combined type: 10/15
ADHD hyperactive/impulsive type: 5/15</td><td>ADHD combined type: 8/12
ADHD hyperactive/impulsive type: 4/12</td></tr>
<tr><td>Comorbidities</td><td>Oppositional defiant disorder: 12/15</td><td>Oppositional defiant disorder: 10/12</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Elimination diet</th><th>Control</th></tr>
<tr><td>N</td><td>15</td><td>12</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Pelsser LM, Frankena K, Toorman J et al. (2009) A randomised controlled trial into the effects of food on ADHD. European Child & Adolescent Psychiatry 18: 12-9

Pelsser LM, Frankena K, Buitelaar JK et al. (2010) Effects of food on physical and sleep complaints in children with ADHD: a randomised controlled pilot study. European Journal of Pediatrics 169: 1129-38</td></tr>
<tr><td></td><td>N (ITT Analysis)</td><td>15</td><td>12</td></tr>
<tr><td></td><td>Drop outs</td><td>2
Sick (1)
Withdrawn (1)</td><td>1
Withdrawn (1)</td></tr>
<tr><td>Intervention</td><td colspan="3">The diet included rice, turkey, lamb, vegetables, fruit, margarine, vegetable oil, tea, pear juice and water. The diet was described as ‘individually composed’ but it was not clear how this was done.</td></tr>
<tr><td>Comparison</td><td colspan="3">Waiting list control (no treatment)</td></tr>
<tr><td>Methods</td><td colspan="3">The study started with a 2-week baseline phase during which children ate their usual diet. Parents kept a diary of diet, behaviour and activities. This was followed by a 5 week treatment phase where participants were randomly allocated to an elimination diet or waiting list control. The waiting list control group continued their usual diet throughout the rest of the study.</td></tr>
<tr><td>Length of follow up</td><td colspan="3">End of 5 week treatment period</td></tr>
<tr><td>Location</td><td colspan="3">The Netherlands, Research setting (ADHD research centre). Children were recruited from referrals to the research centre.</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">ADHD symptoms
Parent – ADHD rating scale, number of ADHD criteria
<table>
<tr><th></th><th>Elimination diet</th><th>Control</th><th>Mean difference</th></tr>
<tr><td>Baseline</td><td>mean=13.8
sd=2.3
n=15</td><td>mean=13.7
sd=2.0
n=12</td><td></td></tr>
<tr><td>End 5 week treatment</td><td>mean=4.1
sd=4.8
n=15</td><td>mean=13.4
sd=3.9
n=12</td><td>mean=9.4
95%CI=5.9 to 12.8</td></tr>
<tr><td>Change from baseline (end - baseline)*</td><td>mean=-9.7
95%CI=-12.6 to -6.8
sd=5.24**
n=15</td><td>mean=-0.3
95%CI=-2.9 to 0.4
sd=2.6**
n=12</td><td>mean=-9.4**
9%CI=-12.43 to -6.37**</td></tr>
</table>
*reported as baseline-end but reversed by reviewer for consistency with other studies</td></tr>
</table>

Bibliographic reference	Pelsser LM, Frankena K, Toorman J et al. (2009) A randomised controlled trial into the effects of food on ADHD. European Child & Adolescent Psychiatry 18: 12-9 Pelsser LM, Frankena K, Buitelaar JK et al. (2010) Effects of food on physical and sleep complaints in children with ADHD: a randomised controlled pilot study. European Journal of Pediatrics 169: 1129-38

****calculated by reviewer**

Teacher – ADHD rating scale, number of ADHD criteria

	Elimination diet	Control	Mean difference
Baseline	mean=12.0 sd=2.9 n=10	mean=10.9 sd=4.3 n=7	
End 5 week treatment	mean=3.5 sd=3.4 n=10	mean=11.9 sd=3.3 n=7	mean=8.4 95%CI=4.8 to 11.9
Change from baseline (end - baseline)*	mean=-8.5 95%CI=-10.7 to -6.4 sd=3.01** n=10	mean=1.0 95%CI=-1.2 to 3.2 sd=3.46** n=12	mean=-9.5** 95%CI=-12.2 to -6.8**

***reported as baseline-end but reversed by reviewer for consistency with other studies**
****calculated by reviewer**

Parent –Connors' abbreviated questionnaire (not used for analysis as measures same outcome as ADHD rating scale above)

	Elimination diet	Control	Mean difference
Baseline	mean=22.7 sd=4.1 n=15	mean=24.9 sd=4.2 n=12	
End 5 week treatment	mean=8.5 sd=7.5 n=15	mean=26.0 sd=4.6 n=12	mean=17.6 95%CI=12.5 to 22.6
Change from baseline	mean=-14.2	mean=1.1	

Bibliographic reference	Pelsser LM, Frankena K, Toorman J et al. (2009) A randomised controlled trial into the effects of food on ADHD. European Child & Adolescent Psychiatry 18: 12-9 Pelsser LM, Frankena K, Buitelaar JK et al. (2010) Effects of food on physical and sleep complaints in children with ADHD: a randomised controlled pilot study. European Journal of Pediatrics 169: 1129-38

(end - baseline)*	95%CI=-18.7 to -9.7 sd=8.13** n=15	95%CI=-0.2 to 2.4 sd=2.05** n=12	

***reported as baseline-end but reversed by reviewer for consistency with other studies**
****calculated by reviewer**

Teacher –Connors' abbreviated questionnaire (not used for analysis as measures same outcome as ADHD rating scale above)

	Elimination diet	Control	Mean difference
Baseline	mean=19.1 sd=5.6 n=10	mean=21.1 sd=6.7 n=7	
End 5 week treatment	mean=7.4 sd=5.3 n=10	mean=20.7 sd=5.9 n=7	mean=13.3 95%CI=7.5 to 19.1
Change from baseline (end - baseline)*	mean=-11.7 95%CI=-15.4 to -8.0 sd=5.17** n=10	mean=-0.4 95%CI=-2.8 to 1.9 sd=3.70** n=12	

***reported as baseline-end but reversed by reviewer for consistency with other studies**
****calculated by reviewer**

Number leaving study early

Few food diet	Control	Relative risk (95% CI)**
2/15 (13.3%)	1/12 (8.3%)	1.6 (0.16 to 15.6)

****calculated by reviewer**

Bibliographic reference	**Pelsser LM, Frankena K, Toorman J et al. (2009) A randomised controlled trial into the effects of food on ADHD. European Child & Adolescent Psychiatry 18: 12-9** **Pelsser LM, Frankena K, Buitelaar JK et al. (2010) Effects of food on physical and sleep complaints in children with ADHD: a randomised controlled pilot study. European Journal of Pediatrics 169: 1129-38**
	Outcomes reported but not extracted: Oppositional defiant disorder symptoms (assessed by structured psychiatric interview).
Source of funding	Foundation for Children's Welfare Stamps Netherlands; Foundation Nuts Ohra; Matty Brand Foundation; and the Foundation of Child and Behaviour.
Comments	**Randomisation:** Subjects were randomly allocated to one of the two groups by means of a sequence of numbered cards in sealed unmarked envelopes that were prepared by an independent paediatrician. **Allocation concealment:** The envelopes were picked and opened by the parents in the presence of the researcher, and treatment was then dispensed in accordance to the allocation on the card. **Blinding:** The study was unblinded. **Other:** ITT analysis used 'last observation carried forward' method.

1 **Table 8: Pelsser 2011**

Bibliographic reference	**Pelsser LM, Frankena K, Toorman J et al. (2011) Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial. Lancet 377: 494-503**
Study type	Randomised controlled trial
Aim	To investigate whether there is a relation between diet and behaviour in children with ADHD.
Patient characteristics	**Inclusion criteria:** - Age 4 to 8 years. - Diagnosis of ADHD (any subtype) by a senior paediatrician using a structured psychiatric interview. - Parents with adequate knowledge of Dutch who were motivated to follow a 5-week elimination diet. **Exclusion criteria:** - Received drugs or behavioural therapy for ADHD. - Children already following a specific diet. - Family circumstances that were likely to prevent completion of the study. **Baseline characteristics**

	Elimination diet	**Control**
Sex (M/F)	44/50	42/50

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Pelsser LM, Frankena K, Toorman J et al. (2011) Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial. Lancet 377: 494-503</td></tr>
<tr><td></td><td colspan="3"><table>
<tr><td>Age (mean,sd)</td><td>6.8 (1.3)</td><td>7.0 (1.3)</td></tr>
<tr><td>Diagnosis</td><td>Combined type: 41/50
Inattentive type: 3/50
Hyperactive type: 6/50</td><td>Combined type: 44/50
Inattentive type: 3/50
Hyperactive type: 3/50</td></tr>
<tr><td>Comorbidities</td><td>Oppositional defiant disorder: 20
Conduct disorder: 3</td><td>Oppositional defiant disorder: 27
Conduct disorder: 5</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td colspan="3"><table>
<tr><td></td><td>Elimination diet</td><td>Control</td></tr>
<tr><td>N</td><td>50</td><td>50</td></tr>
<tr><td>Drop outs</td><td>9
Did not start diet (2)
Did not comply with diet (6)
Became ill (1)</td><td>8
No reason (6)
Not motivated (2)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="3">A ‘few food’ diet (rice, meat, vegetables, pears and water) supplemented with specific foods such as potatoes, wheat and fruits. If no behavioural response was noted by the parent after 2 weeks, the diet was gradually restricted to the ‘few food’ only. The diet was described as individually composed for each child, but it was not clear how this was done.</td></tr>
<tr><td>Comparison</td><td colspan="3">Control: participants were given healthy food advice.</td></tr>
<tr><td>Methods</td><td colspan="3">The study started with a 3-week baseline phase in which no foods were excluded. Outcomes were measured during weeks 1 and repeated in week 3. Subjects were randomised to a 5 week elimination diet or a control group. Outcomes were measured again at the end of the 5 weeks. The study also had a double-blind challenge phase (not reported here).</td></tr>
<tr><td>Length of follow up</td><td colspan="3">Outcomes measured at the end of the 5 week treatment period.</td></tr>
<tr><td>Location</td><td colspan="3">The Netherlands. Research setting (ADHD research centre). Children were recruited at medical health centres and via media announcements.</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">ADHD symptoms
Parent – Attention deficit hyperactivity disorder rating scale (ADHD-RS) total score (range 0-54)<table>
<tr><td></td><td>Elimination diet</td><td>Control</td><td>Mean difference</td></tr>
<tr><td>Baseline</td><td>mean=45.3
sd=4.7</td><td>mean=47.6
sd=4.1</td><td></td></tr>
</table></td></tr>
</table>

Bibliographic reference	Pelsser LM, Frankena K, Toorman J et al. (2011) Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial. Lancet 377: 494-503

	n=50	n=50	
End 5 week treatment	mean=21.1 sd=16.8 n=50	mean=46.2 sd=5.8 n=50	
Change from baseline (end - baseline)*	mean=-24.2 95%CI=-29.0 to -19.5 sd=16.7** n=50	mean=-1.3 95%CI=-2.5 to -0.2 sd=4.05** n=50	mean=23.7* 95%CI=18.6 to 28.8 *adjusted for starting scores and block

***reported as baseline-end but reversed by reviewer for consistency with other studies**
****calculated by reviewer**

Teacher – Attention deficit hyperactivity disorder rating scale (ADHD-RS) total score (range 0-54)

	Elimination diet	**Control**	**Mean difference**
Baseline	mean=34.4 sd=6.7 n=37	mean=39.2 sd=7.8 n=40	
End 5 week treatment	mean=20.1 sd=10.1 n=37	mean=39.6 sd=8.6 n=40	
Change from baseline (end-baseline)*	mean=-14.3 95%CI=-17.1 to -11.6 sd=8.25** n=37	mean=0.4 95%CI=-1.0 to 1.7 sd=4.22** n=40	mean=15.3* 95%CI=12.0 to 18.6 *adjusted for starting scores and block

***reported as baseline-end but reversed by reviewer for consistency with other studies**
****calculated by reviewer**

Parent – Abbreviated Connors scale (range 0-30)

	Elimination diet	**Control**	**Mean difference**
Baseline	mean=23.7	mean=23.5	

Bibliographic reference	Pelsser LM, Frankena K, Toorman J et al. (2011) Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial. Lancet 377: 494-503

	sd=3.4 n=50	sd=3.9 n=50	
End 5 week treatment	mean=11.7 sd=8.7 n=50	mean=23.4 sd=4.7 n=50	
Change from baseline (end-baseline)*	mean=-12.0 95%CI=-14.6 to -9.4 sd=9.15** n=50	mean=-0.1 95%CI=-0.8 to 0.7 sd=2.64** n=50	mean=11.8* 95%CI=9.2 to 14.5 *adjusted for starting scores and block

***reported as baseline-end but reversed by reviewer for consistency with other studies**
****calculated by reviewer**

Teacher – Abbreviated Connors scale range (0-30)

	Elimination diet	**Control**	**Mean difference**
Baseline	mean=18.5 sd=3.8 n=37	mean=19.1 sd=4.5 n=40	
End 5 week treatment	mean=11.9 sd=6.7 n=37	mean=19.9 sd=4.6 n=40	
Change from baseline (end-baseline)*	mean=-6.6 95%CI=-8.4 to -4.9 sd=5.25** n=37	mean=0.8 95%CI=0.3 to 1.4 sd=1.72** n=40	mean=7.5* 95%CI=5.9 to 9.2 *adjusted for starting scores and block

***reported as baseline-end but reversed by reviewer for consistency with other studies**
****calculated by reviewer**

Functional status – Strengths and difficulties questionnaire (web appendix)

Parent, total difficulties score

Bibliographic reference	Pelsser LM, Frankena K, Toorman J et al. (2011) Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial. Lancet 377: 494-503

	Elimination diet	Control	Mean difference
Baseline	mean=19.1 sd=5.1 n=41	mean=18.7 sd=5.1 n=42	
End 5 week treatment	mean=9.8 sd=6.1 n=41	mean=18.0 sd=6.1 n=42	
Change from baseline (end-baseline)*	mean=-9.5 95%CI=-11.5 to -7.5 sd=6.34** n=41	mean=-0.8 95%CI=-2.1 to 0.5 sd=4.17** n=42	mean=8.3* 95%CI=-10.1 to -6.1 *adjusted for starting scores and block

***reported as baseline-end but reversed by reviewer for consistency with other studies**

****calculated by reviewer**

Teacher, total difficulties score

	Elimination diet	Control	Mean difference
Baseline	mean=16.4 sd=4.9 n=33	mean=17.5 sd=5.6 n=42	
End 5 week treatment	mean=12.8 sd=5.7 n=33	mean=16.5 sd=6.0 n=42	
Change from baseline (end-baseline)*	mean=-4.3 95%CI=-6.3 to -2.3 sd=5.64** n=33	mean=-1.1 95%CI=-2.6 to 0.5 sd=4.97** n=42	mean=-3.0* 95%CI=-5.2 to -0.7 *adjusted for starting scores and block

***reported as baseline-end but reversed by reviewer for consistency with other studies**

****calculated by reviewer**

<table>
<tr><td>Bibliographic reference</td><td>Pelsser LM, Frankena K, Toorman J et al. (2011) Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial. Lancet 377: 494-503</td></tr>
<tr><td></td><td>Number leaving study early
<table>
<tr><th>Few food diet</th><th>Control</th><th>Relative risk (95% CI)**</th></tr>
<tr><td>9/50 (18%)</td><td>8/50 (16%)</td><td>-2.25 (-2.82 to -1.67)</td></tr>
</table>
**calculated by reviewer

Outcomes reported but not extracted: IgG, IgE levels, structured psychiatric interview (oppositional defiant disorder score), ADHD-RS subscales, Strength and difficulties questionnaire subscales</td></tr>
<tr><td>Source of funding</td><td>Foundation of Child and Behaviour, Foundation Nuts OHra, Foundation for Children’s Welfare Stamps Netherlands, KF Hein foundation.</td></tr>
<tr><td>Comments</td><td>Randomisation: Randomisation was done by parents picking sealed envelopes that treatment codes.
Allocation concealment: Staff who recruited and assessed patients were not involved in group allocation.
Blinding: Parents, teachers and the researcher who provided advice to parents and teachers during the diet period were not masked to group allocation. The paediatrician who did outcome assessments was masked to group allocation.
The protocol was available on the Lancet website before the study was carried out.</td></tr>
</table>

G.2 Question 2: Polyunsaturated fatty acids (PUFAs) for ADHD

G.2.1 Included studies

Table 9: Assareh 2012

<table>
<tr><td>Bibliographic reference</td><td>Assareh M, Davari AR, Khademi M et al. (2012) Efficacy of Polyunsaturated Fatty Acids (PUFA) in the Treatment of Attention Deficit Hyperactivity Disorder: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. J Atten.Disord</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial</td></tr>
<tr><td>Aim</td><td>To investigate the efficacy of polyunsaturated fatty acids as an adjuvant treatment to methylphenidate for children with ADHD.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Assareh M, Davari AR, Khademi M et al. (2012) Efficacy of Polyunsaturated Fatty Acids (PUFA) in the Treatment of Attention Deficit Hyperactivity Disorder: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. J Atten.Disord</td></tr>
<tr><td></td><td>- Aged 6 to 12 years.
- Diagnosed with ADHD based on DSM-IV criteria (confirmed as part of study)
- Score of 20 or more on the parent ADHD rating scale
Exclusion criteria:
- Psychiatric disorder other than oppositional defiant disorder and learning difficulties
- IQ less than 70
- Use of psychotropic substance, opioid, or other drugs affecting the central nervous system in the last 2 weeks.
- Significant neurological disease
- Use of any combination containing PUFAs more than once weekly

Baseline characteristics
<table>
<tr><th></th><th>PUFA + methylphenidate</th><th>Placebo + methylphenidate</th></tr>
<tr><td>Sex (M/F)</td><td>16/4</td><td>14/6</td></tr>
<tr><td>Age (mean,sd)</td><td>9 (2)</td><td>9.2 (2)</td></tr>
<tr><td>Diagnosis</td><td>ADHD (Type not specified)</td><td>ADHD (type not specified)</td></tr>
<tr><td>Comorbidities</td><td>Oppositional defiant disorder: 11/20</td><td>Oppositional defiant disorder: 10/20</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>PUFA + methylphenidate</th><th>Placebo + methylphenidate</th></tr>
<tr><td>N</td><td>20</td><td>20</td></tr>
<tr><td>Drop outs</td><td>None reported</td><td>None reported</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Capsule (Minami Company, Belgium) containing 241mg Docosahexaenoic acid, 33mg Eicosapentaenoic acid and 180mg omega 6 once daily
Methylphenidate at a dose of 0.3mg/kg/day, increasing to 1mg/kg/day over 2 weeks</td></tr>
<tr><td>Comparison</td><td>Identical placebo capsules
Methylphenidate at a dose of 0.3mg/kg/day, increasing to 1mg/kg/day over 2 weeks</td></tr>
<tr><td>Methods</td><td>Participants were randomised to receive PUFAs and methylphenidate or placebo and methylphenidate. For 10 weeks. The parent ADHD rating scale and drug side effect questionnaire were filled in at baseline and every 2 weeks during treatment.</td></tr>
<tr><td>Length of follow up</td><td>10 week treatment period</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Assareh M, Davari AR, Khademi M et al. (2012) Efficacy of Polyunsaturated Fatty Acids (PUFA) in the Treatment of Attention Deficit Hyperactivity Disorder: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. J Atten.Disord</td></tr>
<tr><td>Location</td><td>Iran, secondary care setting (patients were randomly selected for inclusion from outpatient psychiatry clinic)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Parent – Attention deficit hyperactivity disorder rating scale (ADHD-RS) total score (range 0-54)
<table>
<tr><th></th><th>PUFA + methylphenidate</th><th>Control (methylphenidate)</th><th>Mean difference</th></tr>
<tr><td>Baseline</td><td>mean=34
sd=6
n=20</td><td>mean=37
sd=6
n=20</td><td></td></tr>
<tr><td>10th week of treatment</td><td>mean=13
sd=9
n=20</td><td>mean=13
sd=7
n=20</td><td></td></tr>
<tr><td>Change from baseline* (end - baseline)</td><td>mean=-21
sd=7.94
n=20</td><td>mean=-24
sd=6.56
n=20</td><td>mean=3**
95%CI=-1.51 to 7.51**</td></tr>
</table>
*Imputed by reviewer
**calculated by reviewer

Outcomes reported but not extracted: ADHD rating scale subscales. ADHD rating scale at intermediate visits, number with 25% and 50% reduction in ADHD rating scale score.</td></tr>
<tr><td>Source of funding</td><td>Behavioural sciences research center of Shahid Beheshti University of medical sciences.</td></tr>
<tr><td>Comments</td><td>Randomisation: Method of randomisation not reported.
Allocation concealment: Not reported.
Blinding: Patients and investigator were blind to treatment allocation.
Other: Dose adjustment of methylphenidate was also blind to group allocation (based on treatment response and side effects). The doses for the two groups are not reported, although it is reported that they were not significantly different.</td></tr>
</table>

1

2

3 **Table 10: Barragan 2014**

<table>
<tr><td>Bibliographic reference</td><td>Barragan E, Breuer D, Dopfner M (2014) Efficacy and Safety of Omega-3/6 Fatty Acids, Methylphenidate, and a Combined Treatment in Children With ADHD. J Atten.Disord</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial</td></tr>
<tr><td>Aim</td><td>To compare the efficacy of omega 3/omega 6 fatty acids with methylphenidate and combined treatment in children with ADHD (only the comparison of methylphenidate and combined treatment is extracted here(</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
- Aged 6-12 years
- Newly diagnosed with ADHD of any subtype (DSM-IV-TR criteria)
Exclusion criteria:
- Neurological disorders (epilepsy, brain damage, mental retardation)
- Autism or pervasive developmental disorders
- Known hypersensitivity to components of omega 3/6
- Previous pharmacological treatment for ADHD
- Ongoing chronic conditions (e.g. asthma) or medication for chronic conditions
- Not receiving school assistance

Baseline characteristics (not reported separately for each group – numbers are for all groups including the PUFA only group, for which results are not reported here)
<table>
<tr><td>Sex (M/F)</td><td>60/30</td></tr>
<tr><td>Age (mean,sd)</td><td>8.27 (1.74)</td></tr>
<tr><td>Diagnosis</td><td>ADHD combined type: 51/90
ADHD inattentive: 32/90
ADHD hyperactive: 7/90</td></tr>
<tr><td>Comorbidities</td><td>Not reported</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>PUFA (+methylphenidate)</th><th>Control (Methylphenidate)</th></tr>
<tr><td>N</td><td>30</td><td>30</td></tr>
<tr><td>Drop outs</td><td>3</td><td>10</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="4">Barragan E, Breuer D, Dopfner M (2014) Efficacy and Safety of Omega-3/6 Fatty Acids, Methylphenidate, and a Combined Treatment in Children With ADHD. J Atten.Disord</td></tr>
<tr><td></td><td colspan="4"><table>
<tr><td></td><td>Adverse event (1)
Lost to follow up (1)
No efficacy (1)</td><td>Adverse event (6)
Lost to follow up (2)
No efficacy (2)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="4">Omega 3/6 fatty acid supplement ‘Equizen eye q, 3 capsules twice daily, corresponding to a daily dose of 558mg Eicosapentaenoic acid (omega 3), 174mg Docosahexaenoic acid (omega 3) and 60mg Gamma-linolenic acid (60mg).
Also took methyphenidate at a starting dose of 0.3mg/kg/day, increased to 0.5mg/kg/day after 2 weeks and subsequently increased to a maximum of 1mg/kg/day depending on response and tolerability. Final mean dose was 0.80mg/kg (sd=0.10) – statistically significantly higher than the control group.</td></tr>
<tr><td>Comparison</td><td colspan="4">Methyphenidate at a starting dose of 0.3mg/kg/day, increased to 0.5mg/kg/day after 2 weeks and subsequently increased to a maximum of 1mg/kg/day depending on response and tolerability. Final dose was 1.03mg/kg (sd=0.12)</td></tr>
<tr><td>Methods</td><td colspan="4">Children were allocated to receive omega 3/6 + methylphenidate, methylphenidate only or omega 3/6 only (data for this group not extracted here). Outcomes were measured at baseline and then at 1,3,6 and 12 months.</td></tr>
<tr><td>Length of follow up</td><td colspan="4">12 month treatment period (outcomes measured at 1,3,6 and 12 months)</td></tr>
<tr><td>Location</td><td colspan="4">Mexico, secondary care setting. Participants were referred from a hospital neurology department.</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="4">ADHD symptoms
Parent – Attention deficit hyperactivity disorder rating scale (ADHD-RS) total score (range 0-54)
<table>
<tr><th></th><th>PUFA + methylphenidate</th><th>Control (methylphenidate)</th><th>Mean difference</th></tr>
<tr><td>Baseline</td><td>mean=42.03
sd=4.0
n=30</td><td>mean=41.43
sd=4.3
n=30</td><td></td></tr>
<tr><td>Month 3 treatment</td><td>mean=27.57
sd=5.54
n=30</td><td>mean=27.60
sd=4.98
n=30</td><td></td></tr>
<tr><td>Change from baseline* (month 3 - baseline)</td><td>mean=-14.46
sd=4.95
n=30</td><td>mean=-13.83
sd=4.68
n=30</td><td>mean=-0.63**
95%CI=-3.07 to 1.81**</td></tr>
<tr><td>Month 6 treatment</td><td>mean=25.50
sd=5.01
n=30</td><td>mean=26.23
sd=4.70
n=30</td><td></td></tr>
</table></td></tr>
</table>

Bibliographic reference	Barragan E, Breuer D, Dopfner M (2014) Efficacy and Safety of Omega-3/6 Fatty Acids, Methylphenidate, and a Combined Treatment in Children With ADHD. J Atten.Disord		
	Change from baseline* (month 6 - baseline)	mean=-16.53 sd=4.59 n=30	mean=-15.2 sd=4.51 n=30	**mean=-1.33**** **95%CI=-3.63 to 0.97****
	Month 12 treatment	mean=24.33 sd=5.09 n=30	mean=25.83 sd=4.67 n=30	
	Change from baseline* (month 12 - baseline)	mean=-17.7 sd=4.64 n=30	mean=-15.6 sd=4.50 n=30	**mean=-2.10**** **95%CI=-4.41 to 0.21****

***imputed by reviewer**

Functional status

Clinician rated– Clinical global impression (range 1-7)

	PUFA + methylphenidate	**Control (methylphenidate)**	**Mean difference**
Baseline	mean=6.17 sd=0.53 n=30	mean=6.30 sd=0.65 n=30	
Month 3 treatment	mean=3.33 sd=0.88 n=30	mean=4.27 sd=1.14 n=30	
Change from baseline* (month 3 - baseline)	mean=-2.84 sd=0.77 n=30	mean=-2.03 sd=0.99 n=30	**mean=-0.81**** **95%CI=-1.26 to -0.36****
Month 6 treatment	mean=3.23 sd=0.86 n=30	mean=4.00 sd=1.08 n=30	
Change from baseline* (month 6 - baseline)	mean=-2.94 sd=0.75 n=30	mean=-2.3 sd=0.94 n=30	**mean=-0.64**** **95%CI=-1.07 to -0.21****

Bibliographic reference	Barragan E, Breuer D, Dopfner M (2014) Efficacy and Safety of Omega-3/6 Fatty Acids, Methylphenidate, and a Combined Treatment in Children With ADHD. J Atten.Disord

Month 12 treatment	mean=3.63 sd=0.85 n=30	mean=4.10 sd=1.06 n=30	
Change from baseline* (month 12 - baseline)	mean=-2.54 sd=0.74 n=30	mean=-2.2 sd=0.93 n=30	**mean=-0.34**** **95%CI=-0.77 to 0.09****

***imputed by reviewer**
****calculated by reviewer**

Parent rated – Clinical global impression (range 1-7) (not used in analysis as clinician reported functional status also reported, and considered more reliable – Clinical global impression is assessed by a single question: 'Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?', and is normally rated by clinicians, taking into account information from all sources, including parents)

	PUFA + methylphenidate	Control (methylphenidate)
Baseline	mean=6.17 sd=0.53 n=30	mean=6.27 sd=0.74 n=30
Month 3 treatment	mean=3.30 sd=0.95 n=30	mean=4.27 sd=1.08 n=30
Change from baseline* (month 3 - baseline)	mean=-2.87 sd=0.82 n=30	mean=-2 sd=0.96 n=30
Month 6 treatment	mean=3.23 sd=0.86 n=30	mean=4.00 sd=0.98 n=30
Change from baseline* (month 6 - baseline)	mean=-2.94 sd=0.75 n=30	mean=-2.27 sd=0.88 n=30

Bibliographic reference	Barragan E, Breuer D, Dopfner M (2014) Efficacy and Safety of Omega-3/6 Fatty Acids, Methylphenidate, and a Combined Treatment in Children With ADHD. J Atten.Disord

Month 12 treatment	mean=3.63 sd=0.85 n=30	mean=4.10 sd=0.96 n=30
Change from baseline* (month 12 - baseline)	mean=-2.54 sd=0.74 n=30	mean=-2.17 sd=0.87 n=30

***Imputed by reviewer**

****calculated by reviewer**

Adverse events

Adverse event	PUFA + methylphenidate	Methylphenidate	Relative risk (95%CI)**
Headache	10/30	17/30	0.59 (0.32 to 1.07)
Nausea	0/30	1/30	0.33 (0.01 to 7.87)
Dyspepsia	0/30	0/30	undefined
Diarrhoea	0/30	0/30	undefined

****calculated by reviewer**

Number leaving study early

PUFA + methylphenidate	Methylphenidate	Relative risk (95%CI)**
3/30 (10%)	10/30 (33.3%)	0.3 (0.09 to 0.98)

****calculated by reviewer**

Outcomes reported but not extracted: Adverse events not specified in review protocol

Source of funding	Vifor Pharma (also provided omega3/6 supplements for the study)
Comments	**Randomisation:** Randomisation was via a random number table. **Allocation concealment:** A table was used for randomisation, therefore it is unlikely that allocation was concealed. **Blinding:** Patients, parents and outcome assessors were **not** blinded. **Other:** Used an intention to treat analysis (last observation carried forward). The dose of methylphenidate was

Bibliographic reference	Barragan E, Breuer D, Dopfner M (2014) Efficacy and Safety of Omega-3/6 Fatty Acids, Methylphenidate, and a Combined Treatment in Children With ADHD. J Atten.Disord
	significantly different across groups (dose was adjusted according to response and tolerability by clinicians who were not blinded to group allocation.

1 **Table 11: Behdani 2013**

Bibliographic reference	Behdani F, Hebrani P, Naseraee A et al. (2013) Does omega-3 supplement enhance the therapeutic results of methylphenidate in attention deficit hyperactivity disorder patients? Journal of Research in Medical Sciences 18: 653-8
Study type	Randomised controlled trial
Aim	To investigate the effectiveness of omega 3 PUFAs as an additional treatment to methylphenidate for the treatment of children with ADHD without comorbidities.
Patient characteristics	**Inclusion criteria:** - Aged 7 to 15. - Meet criteria for ADHD (DSMIV-TR). Assessed by a psychiatrist. - Score on the ADHD rating scale IV school version of at least 1.5 standard deviations above norm for age and gender. - Minimum score of 20 on the teacher and parent ADHD rating scale IV (unclear why this additional criterion was applied as well as the criterion above). **Exclusion criteria:** - Co-morbid psychiatric diagnosis - History of or current diagnosis of pervasive developmental disorder, schizophrenia or other psychiatric disorder - Evidence of suicide risk - Mental retardation - Hypertension, hypotension - History of serious organic problems and already under treatment **Baseline characteristics**

	PUFA + methylphenidate	Placebo + methylphenidate
Sex (M/F)	55/14 Not reported separately	
Age (mean,sd)	8.7 (1.7) Not reported separately	
Diagnosis	ADHD combined type: 14 Inattentive type: 10	ADHD combined type: 14 Inattentive type: 5

<table>
<tr><td>Bibliographic reference</td><td colspan="2">Behdani F, Hebrani P, Naseraee A et al. (2013) Does omega-3 supplement enhance the therapeutic results of methylphenidate in attention deficit hyperactivity disorder patients? Journal of Research in Medical Sciences 18: 653-8</td></tr>
<tr><td></td><td colspan="2"><table>
<tr><td></td><td>Hyperactive type: 12</td><td>Hyperactive type: 14</td></tr>
<tr><td>Comorbidities</td><td>None (Exclusion criterion)</td><td>None (Exclusion critierion)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td colspan="2"><table>
<tr><td></td><td>PUFA + methylphenidate</td><td>Placebo + methylphenidate</td></tr>
<tr><td>N</td><td>38</td><td>37</td></tr>
<tr><td>Drop outs</td><td>2
1 personal reasons
1 side effects</td><td>4
4 personal reasons</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="2">Omega-3 (Novartis) in two 1000mg capsules, each containing 240g Docosahexaenoic acid and 360g Eicosapentaenoic acid)
Methylphenidate at an initial dose of 2.5 to 5 mg/day, increasing by 2.5 to 5mg/day weekly to a target dose of 1mg/kg/day with a maximum dose of 60mg/day. Dose was adjusted by psychiatrists who were not blinded to treatment allocation</td></tr>
<tr><td>Comparison</td><td colspan="2">Placebo capsules
Same methylphenidate treatment schedule as for the intervention group.</td></tr>
<tr><td>Methods</td><td colspan="2">Participants were randomised to receive omega 3 with methylphenidate or placebo and methylphenidate for 8 weeks. Outcomes were assessed before and after treatment.</td></tr>
<tr><td>Length of follow up</td><td colspan="2">8 week treatment duration.</td></tr>
<tr><td>Location</td><td colspan="2">Iran, secondary care (participants were referred to an outpatient child and adolescent psychiatry clinic)</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="2">ADHD symptoms
Parent – Attention deficit hyperactivity disorder rating scale (ADHD-RS) total score (not included in analysis due to unclear reported of standard deviations**)<table>
<tr><td></td><td>PUFA + methylphenidate</td><td>Placebo + methylphenidate</td></tr>
<tr><td>Baseline</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>End of treatment (8 weeks)</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Change from baseline (end – baseline)*</td><td>mean=-12.44
sd= unclearly reported**
n=36</td><td>mean=-14.00
sd= unclearly reported**
n=33</td></tr>
</table>*reported as end – baseline, sign reversed by reviewer for comparison with other studies</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Behdani F, Hebrani P, Naseraee A et al. (2013) Does omega-3 supplement enhance the therapeutic results of methylphenidate in attention deficit hyperactivity disorder patients? Journal of Research in Medical Sciences 18: 653-8</td></tr>
<tr><td></td><td>
**reported standard deviations are unclear (reported as 0/00 in some instances in and 0.00 in others, so unclear whether to interpret '/' as a ratio or decimal point)

Teacher – Attention deficit hyperactivity disorder rating scale (ADHD-RS) total score (not included in analysis due to unclear reported of standard deviations**)
<table>
<tr><th></th><th>PUFA + methylphenidate</th><th>Placebo + methylphenidate</th></tr>
<tr><td>Baseline</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>End of treatment (8 weeks)</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Change from baseline (end – baseline)*</td><td>mean=-6.75
sd=unclearly reported**
n=36</td><td>mean=-11.76
sd= unclearly reported**
n=33</td></tr>
</table>
*reported as end – baseline, sign reversed by reviewer for comparison with other studies
**reported standard deviations are unclear (reported as 0/00 in some instances in and 0.00 in others, so unclear whether to interpret '/' as a ratio or decimal point)

Number leaving study early
<table>
<tr><th>PUFA + methylphenidate</th><th>Placebo + Methylphenidate</th><th>Relative risk (95%CI)**</th></tr>
<tr><td>2/38 (5.3%)</td><td>4/37 (10.8%)</td><td>0.49 (0.09 to 2.50)</td></tr>
</table>
**calculated by reviewer
**reported standard deviations are unclear (reported as 0/00 in some instances in and 0.00 in others, so unclear whether to interpret '/' as a ratio or decimal point)

Outcomes reported but not extracted: Data at intermediate time points during treatment
</td></tr>
<tr><td>Source of funding</td><td>None</td></tr>
<tr><td>Comments</td><td>Randomisation: Participants were randomised in a 1:1 ratio using computer generated code.
Allocation concealment: Not reported
Blinding:. The study was described as double blind. Investigators who performed efficacy and tolerability rating were blind to treatment group. Psychiatrists who monitored clinical signs, symptoms and adverse effects and adjusted medication doses were not blinded.</td></tr>
</table>

Bibliographic reference	**Behdani F, Hebrani P, Naseraee A et al. (2013) Does omega-3 supplement enhance the therapeutic results of methylphenidate in attention deficit hyperactivity disorder patients? Journal of Research in Medical Sciences 18: 653-8**
	Other: Per protocol analysis (dropouts not accounted for). Some uncertainty in the way standard deviations were reported (some reported with decimal indicated by '.' and some indicated by '/'.

1

2 **Table 12: Bélanger 2009**

Bibliographic reference	**Bélanger SA, Vanasse M, Spahis S et al. (2009) Omega-3 fatty acid treatment of children with attention-deficit hyperactivity disorder: A randomized, double-blind, placebo-controlled study. Paediatrics & Child Health 14: 89-98**
Study type	Randomised controlled trial
Aim	To determine the efficacy and safety of n-3 PUFA supplementation on children with ADHD.
Patient characteristics	**Inclusion criteria:** - Aged 6 years 11 months to 11 years 11 months - Diagnosis of ADHD according to DSM-IV criteria - IQ above 85 **Exclusion criteria:** - Mental health disorders, except those characteristically comorbid with ADHD - Receiving psychostimulants or non-stimulants, sedatives, anxiolytics, antipsychotics - Medical condition requiring long-term treatment - Chronic neurological condition or paroxysmal disorder - Allergy to sunflower oil or fish - Coagulation abnormalities - Candidates for surgery - Receiving anticoagulants - Only one child per family was permitted to participate - Subjects consuming fish, flaxseed oil and foods enriched with n-3 PUFA were excluded post hoc. **Baseline characteristics (only reported for participants completing second open-label phase –not reported here)**

	PUFA	**Placebo**
Sex (M/F)	9/4	9/4

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Bélanger SA, Vanasse M, Spahis S et al. (2009) Omega-3 fatty acid treatment of children with attention-deficit hyperactivity disorder: A randomized, double-blind, placebo-controlled study. Paediatrics & Child Health 14: 89-98</td></tr>
<tr><td></td><td colspan="3"><table>
<tr><td>Age (mean,sd)</td><td>9.27 (0.40)</td><td>9.09 (0.50)</td></tr>
<tr><td>Diagnosis</td><td>ADHD (type not specified)</td><td>ADHD (type not specified)</td></tr>
<tr><td>Comorbidities</td><td>Not reported</td><td>Not reported</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td colspan="3"><table>
<tr><td></td><td>PUFA</td><td>Control</td></tr>
<tr><td>N</td><td>19</td><td>18</td></tr>
<tr><td>Drop outs</td><td>5</td><td>3</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="3">Capsules containing 250mg of Eicosapentaenoic acid, 100mg Docosahexaenoic acid and 3.75 U of vitamin E (preservative). Participants weighing 16 to 25 Kg received 2 capsules daily, those weighing 26 to 35 Kg received 3 capsules daily and those weighing 36 to 45 Kg received 4 capsules.</td></tr>
<tr><td>Comparison</td><td colspan="3">Capsules containing sunflower oil and a similar amount of vitamin E as the intervention capsules. The number of placebo capsules given daily was not reported.</td></tr>
<tr><td>Methods</td><td colspan="3">Participants were randomised to receive n-3 PUFAs or placebo for 8 weeks. There was also a second phase where both groups received n-3 PUFAs (not reported here).</td></tr>
<tr><td>Length of follow up</td><td colspan="3">8 weeks treatment duration (a further 8 week non-comparative phase was also included, but not reported here)</td></tr>
<tr><td>Location</td><td colspan="3">Canada Secondary care (Participants were enrolled from an ADHD clinic)</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">Number leaving study early<table>
<tr><td>PUFA</td><td>Placebo</td><td>Relative risk (95%CI)**</td></tr>
<tr><td>5/19 (26.3%)</td><td>3/18 (16.7%)</td><td>1.58 (0.44 to 5.67)</td></tr>
</table>**calculated by reviewer

Outcomes reported but not extracted: Plasma fatty acid profiles, Connors’ rating scale changes from baseline (no measure of variability such as standard deviation reported or calculable),</td></tr>
<tr><td>Source of funding</td><td colspan="3">JA DeSève (supported research chair in nutrition). NutriSante provided financial support and capsules.</td></tr>
<tr><td>Comments</td><td colspan="3">Randomisation: Randomisation method not reported
Allocation concealment: Not reported
Blinding: Described as ‘double blind’ but further details not reported.
Other: Per protocol analysis (dropouts not accounted for).</td></tr>
</table>

1 **Table 13: Bos 2015**

<table>
<tr><td>Bibliographic reference</td><td>Bos DJ, Oranje B, Veerhoek ES et al. (2015) Reduced Symptoms of Inattention after Dietary Omega-3 Fatty Acid Supplementation in Boys with and without Attention Deficit/Hyperactivity Disorder. Neuropsychopharmacology [epub ahead of print]</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial</td></tr>
<tr><td>Aim</td><td>In this study, we investigated the effects of dietary omega-3 fatty acid supplementation on ADHD symptoms and cognitive control in young boys with and without ADHD (data from group without ADHD not reported here).</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
- Aged 8 to 14 years
- Diagnosis of ADHD according to DSM-IV criteria (confirmed as part of study)
- Male
- Medication naïve or taking methylphenidate (methylphenidate use was continued through the study and managed outside of the study)
Exclusion criteria:
- Using psychostimulant medication other than methylphenidate

Baseline characteristics (not reported separately for each group)
<table>
<tr><td>Sex (M/F)</td><td>40/0</td></tr>
<tr><td>Age (mean,sd)</td><td>10.3 (2.0)</td></tr>
<tr><td>Diagnosis</td><td>ADHD (subtypes not reported)</td></tr>
<tr><td>Comorbidities</td><td>Not reported</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><td></td><td>omega-3 PUFA</td><td>Placebo</td></tr>
<tr><td>N</td><td>20</td><td>20</td></tr>
<tr><td>Drop outs</td><td>1
Excluded from analysis due to non-compliance (1)</td><td>1
Adverse event (1)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Margarine containing 650 mg Docosahexaenoic acid and 650 mg Eicosapentaenoic acid per 10 g serving. Participants were instructed to consume 10g of margarine per day.</td></tr>
<tr><td>Comparison</td><td>Placebo: Margarine with the same sensory properties but monounsaturated fatty acids rather than Docosahexaenoic acid and Eicosapentaenoic acid. Participants were instructed to consume 10g of margarine per day (had the same total quantity of fatty acids and omega 6 PUFAs as the active intervention)</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Bos DJ, Oranje B, Veerhoek ES et al. (2015) Reduced Symptoms of Inattention after Dietary Omega-3 Fatty Acid Supplementation in Boys with and without Attention Deficit/Hyperactivity Disorder. Neuropsychopharmacology [epub ahead of print]</td></tr>
<tr><td>Methods</td><td>Participants were randomised to receive margarine enriched with PUFAs or non-enriched margarine for 16 weeks. Compliance was assessed by weighing the remaining margarine at the end of the study. Participants and parents also kept a calendar of daily margarine consumption. Participants were not allowed to use other omega 3 supplements or foods fortified with Eicosapentaenoic acid or Docosahexaenoic acid during the study, and were not allowed to consume fatty fish more than once per week. A non-ADHD control group was also included (data not reported here).</td></tr>
<tr><td>Length of follow up</td><td>16 weeks treatment duration</td></tr>
<tr><td>Location</td><td>The Netherlands, Secondary care setting (Participants recruited from Department of Psychiatry and through advertising)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>ADHD symptoms
Parent rated - Child behaviour checklist – ADHD scale
<table>
<tr><th></th><th>Omega-3 PUFA</th><th>Placebo</th><th>Mean difference</th></tr>
<tr><td>Baseline</td><td>mean=8.8
sd=2.1
n=20</td><td>mean=9.0
sd=3.1
n=20</td><td></td></tr>
<tr><td>End (16 weeks treatment)</td><td>mean=7.6
sd=3.5
n=20</td><td>mean=10.1
sd=2.2
n=20</td><td></td></tr>
<tr><td>Change from baseline* (end-baseline)</td><td>mean=-1.2
sd=3.05
n=20</td><td>mean=1.1
sd=2.76
n=20</td><td>mean=-2.3**
95%CI=-4.10 to -0.50**</td></tr>
</table>
*imputed by reviewer
**calculated by reviewer

Number leaving study early
<table>
<tr><th>PUFA</th><th>Placebo</th><th>Relative risk (95%CI)**</th></tr>
<tr><td>0/20 (0%)</td><td>1/20 (5%)</td><td>0.33 (0.01 to 7.72)</td></tr>
</table>
**calculated by reviewer

Outcomes reported but not extracted: Child behaviour checklist – Attention problems, Rule breaking, Aggressive behaviour scales, Cheek swab plasma fatty acids, urine homovanillic acid, essential fatty acid questionnaire, fMRI</td></tr>
</table>

Bibliographic reference	**Bos DJ, Oranje B, Veerhoek ES et al. (2015) Reduced Symptoms of Inattention after Dietary Omega-3 Fatty Acid Supplementation in Boys with and without Attention Deficit/Hyperactivity Disorder. Neuropsychopharmacology [epub ahead of print]**
	analysis
Source of funding	Unilever: declared that Unilever were involved in the design of the study and provided the PUFA capsules. Two of the study authors were Unilever employees.
Comments	**Randomisation:** Method of randomisation not reported **Allocation concealment:** Not reported **Blinding:** Described as double blind. Investigators, parents and participants were all blind to group allocation **Other:** Used an intention to treat analysis to take dropouts into account. A trial protocol was registered before the study began. Teacher report form data was collected, but the response rate was poor and so the analysis was not presented. Data for the SWAN questionnaire (ADHD symptom score) was collected but not reported (it was simply reported that there were no significant differences between groups).

1

2 **Table 14: Dubnov-Raz 2014**

Bibliographic reference	**Dubnov-Raz G, Khoury Z, Wright I et al. (2014) The effect of alpha-linolenic acid supplementation on ADHD symptoms in children: a randomized controlled double-blind study. Frontiers in Human Neuroscience 8: 780**
Study type	Randomised controlled trial
Aim	To examine the effectiveness of alpha-linolenic acid (an omega-3) in the treatment of children with ADHD.
Patient characteristics	**Inclusion criteria:** - Aged 6 to 16 - Recently diagnosed with ADHD (criteria for recent not specified) - Drug naïve and untreated **Exclusion criteria:** - History of chronic health conditions other than ADHD - Use of chronic medications or dietary supplements **Baseline characteristics (not including dropouts)**

	PUFA	**Placebo**
Sex (M/F)	4/4	6/3
Age (mean,sd)	11.1 (3.0)	10.9 (2.3)

<table>
<tr><td>Bibliographic reference</td><td colspan="4">Dubnov-Raz G, Khoury Z, Wright I et al. (2014) The effect of alpha-linolenic acid supplementation on ADHD symptoms in children: a randomized controlled double-blind study. Frontiers in Human Neuroscience 8: 780</td></tr>
<tr><td></td><td colspan="4"><table>
<tr><td>Diagnosis</td><td>ADHD (subtypes not specified)</td><td>ADHD (subtypes not specified)</td></tr>
<tr><td>Comorbidities</td><td>Not reported</td><td>Not reported</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td colspan="4"><table>
<tr><td></td><td>PUFA</td><td>Placebo</td></tr>
<tr><td>N</td><td>20</td><td>20</td></tr>
<tr><td>Drop outs</td><td>12</td><td>11</td></tr>
<tr><td></td><td colspan="2">Reasons not reported separately for each group:
Difficulty taking capsules (7)
Lack of efficacy (4)
Loss to follow up (5)
Did not wish to complete second assessment (5)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="4">Sage oil (2g per day). The composition was reported to vary slightly by crop year, but estimated as is 50–54% Alpha linolenic acid (omega 3), 16–18% linoleic acid (omega 6), 20–23% oleic acid (not PUFA), , 6– 7% palmitic acid (not PUFA), and 2–3% stearic acid (not PUFA). This was estimated to correspond to a dose of 1g/day Alpha-linolenic acid (an omega-3 fatty acid).</td></tr>
<tr><td>Comparison</td><td colspan="4">Identical lactose placebo in gel capsules</td></tr>
<tr><td>Methods</td><td colspan="4">Participants were randomised to receive sage oil or placebo for 8 weeks. Outcomes were assessed before, and at the end of treatment.</td></tr>
<tr><td>Length of follow up</td><td colspan="4">8 week treatment period</td></tr>
<tr><td>Location</td><td colspan="4">Israel, secondary care (Patients recruited from 2 ADHD clinics in Israel)</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="4">ADHD symptoms
Parent – Connors ADHD index (total score not reported). Mean difference not reported or calculable so not included in analysis<table>
<tr><td></td><td>PUFA</td><td>Control</td><td>Group difference</td></tr>
<tr><td>Baseline</td><td>median=76
range=71 to 90
n=8</td><td>median=62
range=47 to 70
n=9</td><td>significant different at baseline</td></tr>
<tr><td>End (8 weeks of treatment)</td><td>median=79
range=54 to 89
n=8</td><td>median=62
range=46 to 64
n=9</td><td>No significant different between change scores from baseline (Mann whitney U test, p=0</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Dubnov-Raz G, Khoury Z, Wright I et al. (2014) The effect of alpha-linolenic acid supplementation on ADHD symptoms in children: a randomized controlled double-blind study. Frontiers in Human Neuroscience 8: 780</td></tr>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td></td><td>79)</td></tr>
</table>
Teacher – Connors ADHD index (total score not reported)
<table>
<tr><td></td><td>PUFA</td><td>Control</td><td>Group difference</td></tr>
<tr><td>Baseline</td><td>median=69
range=53 to 89
n=8</td><td>median=59
range=59 to 75
n=9</td><td></td></tr>
<tr><td>End (8 weeks of treatment)</td><td>median=69
range=58 to 87
n=8</td><td>median=61
range=59 to 69
n=9</td><td>No significant different between change scores from baseline (Mann whitney U test, p=0
26)</td></tr>
</table>
Number leaving study early
<table>
<tr><td>PUFA</td><td>Placebo</td><td>Relative risk (95%CI)**</td></tr>
<tr><td>12/20 (60%)</td><td>11/20 (55%)</td><td>1.09 (0.64 to 1.86)</td></tr>
</table>
**calculated by reviewer

Outcomes reported but not extracted: Connors’ global index, Connors’ DSM-IV index, MOXO-CPT test (lab-based measure of attention)</td></tr>
<tr><td>Source of funding</td><td>The oil supplement and placebo were supplied by Magnetika Ltd.,Israel. The study was funded by the Israeli Association of Ambulatory Pediatrics.</td></tr>
<tr><td>Comments</td><td>Randomisation: Randomisation method not reported.
Allocation concealment:.Capsules were supplied in identical numbers bottles that were prepared by an independent person. Bottles were supplied in consecutive order on enrolment.
Blinding: Participants, parents, teachers, and study personnel were blinded to the allocation until completion of all data collection.
Other: Per protocol analysis (did not account for drop outs) and very high dropout rate (>50%).</td></tr>
</table>

1

2 **Table 15: Gustafsson 2010**

<table>
<tr><td>Bibliographic reference</td><td>Gustafsson PA, Birberg-Thornberg U, Duchen K et al. (2010) EPA supplementation improves teacher-rated behaviour and oppositional symptoms in children with ADHD. Acta Paediatrica 99: 1540-9</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial</td></tr>
<tr><td>Aim</td><td>To determine the efficacy of eicosapentaenoic acid for children with ADHD.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
- Aged 7 to 12 years
- Clinical diagnosis of ADHD combined type (DSM-IV criteria)
- Any neuropsychiatric comorbidity
- Been evaluated for pharmacological treatment
Exclusion criteria:
- IQ<70
- Autism
- Major depression
- Epileptic seizures in the preceding 2 years
- Neurological disorder
- Endocrinological disorder
- Fish allergic
- Severely impaired hearing or vision
- Severe sleeping disorder
- Psychotic symptoms
- Ongoing medication

Baseline characteristics (reported for randomised participants who took at least 1 dose of PUFA/placebo)
<table>
<tr><td></td><td>PUFA</td><td>Placebo</td></tr>
<tr><td>Sex (M/F)</td><td>not reported</td><td>not reported</td></tr>
<tr><td>Age (mean,sd)</td><td>not reported</td><td>not reported</td></tr>
<tr><td>Diagnosis</td><td>ADHD combined type</td><td>ADHD combined type</td></tr>
<tr><td>Comorbidities</td><td colspan="2">Reportedly did not differ between groups (not reported separately):
61% had oppositional behaviour
48% had neuromotor problems</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="4">Gustafsson PA, Birberg-Thornberg U, Duchen K et al. (2010) EPA supplementation improves teacher-rated behaviour and oppositional symptoms in children with ADHD. Acta Paediatrica 99: 1540-9</td></tr>
<tr><td></td><td colspan="4">47% had objective hyperactivity/impulsivity
26% had tics
23% had anxiety problems</td></tr>
<tr><td>Number of Patients</td><td colspan="4"><table>
<tr><td></td><td>PUFA</td><td>Placebo</td></tr>
<tr><td>N</td><td>57</td><td>52</td></tr>
<tr><td>N (ITT Analysis)</td><td>46</td><td>46</td></tr>
<tr><td>Drop outs</td><td>6
Lost to follow up (6)</td><td>6
Lost to follow up (6)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="4">One daily capsule of ‘PlusEPA’ containing 500mg of eicosapentaenoic acid, 2.7mg of Docosahexaenoic acid and 10mg vitamin E</td></tr>
<tr><td>Comparison</td><td colspan="4">One daily placebo capsule of rapeseed oil, which was reported to have <10% of the PUFAs in the active capsule.</td></tr>
<tr><td>Methods</td><td colspan="4">ADHD symptoms were assessed at baseline and the end of the study (15 weeks) by the conners’ parent and teacher rating scales (filled in by parents and teachers, respectively). During the treatment period, the participants returned to the clinic every 5 weeks to get more medication, and were asked about adverse events.</td></tr>
<tr><td>Length of follow up</td><td colspan="4">15 weeks treatment duration</td></tr>
<tr><td>Location</td><td colspan="4">Sweden, secondary treatment centres</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="4">ADHD symptoms
Parent – Connors’ Parent rating scale total score<table>
<tr><td></td><td>PUFA</td><td>Placebo</td><td>Mean difference</td></tr>
<tr><td>Baseline</td><td>mean=51.0
sd=16.5
n=46</td><td>mean=46.0
sd=15.5
n=46</td><td></td></tr>
<tr><td>15 weeks treatment</td><td>mean=43.8
sd=18.6
n=46</td><td>mean=39.4
sd=18.4
n=46</td><td></td></tr>
<tr><td>change from baseline* (end-baseline)</td><td>mean=-7.2
sd=17.64
n=46</td><td>mean=-6.6
sd=17.14
n=46</td><td>mean=-0.60**
95%CI=-7.71 to 6.51**</td></tr>
</table>*imputed by reviewer</td></tr>
</table>

Bibliographic reference	Gustafsson PA, Birberg-Thornberg U, Duchen K et al. (2010) EPA supplementation improves teacher-rated behaviour and oppositional symptoms in children with ADHD. Acta Paediatrica 99: 1540-9

****calculated by reviewer**

Teacher – Connors' Teacher rating scale total score

	PUFA	Placebo	Mean difference
Baseline	mean=49.7 sd=18.0 n=46	mean=43.5 sd=14.9 n=46	
15 weeks treatment	mean=43.1 sd=18.8 n=46	mean=40.7 sd=17.9 n=46	
change from baseline* (end-baseline)	mean=-6.6 sd=18.41 n=46	mean=-2.8 sd=16.6 n=46	**mean=-3.80**** **95%CI=-10.96 to 3.36****

****calculated by reviewer**

Adverse events

	PUFA	Placebo	Relative risk (95%CI)**
Nausea	5/46	6/46	**0.83 (0.27 to 2.54)**
Diarrhoea	3/46	4/46	**0.75 (0.18 to 3.17)**

****calculated by reviewer**

Number leaving study early

PUFA	Placebo	Relative risk (95%CI)**
6/57 (10.5%)	6/52 (11.5%)	**0.91 (0.31 to 2.65)**

****calculated by reviewer**

Outcomes reported but not extracted: Membrane and serum phospholipids, dietary habits, Connors' rating scale subscales, subgroup for Connors' teacher rating scale with 'oppositional behaviour' (defined post hoc, based on baseline rating scale and not clinical diagnosis of oppositional defiant disorder), adverse events not specified in review protocol

Bibliographic reference	**Gustafsson PA, Birberg-Thornberg U, Duchen K et al. (2010) EPA supplementation improves teacher-rated behaviour and oppositional symptoms in children with ADHD. Acta Paediatrica 99: 1540-9**
Source of funding	Hela Pharma AB, Minami Nutrition, Qb-tech medical engineering, Medical research council of Southeast Sweden
Comments	**Randomisation:** Participants were assigned to PUFA or placebo in a 1:1 ratio using computer-generated code. Randomisation was stratified by centre but not on any other variables. **Allocation concealment:** Not reported. **Blinding:** The study was described as 'double blind' but no further details are provided. **Other:** 17 patients dropped out before treatment started and were not included in the analysis (9 refused to participate and 8 could not swallow capsules). The analysis followed an intention to treat principle with the last observation carried forward for dropouts (though those that dropped out before treatment started were not included).

1 **Table 16: Hariri 2012**

Bibliographic reference	**Hariri M, Djazayery A, Djalali M et al. (2012) Effect of n-3 supplementation on hyperactivity, oxidative stress and inflammatory mediators in children with attention-deficit-hyperactivity disorder. Malaysian Journal of Nutrition 18: 329-35**
Study type	Randomised controlled trial
Aim	To determine the effect of n-3 supplementation on hyperactivity, oxidative stress and inflammatory mediators in children with ADHD.
Patient characteristics	**Inclusion criteria:** - Aged 6-11 years - Diagnosed with ADHD (diagnostic criteria not specified) - Taking methylphenidate - Conners' abbreviated questionnaire score (ASQ-P) for hyperactivity greater than 14. **Exclusion criteria:** - infectious diseases, diabetes - hyperthyroidism, - convulsion, epilepsy - consumption of n-3 fatty acids supplements. **Baseline characteristics (only participants who completed the study are reported)**

	PUFA	**Placebo**
Sex (M/F)	35/18	32/18
Age (mean,sd)	7.9 (1.53)	7.9 (1.45)

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Hariri M, Djazayery A, Djalali M et al. (2012) Effect of n-3 supplementation on hyperactivity, oxidative stress and inflammatory mediators in children with attention-deficit-hyperactivity disorder. Malaysian Journal of Nutrition 18: 329-35</td></tr>
<tr><td></td><td colspan="3">
<table>
<tr><td>Diagnosis</td><td>ADHD (subtype not specified)</td><td>ADHD (subtype not specified)</td></tr>
<tr><td>Comorbidities</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td colspan="3">
<table>
<tr><td></td><td>PUFA</td><td>Placebo</td></tr>
<tr><td>N</td><td>60</td><td>60</td></tr>
<tr><td>Drop outs</td><td>7
Steatorrhea (2)
Lost to follow up (3)
Refused to give blood samples (2)</td><td>10
Skin rash (3)
Non-compliance (5)
Refused to give blood samples (2)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td colspan="3">Soft gel capsules of n-3 fatty acids with a total daily dose of 900mg n-3 fatty acids (635mg Eicosapentaenoic acid, 165mg Docosahexaenoic acid and 100mg other n-3 fatty acids (Minami Nutrition, Belgium)</td></tr>
<tr><td>Comparison</td><td colspan="3">Visually similar capsules containing 900mg olive oil.</td></tr>
<tr><td>Methods</td><td colspan="3">Participants received n-3 fatty acids or placebo for 8 weeks. Compliance was assessed by counting pills (considered if consumed >90% of the medication).</td></tr>
<tr><td>Length of follow up</td><td colspan="3">8 weeks treatment duration</td></tr>
<tr><td>Location</td><td colspan="3">Iran, secondary care setting (participants were referred from secondary care clinic to participate in the study)</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">ADHD symptoms
Parent – Connors’ abbreviated questionnaire score (ASQ-P) Total score
<table>
<tr><td></td><td>PUFA</td><td>Placebo</td><td>Mean difference</td></tr>
<tr><td>Baseline</td><td>mean=24.45
sd=4.95
n=53</td><td>mean=24.12
sd=4.86
n=50</td><td></td></tr>
<tr><td>Week 8 treatment</td><td>mean=21.03
sd=3.98
n=53</td><td>mean=24.02
sd=4.22
n=50</td><td></td></tr>
<tr><td>Change from baseline* (end-baseline)</td><td>mean=-3.42
sd=4.54
n=53</td><td>mean=-0.1
sd=4.57
n=50</td><td>mean=-3.32**
95%CI=-5.08 to -1.56**</td></tr>
</table>
*imputed by reviewer
**calculated by reviewer</td></tr>
</table>

Bibliographic reference	**Hariri M, Djazayery A, Djalali M et al. (2012) Effect of n-3 supplementation on hyperactivity, oxidative stress and inflammatory mediators in children with attention-deficit-hyperactivity disorder. Malaysian Journal of Nutrition 18: 329-35**
	Number leaving study early **PUFA** | **Placebo** | **Relative risk (95%CI)**** 7/60 (11.7%) | 10/60 (16.7%) | 0.7 (0.29 to 1.72) ****calculated by reviewer** **Outcomes reported but not extracted:** Plasma inflammatory and oxidative stress mediators
Source of funding	Not reported
Comments	**Randomisation:** Method of randomisation not reported. **Allocation concealment:** Not reported. **Blinding:** Study described as double blind – no further details reported. **Other:** Per protocol analysis (drop outs not accounted for).

1 **Table 17: Johnson 2009, Johnson 2012**

Bibliographic reference	**Johnson M, Ostlund S, Fransson G et al. (2009) Omega-3/omega-6 fatty acids for attention deficit hyperactivity disorder: a randomized placebo-controlled trial in children and adolescents. Journal of Attention Disorders 12: 394-401** **Johnson M, Mansson JE, Ostlund S et al. (2012) Fatty acids in ADHD: plasma profiles in a placebo-controlled study of Omega 3/6 fatty acids in children and adolescents. Attention Deficit and Hyperactivity Disorders 4: 199-204**
Study type	Randomised controlled trial
Aim	To assess omega 3/6 fatty acids (eye q) in children with ADHD.
Patient characteristics	**Inclusion criteria:** - Aged 8 to 18 years - Meet DSM-IV criteria for ADHD of any subtype - Score at least 1.5 standard deviations above the age norm on the ADHD rating scale IV **Exclusion criteria:** - Autism (autistic symptoms, asperger syndrome, or any of the other autism spectrum disorders were not an exclusion criterion) - Psychosis, bipolar disorder, mental retardation, uncontrolled seizure disorder, hyper- or hypothyroidism,

<table>
<tr><td>Bibliographic reference</td><td>Johnson M, Ostlund S, Fransson G et al. (2009) Omega-3/omega-6 fatty acids for attention deficit hyperactivity disorder: a randomized placebo-controlled trial in children and adolescents. Journal of Attention Disorders 12: 394-401

Johnson M, Mansson JE, Ostlund S et al. (2012) Fatty acids in ADHD: plasma profiles in a placebo-controlled study of Omega 3/6 fatty acids in children and adolescents. Attention Deficit and Hyperactivity Disorders 4: 199-204</td></tr>
<tr><td></td><td>significant other medical conditions.
- Weight below 20 kg, alcohol or drug abuse, or the use of any psychoactive drugs or omega 3 preparations in the past 3 months.

Baseline characteristics (only participants who completed the study are reported)
<table>
<tr><th></th><th>PUFA</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>33/4</td><td>31/7</td></tr>
<tr><td>Age (mean,sd)</td><td>11.8 (2.14)</td><td>12.2 (2.19)</td></tr>
<tr><td>Diagnosis</td><td>ADHD combined type: 19
Hyperactive/impulsive: 0
Inattentive: 18</td><td>ADHD combined type: 16
Hyperactive/impulsive: 0
Inattentive: 22</td></tr>
<tr><td>Comorbidities</td><td>Reading writing disorder: 12
Oppositional defiant disorder: 8
Developmental coordination disorder :10
Learning difficulties: 3
Autistic traits: 6
Autism-like condition or Asperger: 7
Tourette syndrome: 0
Depression or anxiety: 2
Obsessive compulsive disorder: 1</td><td>Reading writing disorder: 20
Oppositional defiant disorder: 10
Developmental coordination disorder :13
Learning difficulties: 6
Autistic traits: 2
Autism-like condition or Asperger: 4
Tourette syndrome: 2
Depression or anxiety: 4
Obsessive compulsive disorder: 0</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>PUFA</th><th>Placebo</th></tr>
<tr><td>N</td><td>37</td><td>38</td></tr>
<tr><td>Drop outs</td><td>3
Unmotivated to continue or problems swallowing capsules (1)
Side effects (2)</td><td>8
Unmotivated to continue or problems swallowing capsules (6)
Side effects (1)
Blinded code broken due to marked increase in</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Johnson M, Ostlund S, Fransson G et al. (2009) Omega-3/omega-6 fatty acids for attention deficit hyperactivity disorder: a randomized placebo-controlled trial in children and adolescents. Journal of Attention Disorders 12: 394-401

Johnson M, Mansson JE, Ostlund S et al. (2012) Fatty acids in ADHD: plasma profiles in a placebo-controlled study of Omega 3/6 fatty acids in children and adolescents. Attention Deficit and Hyperactivity Disorders 4: 199-204</td></tr>
<tr><td></td><td><table><tr><td></td><td></td><td>irritability (1)</td></tr></table></td></tr>
<tr><td>Intervention</td><td>Omega 3/6 (Equazen eyeq) in a dose of three capsules twice daily, corresponding to a daily dose of 558 mg Eicosapentaenoic acid, 174 mg Docosahexaenoic acid (omega-3 fatty acids), 60 mg gamma linoleic acid (omega 6 fatty acid), and 10.8 mg Vitamin E</td></tr>
<tr><td>Comparison</td><td>Placebo (identical capsules containing olive oil).</td></tr>
<tr><td>Methods</td><td>Participants were randomised to receive PUFAs or placebo for 3 months. There was also an open-label extension (not reported here).</td></tr>
<tr><td>Length of follow up</td><td>3 month treatment period (plus 2 month non-comparative extension not reported here)</td></tr>
<tr><td>Location</td><td>Sweden, secondary care setting (participants recruited from children diagnosed with ADHD at participating clinics)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>ADHD symptoms
Clinician rated parent interview (treated as parent rated for analysis purposes)- ADHD-RS IV Total score (range 0-54)
<table>
<tr><th></th><th>PUFA</th><th>Placebo</th><th>Mean difference</th></tr>
<tr><td>Baseline</td><td>mean=33.5
sd=7.7
n=34</td><td>mean=32.4
sd=8.0
n=30</td><td></td></tr>
<tr><td>End (3 months treatment)</td><td>not reported</td><td>not reported</td><td></td></tr>
<tr><td>Change from baseline (end – baseline)</td><td>mean=-3.78
sd=7.14
n=34</td><td>mean=-1.65
sd=4.54
n=30</td><td>mean=-2.13**
95%CI=-5.03 to 0.77**</td></tr>
</table>
**calculated by reviewer

Clinician rated parent interview- ADHD-RS IV Total score Responder (25% reduction)
<table>
<tr><td></td><td></td><td>PUFA</td><td>Placebo</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Johnson M, Ostlund S, Fransson G et al. (2009) Omega-3/omega-6 fatty acids for attention deficit hyperactivity disorder: a randomized placebo-controlled trial in children and adolescents. Journal of Attention Disorders 12: 394-401** **Johnson M, Mansson JE, Ostlund S et al. (2012) Fatty acids in ADHD: plasma profiles in a placebo-controlled study of Omega 3/6 fatty acids in children and adolescents. Attention Deficit and Hyperactivity Disorders 4: 199-204**

	All participants	9/34	2/30
Age	**8-12 years**	4/25	1/18
	13-18 years	5/9	1/11
Co-morbidities	**Learning disability**	0/3	0/5
	Oppositional defiant disorder	0/8	0/10

Conduct disorder also listed, but not specified how many children in the denominator for each group

Functional status

Clinician rated - Clinical global impression (range 0-7)

	PUFA	**Placebo**	**Mean difference**
Baseline	Not reported separately for each group mean=4.67 sd=0.58		
End (3 months treatment)	not reported	not reported	
Change from baseline (end – baseline)	mean=-0.58 sd=0.87 n=34	mean=-0.13 sd=0.50 n=30	**mean=-0.45**** **95%CI=-0.79 to -0.11****

***unclear how many participants were included. Have used the lower bound to be conservative

****calculated by reviewer**

Number leaving study early

PUFA	**Placebo**	**Relative risk (95%CI)****
3/37 (8.1%)	8/38 (21.1%)	0.39 (0.11 to 1.34)

Bibliographic reference	**Johnson M, Ostlund S, Fransson G et al. (2009) Omega-3/omega-6 fatty acids for attention deficit hyperactivity disorder: a randomized placebo-controlled trial in children and adolescents. Journal of Attention Disorders 12: 394-401** **Johnson M, Mansson JE, Ostlund S et al. (2012) Fatty acids in ADHD: plasma profiles in a placebo-controlled study of Omega 3/6 fatty acids in children and adolescents. Attention Deficit and Hyperactivity Disorders 4: 199-204**
	****calculated by reviewer** **Outcomes reported but not extracted:** Plasma fatty acid composition
Source of funding	Equazen UK Ltd (PUFA supplement manufacturers)
Comments	**Randomisation:** Method of random sequence generation not described. **Allocation concealment:** The manufacturer of omega 3/6 provided consecutively numbered identical bottles of which 50% contained active treatment and 50% placebo in random order according to a code list that was not accessible to the investigators. The code was broken by a third party when all patients had completed the study **Blinding:** The study was double blind. Group allocation was only broken by a third party after all participants had completely the study. **Other:** Dropouts not accounted for in analysis (only those with post-baseline data included)

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2

3 **Table 18: Manor 2012, Manor 2013**

Bibliographic reference	**Manor I, Magen A, Keidar D et al. (2012) The effect of phosphatidylserine containing Omega3 fatty-acids on attention-deficit hyperactivity disorder symptoms in children: a double-blind placebo-controlled trial, followed by an open-label extension. European Psychiatry: the Journal of the Association of European Psychiatrists 27: 335-42** **Manor I, Magen A, Keidar D et al. (2013) Safety of phosphatidylserine containing omega3 fatty acids in ADHD children: a double-blind placebo-controlled trial followed by an open-label extension. European Psychiatry: the Journal of the Association of European Psychiatrists 28: 386-91**
Study type	Randomised controlled trial
Aim	To study the efficacy and safety of phoshatidylserine containing omega-3 PUFAs for ADHD in children.
Patient characteristics	**Inclusion criteria:**

Bibliographic reference	**Manor I, Magen A, Keidar D et al. (2012) The effect of phosphatidylserine containing Omega3 fatty-acids on attention-deficit hyperactivity disorder symptoms in children: a double-blind placebo-controlled trial, followed by an open-label extension. European Psychiatry: the Journal of the Association of European Psychiatrists 27: 335-42** **Manor I, Magen A, Keidar D et al. (2013) Safety of phosphatidylserine containing omega3 fatty acids in ADHD children: a double-blind placebo-controlled trial followed by an open-label extension. European Psychiatry: the Journal of the Association of European Psychiatrists 28: 386-91**

- Aged 6 to 13
- Normal weight and height according to the Israeli standards
- Regularly attend school
- Confirmed ADHD diagnosis by DSM-IV criteria
- Score of at least 1.5 standard deviations above the norm for the patient's age in the teacher rated ADHD rating scale
- Score of 4 or higher (moderately ill or worse) in the clinical global impression of severity of illness (CGI-S)
- Willingness of parent and teacher who is familiar with the child to participate

Exclusion criteria:

- Girls who had reached menarche and had 3 previous menstrual cycles
- History or current diagnosis of any serious systemic or neurological condition
- Failure to respond to two or more adequate courses of stimulant treatment
- Pervasive developmental disorder or nonverbal learning disability
- Any evidence of suicidal risk or any current psychiatric comorbidity that required psychiatric pharmacotherapy
- Concomitant use of prescription or non-prescription agents with potentially psychotropic properties (including ADHD treatments) 4 weeks before study entry
- History of alcohol or substance abuse as defined by DSM-IV critieria
- Consumption of >250mg/day of caffeine
- History of allergic reactions or sensitivity to marine products, soy or corn
- Any illness that could jeopardize the participants health or limit their successful completion of the trial

Baseline characteristics

	PUFA	**Placebo**
Sex (M/F)	72/28	32/15
Age (mean, sd)	9.2 (2.0)	9.2 (1.8)
Diagnosis	ADHD Combined: 66/100 ADHD Inattentive: 31/100	ADHD Combined: 31/47 ADHD Inattentive: 16/47

<table>
<tr><td>Bibliographic reference</td><td colspan="2">Manor I, Magen A, Keidar D et al. (2012) The effect of phosphatidylserine containing Omega3 fatty-acids on attention-deficit hyperactivity disorder symptoms in children: a double-blind placebo-controlled trial, followed by an open-label extension. European Psychiatry: the Journal of the Association of European Psychiatrists 27: 335-42

Manor I, Magen A, Keidar D et al. (2013) Safety of phosphatidylserine containing omega3 fatty acids in ADHD children: a double-blind placebo-controlled trial followed by an open-label extension. European Psychiatry: the Journal of the Association of European Psychiatrists 28: 386-91</td></tr>
<tr><td></td><td colspan="2"><table>
<tr><td></td><td>Hyperactive: 3/100</td><td>Hyperactive: 0/47</td></tr>
<tr><td>Comorbidities</td><td>Oppositional defiant disorder: 11/100
Enuresis: 2/100
Tic disorder: 3/100
Anxiety disorder: 2/100
Social Anxiety: 2/100
Specific Phobia
Conduct disorder
Encopresis
Obsessive compulsive disorder</td><td>Oppositional defiant disorder
Enuresis
Tic disorder
Anxiety disorder
Social Anxiety
Specific Phobia
Conduct disorder
Encopresis
Obsessive compulsive disorder</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td colspan="2"><table>
<tr><td></td><td>PUFA</td><td>Placebo</td></tr>
<tr><td>N</td><td>137</td><td>63</td></tr>
<tr><td>Drop outs</td><td>27
Voluntary withdrawal (22)
Adverse events (2)
Poor compliance (3)

Additionally 9 excluded from analysis because of compliance <65% and 1 because of protocol violation</td><td>11
Voluntary withdrawal (9)
Adverse event (1)
Poor compliance (1)

Additionally 5 excluded from analysis because of compliance <65%</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="2">4 capsules of PS-Omega-3 containing 300mg of PS and120mg of Eicosapentaenoic acid/ Docosahexaenoic acid with a ratio of 2:1</td></tr>
<tr><td>Comparison</td><td colspan="2">Matching placebo capsules containing cellulose</td></tr>
<tr><td>Methods</td><td colspan="2">Participants were randomly allocated to PUFAs or placebo (in a ratio of 2:1) for 15 weeks at a single centre. This was followed by an open label extension (not reported here)</td></tr>
<tr><td>Length of follow up</td><td colspan="2">15 week treatment period</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Manor I, Magen A, Keidar D et al. (2012) The effect of phosphatidylserine containing Omega3 fatty-acids on attention-deficit hyperactivity disorder symptoms in children: a double-blind placebo-controlled trial, followed by an open-label extension. European Psychiatry: the Journal of the Association of European Psychiatrists 27: 335-42

Manor I, Magen A, Keidar D et al. (2013) Safety of phosphatidylserine containing omega3 fatty acids in ADHD children: a double-blind placebo-controlled trial followed by an open-label extension. European Psychiatry: the Journal of the Association of European Psychiatrists 28: 386-91</td></tr>
<tr><td>Location</td><td>Israel, research setting (recruited through adverts on the internet, in newspapers and in medical centres)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>ADHD symptoms
Parent – Connors’ rating scale ADHD index (total score not reported)
<table>
<tr><th></th><th>PUFA</th><th>Placebo</th><th>Mean difference</th></tr>
<tr><td>Baseline</td><td>mean=69.33
sd=9.87
n=98</td><td>mean=69.36
sd=9.23
n=42</td><td></td></tr>
<tr><td>End (15 weeks treatment)</td><td>not reported</td><td>not reported</td><td></td></tr>
<tr><td>Change from baseline (end - baseline)*</td><td>mean=-5.36
sd=9.46
n=98</td><td>mean=-3.10
sd=9.61
n=42</td><td>mean=-2.26**
95%CI=-5.72 to 1.20**</td></tr>
</table>
**calculated by reviewer

Teacher – Connors’ rating scale ADHD index (total score not reported)
<table>
<tr><th></th><th>PUFA</th><th>Placebo</th><th>Mean difference</th></tr>
<tr><td>Baseline</td><td>mean=66.37
sd=11.81
n=93</td><td>mean=68.10
sd=10.39
n=42</td><td></td></tr>
<tr><td>End (15 weeks treatment)</td><td>not reported</td><td>not reported</td><td></td></tr>
<tr><td>Change from baseline (end – baseline)</td><td>mean=-1.80
sd=9.97
n=93</td><td>mean=-2.21
sd=11.29
n=42</td><td>mean=-0.41**
95%CI=-3.56 to 4.38**</td></tr>
</table>
**calculated by reviewer</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Manor I, Magen A, Keidar D et al. (2012) The effect of phosphatidylserine containing Omega3 fatty-acids on attention-deficit hyperactivity disorder symptoms in children: a double-blind placebo-controlled trial, followed by an open-label extension. European Psychiatry: the Journal of the Association of European Psychiatrists 27: 335-42

Manor I, Magen A, Keidar D et al. (2013) Safety of phosphatidylserine containing omega3 fatty acids in ADHD children: a double-blind placebo-controlled trial followed by an open-label extension. European Psychiatry: the Journal of the Association of European Psychiatrists 28: 386-91</td></tr>
<tr><td></td><td>Side effects (participants in whom side effect was rated 1 or higher on a severity scale of 1-9)
<table>
<tr><th></th><th>PUFA</th><th>Placebo</th><th>Relative risk (95%CI)**</th></tr>
<tr><td>Decreased appetite</td><td>45/137 32.7%</td><td>21/63 32.7%</td><td>0.99 (0.65 to 1.50)</td></tr>
<tr><td>Headaches</td><td>47/137 34.6%</td><td>24/63 38.2%</td><td>0.90 (0.61 to 1.33)</td></tr>
<tr><td>Stomach ache</td><td>63/137 46.2%</td><td>25/63 39.5%</td><td>1.16 (0.81 to 1.65)</td></tr>
</table>
*numbers calculated by reviewer from reported percentages (unclear whether denominator should be all participants or only ones who did not drop out)
**calculated by reviewer

Number leaving study early
<table>
<tr><th>PUFA</th><th>Placebo</th><th>Relative risk (95%CI)**</th></tr>
<tr><td>27/137 (19.7%)</td><td>11/63 (17.5%)</td><td>1.13 (0.60 to 2.13)</td></tr>
</table>
**calculated by reviewer

Outcomes reported but not extracted: Child health questioner, subgroup analysis based on gender, blood pressure, height, weight, heart rate, haematological and biochemical parameters</td></tr>
<tr><td>Source of funding</td><td>Enzymotec Ltd. Employees of enzymotec were also authors on the manuscript.</td></tr>
<tr><td>Comments</td><td>Randomisation: Randomisation was by a computerised process.
Allocation concealment: A web-based allocation procedure was used to unsure concealment
Blinding: The study was described as ‘double blind’, but further details are not reported.
Other: A per protocol analysis was used for efficacy data (did not account for dropouts). Unclear analysis type for side effect data.</td></tr>
</table>

1

1 **Table 19: Perera 2012**

<table>
<tr><td>Bibliographic reference</td><td>Perera H, Jeewandara KC, Seneviratne S et al. (2012) Combined omega3 and omega6 supplementation in children with attention-deficit hyperactivity disorder (ADHD) refractory to methylphenidate treatment: a double-blind, placebo-controlled study. Journal of Child Neurology 27: 747-53</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial</td></tr>
<tr><td>Aim</td><td>To assess the efficacy of omega 3 and omega 6 supplementation for children with ADHD whose parents had not noticed an improvement in behaviour after 6 months of therapy with methylphenidate and standard behavioural therapy.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
- Aged 6 to 12 years
- Part of an outpatient treatment programme for ADHD with methylphenidate and standard behavioural therapy for at least 6 months, and refractory to treatment (judged by persistent ADHD symptoms on parent questionnaire, clinical interview and examination of school work).
- Clinical ADHD diagnosis according to DSM-IV criteria. Supported by positive scores in the Swanson, Nolan and Pelham version IV (SNAP) parent and teacher evaluation
Exclusion criteria:
- Hyperactivity primarily related to intellectual impairment, brain injury or insult
- Missed follow up appointments or medication refills in 6 month treatment period with methylphenidate and standard behavioural therapy.

Baseline characteristics (reported for randomised participants who took at least 1 dose of PUFA/placebo)
<table>
<tr><td></td><td>PUFA</td><td>Placebo</td></tr>
<tr><td>Sex (M/F)</td><td>34/14</td><td>35/11</td></tr>
<tr><td>Age (mean,sd)</td><td>9.4 (1.5)</td><td>9.2 (1.5)</td></tr>
<tr><td>Diagnosis</td><td>ADHD diagnosis (type not specified)</td><td>ADHD diagnosis (type not specified)</td></tr>
<tr><td>Comorbidities</td><td>Not reported</td><td>Not reported</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><td></td><td>PUFA</td><td>Placebo</td></tr>
<tr><td>N</td><td>49</td><td>49</td></tr>
<tr><td>Drop outs</td><td>1
Non-compliance (1)</td><td>3
Non-compliance (2)
Other (1)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>2 capsules of supplement ‘Vegepa’ each containing 296mg of omega 3 from fish oil and 181 mg of omega 6 from evening primrose oil. Treatment duration was 6 months.</td></tr>
<tr><td>Comparison</td><td>2 capsules of sunflower oil (identical in appearance). Treatment duration was 6 months.</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Perera H, Jeewandara KC, Seneviratne S et al. (2012) Combined omega3 and omega6 supplementation in children with attention-deficit hyperactivity disorder (ADHD) refractory to methylphenidate treatment: a double-blind, placebo-controlled study. Journal of Child Neurology 27: 747-53</td></tr>
<tr><td>Methods</td><td>Participants had all taken methylphenidate and received standard behavioural treatment for at least 6 months before the study, and continued to receive this treatment throughout. Children all also received micronutrients in recommended doses for age.</td></tr>
<tr><td>Length of follow up</td><td>6 month treatment duration.</td></tr>
<tr><td>Location</td><td>Sri Lanka, secondary care</td></tr>
<tr><td>Outcomes measures and effect size</td><td>ADHD symptoms
Parent – local symptom checklist (reported test-retest reliability of 96.1% and content validity of +1 using Delphi technique). 11 item checklist with each item scored as better (1), same (2) or worse (3) than before (range 11-33, higher scores worse). Not used in analysis (see ***)
<table>
<tr><th></th><th>PUFA</th><th>Placebo</th><th>Mean difference</th></tr>
<tr><td>Month 3 treatment</td><td>mean=16.35
sd=3.65
n=48</td><td>mean=20.50
sd=14*
n=46</td><td>mean=-4.15**
95%CI=-0.417 to 2.209***</td></tr>
<tr><td>Month 6 treatment</td><td>mean=15.46
sd=3.65
n=46</td><td>mean=20.74
sd=293*
n=46</td><td>mean=-5.28**
95%CI=-6.633 to -3.928</td></tr>
</table>
*These standard deviations seem spuriously large, and there is no comment on this in the manuscript.
**Calculated by reviewer
***reported confidence intervals do not incorporate calculated mean difference. These data are therefore not presented in the analysis as are potentially unreliable

Number leaving study early
<table>
<tr><th>PUFA</th><th>Placebo</th><th>Relative risk (95%CI)**</th></tr>
<tr><td>1/49 (2%)</td><td>3/49 (6.1%)</td><td>0.33 (0.04 to 3.09)</td></tr>
</table>
** Calculated by reviewer

Outcomes reported but not extracted: Individual symptom scores</td></tr>
<tr><td>Source of funding</td><td>Igennus Ltd, Gpristine Pvt Ltd</td></tr>
<tr><td>Comments</td><td>Randomisation: Random sequence generation method not reported
Allocation concealment: Placebo and active treatments were coded and allocation was conducted by an independent person.</td></tr>
</table>

Bibliographic reference	**Perera H, Jeewandara KC, Seneviratne S et al. (2012) Combined omega3 and omega6 supplementation in children with attention-deficit hyperactivity disorder (ADHD) refractory to methylphenidate treatment: a double-blind, placebo-controlled study. Journal of Child Neurology 27: 747-53**
	Blinding: Researchers and patients were masked to group allocation. **Other:** ADHD symptom ratings from this study was not included in the analysis because of inconsistencies in the reported data that mean it is potentially unreliable (see above for details).

1 **Table 20: Stevens 2003**

Bibliographic reference	**Stevens L, Zhang W, Peck L et al. (2003) EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. Lipids 38: 1007-21**
Study type	Randomised controlled trial
Aim	To evaluate the effects of supplementation with polyunsaturated fatty acids (PUFAs) on blood fatty acid composition in children with ADHD.
Patient characteristics	**Inclusion criteria:** - Aged 6 to 13. - Parents reported a diagnosis of ADHD from clinical psychologist, psychiatrist or paediatrician (not confirmed as part of the study). - Thirst/skin score of 4 or greater (excessive thirst, frequent urination, dry hair, dry skin, brittle nails, dandruff, follicular keratoses were scored from 0 to 4 by parents and the score summed) **Exclusion criteria:** - Chronic health problems (parent reported) **Baseline characteristics (reported for randomised participants who took at least 1 dose of PUFA/placebo)**

	PUFA	Placebo
Sex (M/F)	19/3	22/3
Age (mean,sd)	9.5 (1.7)	10.1 (2.0)
Diagnosis	not reported	not reported
Comorbidities	not reported	not reported

Number of Patients

	PUFA	Placebo
N	25	25
Drop outs	7	10

<table>
<tr><td>Bibliographic reference</td><td colspan="4">Stevens L, Zhang W, Peck L et al. (2003) EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. Lipids 38: 1007-21</td></tr>
<tr><td></td><td colspan="4"><table><tr><td></td><td>(reasons for dropout not reported)</td><td>(reasons for dropout not reported)</td></tr></table></td></tr>
<tr><td>Intervention</td><td colspan="4">8 capsules of PUFAs (Efalex supplied by Efamol) each day for 4 months. Each capsule contained 60mg Docosahexaenoic acid (omega 3), 10mg Eicosapentaenoic acid (omega 3), 5mg arachidonic acid (omega 6), 12mg gamma-linolenic acid (omega 6) and 3mg Vitamin E.</td></tr>
<tr><td>Comparison</td><td colspan="4">8 capsules of olive oil each day for 4 months. Each capsule contained 0.8mg olive oil. Capsules were ‘comparable’ in odour and appearance to the PUFA capsules.</td></tr>
<tr><td>Methods</td><td colspan="4">A control group (without ADHD) was included for comparison of blood fatty acid measured (not reported here).</td></tr>
<tr><td>Length of follow up</td><td colspan="4">4 month treatment period.</td></tr>
<tr><td>Location</td><td colspan="4">USA, University research setting. Participants recruited from the community and screened by telephone.</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="4">ADHD symptoms
Parent – Connors’ abbreviated symptom questionnaire. Not included in analysis as mean difference not reported or calculable.
<table>
<tr><th></th><th>PUFA</th><th>Placebo</th><th>Group difference</th></tr>
<tr><td>Baseline</td><td>mean=16.5
sd=4.9
n=25</td><td>mean=19.9
sd=4.5
n=22</td><td></td></tr>
<tr><td>End (4 months treatment)</td><td>not reported</td><td>not reported</td><td></td></tr>
<tr><td>Change from baseline (baseline – end)</td><td>mean=4.3
range=-3 to 12
n=15</td><td>mean=2.9
range=-3 to 9
n=18</td><td>Kruskal wallis test p=0.29</td></tr>
</table>
Teacher – Connors’ abbreviated symptom questionnaire. Not included in analysis as mean difference not reported or calculable.
<table>
<tr><th></th><th>PUFA</th><th>Placebo</th><th>Group difference</th></tr>
<tr><td>Baseline</td><td>mean=10.5
sd=7.4
n=25</td><td>mean=13.1
sd=7.7
n=22</td><td></td></tr>
<tr><td>End (4 months</td><td>not reported</td><td>not reported</td><td></td></tr>
</table></td></tr>
</table>

Bibliographic reference	Stevens L, Zhang W, Peck L et al. (2003) EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. Lipids 38: 1007-21

treatment)			
Change from baseline (baseline – end)	mean=1.4 range=-9 to 11 n=9	mean=1.9 range=-3 to 8 n=17	**Kruskal wallis test p=1.0**

Academic performance

Woodcock-Johnson Psycho-educational test battery – revised (processing speed) Not included in analysis as mean difference not reported or calculable.

	PUFA	**Placebo**	**Group difference**
Baseline	mean=99.8 sd=22.6 n=25	mean=93.2 sd=15.5 n=22	
End (4 months treatment)	not reported	not reported	
Change from baseline (baseline – end)	mean=0.9 range=-11 to 17 n=15	mean=-0.1 range=-8 to 13 n=18	**Kruskal wallis test p=0.54**

Woodcock-Johnson Psycho-educational test battery – revised (short-term memory) Not included in analysis as mean difference not reported or calculable.

	PUFA	**Placebo**	**Group difference**
Baseline	mean=101.4 sd=17 n=25	mean=95.9 sd=15.9 n=22	
End (4 months treatment)	not reported	not reported	
Change from baseline (baseline – end)	mean=-1.4 range=-20 to 26	mean=-0.8 range=-10 to 17	**Kruskal wallis test p=0.55**

Bibliographic reference	Stevens L, Zhang W, Peck L et al. (2003) EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. Lipids 38: 1007-21

	n=15	n=18	

Woodcock-Johnson Psycho-educational test battery – revised (visual processing) Not included in analysis as mean difference not reported or calculable.

	PUFA	Placebo	Group difference
Baseline	mean=107.1 sd=16.1 n=25	mean=104.8 sd=14.2 n=22	
End (4 months treatment)	not reported	not reported	
Change from baseline (baseline – end)	mean=-3.7 range=-21 to 16 n=15	mean=-4.9 range=-23 to 10 n=18	**Kruskal wallis test p=0.69**

Woodcock-Johnson Psycho-educational test battery – revised (auditory processing) Not included in analysis as mean difference not reported or calculable.

	PUFA	Placebo	Group difference
Baseline	mean=98.6 sd=12.8 n=25	mean=96.4 sd=12.4 n=22	
End (4 months treatment)	not reported	not reported	
Change from baseline (baseline – end)	mean=-5.1 range=-23 to 14 n=15	mean=-5.4 range=-21 to 7 n=18	**Kruskal wallis test p=0.86**

Number leaving study early

PUFA	Placebo	Relative risk (95% CI)

Bibliographic reference	**Stevens L, Zhang W, Peck L et al. (2003) EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. Lipids 38: 1007-21**
	7/25 (28%) | 10/25 (40%) | 0.70 (0.32 to 1.54) **Outcomes reported but not extracted:** Blood fatty acid composition, disruptive behaviours disorders rating scale, hit reaction times, thirst/skin symptoms total score, connors' continuous performance test (measure of attention), disruptive behaviour disorders rating scale
Source of funding	National institute of Mental Health, Scotia Pharmaceuticals, the National Fisheries institute
Comments	**Randomisation:** Groups were balanced for gender and medication use. Method used for randomisation not reported. **Allocation concealment:** Not reported. **Blinding:** Described as 'double blind' but details not reported. **Other:** ADHD diagnosis was not confirmed as part of the study, but instead based on parent-reported diagnosis by a healthcare professional. Olive oil was possibly not an inert placebo as it resulted in significant changes in blood fatty acid composition from baseline.

1 **Table 21: Vaisman 2008**

Bibliographic reference	**Vaisman N, Kaysar N, Zaruk-Adasha Y et al. (2008) Correlation between changes in blood fatty acid composition and visual sustained attention performance in children with inattention: effect of dietary n-3 fatty acids containing phospholipids. American Journal of Clinical Nutrition 87: 1170-80**
Study type	Randomised controlled trial
Aim	To investigate whether omega-3 fatty acids conjugated to phospholipids or fish oil affects blood fatty acids, executive function and behaviour in children with ADHD.
Patient characteristics	**Inclusion criteria:** - 8 to 13 years - Received previous diagnosis of ADHD from a clinical psychiatrist, neurologist or paediatrician (not confirmed as part of the study) **Exclusion criteria:** - Significant sensory or neurological limitations, epilepsy, mental retardation, psychosis or pervasive developmental disorder. - Taking medications with known central nervous system effects including stimulants or dietary supplements other than vitamins. **Baseline characteristics**

	PUFA – phospholipids	**PUFA – fish oil**	**Placebo**

<table>
<tr><td>Bibliographic reference</td><td colspan="4">Vaisman N, Kaysar N, Zaruk-Adasha Y et al. (2008) Correlation between changes in blood fatty acid composition and visual sustained attention performance in children with inattention: effect of dietary n-3 fatty acids containing phospholipids. American Journal of Clinical Nutrition 87: 1170-80</td></tr>
<tr><td></td><td colspan="4">
<table>
<tr><td>Sex (M/F)</td><td>15/3</td><td>15/6</td><td>15/6</td></tr>
<tr><td>Age (mean, sd)</td><td>9.17 (1.27)</td><td>9.40 (1.06)</td><td>9.31 (1.28)</td></tr>
<tr><td>Diagnosis</td><td>ADHD (subtypes not reported)</td><td>ADHD (subtypes not reported)</td><td>ADHD (subtypes not reported)</td></tr>
<tr><td>Comorbidities</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td colspan="4">
<table>
<tr><td></td><td>PUFA – phospholipids</td><td>PUFA – fish oil</td><td>Placebo</td></tr>
<tr><td>N</td><td>29</td><td>28</td><td>26</td></tr>
<tr><td>Drop outs</td><td>11
Poor taste (4)
Failure to comply (4)
Adverse event (2 vomiting & rash)
Treatment by methylphenidate (1)</td><td>7
Poor taste (4)
Failure to comply (0)
Adverse event (2 vomiting)
Treatment by methylphenidate (1)</td><td>5
Poor taste (2)
Failure to comply (2)
Adverse event (0)
Treatment by methylphenidate (1)</td></tr>
</table>
</td></tr>
<tr><td>Intervention 1</td><td colspan="4">Chocolate spread enriched with omega-3 conjugated to phospholipids (enzymotec Ltd, Israel). Daily aquilot on a slice of bread. (see methods for composition)</td></tr>
<tr><td>Intervention 2</td><td colspan="4">Chocolate spread enriched with fish oil (Ocean nutrition Ltd, Halifax, Canada). Daily aquilot on a slice of bread. (see methods for composition</td></tr>
<tr><td>Comparison</td><td colspan="4">Placebo chocolate spread (details not reported) Daily aquilot on a slice of bread. (see methods for composition</td></tr>
<tr><td>Methods</td><td colspan="4">Participants were supplied with chocolate spread randomised to contain omega 3 conjugated to phospholipids, fish oil or placebo. The daily dose of phospholipids and fatty acids is shown for each intervention in the table below (ND=not detected). The intervention lasted for 3 months. Outcomes were measured at baseline and at the end of the intervention.
<table>
<tr><td></td><td>PUFA – phospholipids (mg/d)</td><td>PUFA – Fish oil (mg/d)</td><td>Placebo (mg/d)</td></tr>
<tr><td>Phospholipids</td><td></td><td></td><td></td></tr>
<tr><td>Phosphatidylserine</td><td>3001</td><td>ND</td><td>ND</td></tr>
<tr><td>Phosphatidylethanolamine</td><td>66</td><td>ND</td><td>ND</td></tr>
<tr><td>Phosphatidic acid</td><td>48</td><td>ND</td><td>ND</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Vaisman N, Kaysar N, Zaruk-Adasha Y et al. (2008) Correlation between changes in blood fatty acid composition and visual sustained attention performance in children with inattention: effect of dietary n-3 fatty acids containing phospholipids. American Journal of Clinical Nutrition 87: 1170-80**

Lysophospholipids	24	ND	ND
Phosphatidylcholine	18	ND	ND
Phosphatidylinositol	12	ND	ND
Total	468	ND	ND
Fatty acids			
14:0	19	63	ND
16:0	141	147	30
18:0	7	31	13
20:0	0	2	5
22:0	1	2	3
24:0	0	4	1
16:1n7	19	68	1
18:1n9	37	95	415
18:1n7	44	25	ND
20:1n9	5	12	13
22:1n9	5	7	4
18:2n6	11	18	150
18:3n6	1	2	0
20:4n6	4	7	0
18:3n3	7	25	69
20:5n3	156	153	ND
22:5n3	4	0	0
22:6n3	95	96	ND
Rest	24	41	37
Total	580	799	742

Length of follow up	3 months treatment duration
Location	Israel, secondary care setting (participants were recruited via newspaper advert)
Outcomes measures and	**ADHD symptoms**

Bibliographic reference	**Vaisman N, Kaysar N, Zaruk-Adasha Y et al. (2008) Correlation between changes in blood fatty acid composition and visual sustained attention performance in children with inattention: effect of dietary n-3 fatty acids containing phospholipids. American Journal of Clinical Nutrition 87: 1170-80**
effect size	**Parent – Abbreviated Conner's rating scale**

	PUFA - phospholipid	**PUFA – fish oil**	**Combined PUFA****	**Placebo**	**Mean difference (combined PUFA – Placebo)**
Baseline	mean=14.33 sd=6.67 n=18	mean=17.10 sd=5.26 n=21		mean=15.05 sd=6.2 n=21	
End – 3 months treatment	not reported	not reported		not reported	
Change from baseline (end-baseline)*	mean=-5.00 sd=8.32 n=18	mean=-3.20 sd=6.05 n=21	mean=-4.03 sd=7.15 n=39	mean=-2.35 sd=3.73 n=21	**mean=-1.68***** **95%CI=-4.43 to 1.07*****

***Reported as (end – baseline). Sign reversed for clarity.**

****calculated by reviewer for analysis. The authors reported that there was no statistically significant difference between phospholipid and fish oil groups.**

*****calculated by reviewer**

Number leaving study early

PUFA - phospholipid	**PUFA – fish oil**	**Combined PUFA****	**Placebo**	**Relative risk (95%CI)*** (combined PUFA – Placebo)**
11/29 (37.9%)	7/28 (25.0%)	18/57 (31.6%)	5/26 (19.2%)	1.64 (0.68 to 3.94)

****calculated by reviewer for analysis**

*****calculated by reviewer**

Outcomes reported but not extracted: Plasma phospholipids, erythrocyte phospholipids, computerised test of

Bibliographic reference	**Vaisman N, Kaysar N, Zaruk-Adasha Y et al. (2008) Correlation between changes in blood fatty acid composition and visual sustained attention performance in children with inattention: effect of dietary n-3 fatty acids containing phospholipids. American Journal of Clinical Nutrition 87: 1170-80**
	visual attention, correlations between biochemical parameters and attention test, Child behaviour checklist (mood or emotional liability scale)
Source of funding	Enzymotec Ltd, Migdal-HaEmeq, Israel. Two of the study authors were enzymotec employees.
Comments	**Randomisation:** Randomisation method not reported **Allocation concealment:** Not reported **Blinding:** Study described as 'double blind', but details not reported. **Other:** Per protocol analysis (dropouts not taken into account) requiring <70% compliance

1

2 **Table 22: Voigt 2001**

Bibliographic reference	**Voigt RG, Llorente AM, Jensen CL et al. (2001) A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. Journal of Pediatrics 139: 189-96**
Study type	Randomised controlled trial
Aim	To determine whether docosahexaenoic acid (Docosahexaenoic acid) supplementation for 4 months decreases the symptoms of ADHD in children.
Patient characteristics	**Inclusion criteria:** - Previously given a diagnosis of ADHD by a physician and confirmed by diagnostic interview with a neurodevelopmental paediatrician (DSM-IV criteria) - Being successfully treated with stimulant medication **Exclusion criteria:** - Ineffective treatment with stimulant medication - Treatment with other psychotropic medication - Previous diagnosis of other psychiatric disorder - Use of dietary supplements other than vitamins - Occurrence of a significant life event within 6 months - History of head injury or seizures - Receipt of special educational services for mental retardation or pervasive developmental disorder - Premature birth - Exposure to alcohol, tobacco or other drugs in utero - Diagnosis of a disorder of lipid metabolism or other chronic medical condition

<table>
<tr><td>Bibliographic reference</td><td>Voigt RG, Llorente AM, Jensen CL et al. (2001) A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. Journal of Pediatrics 139: 189-96</td></tr>
<tr><td></td><td>Baseline characteristics
<table>
<tr><td></td><td>PUFA</td><td>Placebo</td></tr>
<tr><td>Sex (M/F)</td><td>21/6</td><td>21/6</td></tr>
<tr><td>Age (mean, sd)</td><td>9.1 (2.1)</td><td>9.5 (1.7)</td></tr>
<tr><td>Diagnosis</td><td>ADHD (subtypes not specified)</td><td>ADHD (subtypes not specified)</td></tr>
<tr><td>Comorbidities</td><td>Not reported</td><td>Not reported</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><td></td><td>PUFA</td><td>Placebo</td></tr>
<tr><td>N</td><td>32</td><td>31</td></tr>
<tr><td>Drop outs</td><td>5
Refused venepuncture (2)
Family emergencies (3)</td><td>4
Refused venepuncture (2)
Family emergencies (2)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Algae-derived triglyceride capsule (DHASCO; Martek Bioscience corporation, Columbia), providing 345mg of Docosahexaenoic acid per day</td></tr>
<tr><td>Comparison</td><td>Placebo capsule, identical in appearance</td></tr>
<tr><td>Methods</td><td>Participants were randomised to receive fatty acids or placebo for 4 months. Plasma phospholipid fatty acids patterns, and measures of attention and impulsivity were taken at baseline and at the end of treatment</td></tr>
<tr><td>Length of follow up</td><td>4 month treatment period</td></tr>
<tr><td>Location</td><td>US, Research setting (participants recruited by general advertisement)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Number leaving study early
<table>
<tr><td>PUFA</td><td>Placebo</td><td>Relative risk (95%CI)**</td></tr>
<tr><td>5/32 (15.6%)</td><td>4/31 (12.9%)</td><td>1.21 (0.36 to 4.10)</td></tr>
</table>
**Calculated by reviewer

Outcomes reported but not extracted: Blood fatty acid levels, lab-based measures of attention, child behaviour checklist (internalising behaviour, externalising behaviour, socialisation problems, though problems and attention problems scales), colour trails test (measure of visual attention and sequencing)</td></tr>
<tr><td>Source of funding</td><td>US department of agriculture and Martek Bioscience corporation, Columbia (also supplied supplements)</td></tr>
<tr><td>Comments</td><td>Randomisation: Randomisation was by a computer-generated randomisation scheme
Allocation concealment: Not reported</td></tr>
</table>

Bibliographic reference	**Voigt RG, Llorente AM, Jensen CL et al. (2001) A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. Journal of Pediatrics 139: 189-96**
	Blinding: The study was described as 'double blind' but no further details provided **Other:** Per protocol analysis (dropouts not accounted for). Connors rating scale (ADHD symptoms) was used, but data were not reported (there was reportedly no significant difference between groups), indicating possible selective reporting bias.

1

2 **Table 23: Widenhorn-Muller 2014**

Bibliographic reference	**Widenhorn-Muller K, Schwanda S, Scholz E et al. (2014) Effect of supplementation with long-chain omega-3 polyunsaturated fatty acids on behavior and cognition in children with attention deficit/hyperactivity disorder (ADHD): a randomized placebo-controlled intervention trial. Prostaglandins Leukotrienes & Essential Fatty Acids 91: 49-60**
Study type	Randomised controlled trial
Aim	To determine whether supplementation with omega 3 polyunsaturated fatty acids (PUFAs) affects behavioural symptoms and cognitive impairments in children with ADHD.
Patient characteristics	**Inclusion criteria:** - Fulfilling diagnosis criteria for ADHD (DSM-IV). Diagnosis could have been make before or as part of the study. **Exclusion criteria:** - IQ<=70 - Use of stimulant medication or other psychoactive medication - Fatty acid supplementation within the last 6 months - Allergy to fish or fish products **Baseline characteristics**

	PUFA	**Placebo**
Sex (M/F)	8.9 (1.48)	8.92 (1.24)
Age (mean, sd)	35/11	39/10
Diagnosis	ADHD combined type (21) ADHD inattentive (24) ADHD hyperactive/impulsive (1)	ADHD combined type (20) ADHD inattentive (28) ADHD hyperactive/impulsive (1)

<table>
<tr><td>Bibliographic reference</td><td colspan="4">Widenhorn-Muller K, Schwanda S, Scholz E et al. (2014) Effect of supplementation with long-chain omega-3 polyunsaturated fatty acids on behavior and cognition in children with attention deficit/hyperactivity disorder (ADHD): a randomized placebo-controlled intervention trial. Prostaglandins Leukotrienes & Essential Fatty Acids 91: 49-60</td></tr>
<tr><td></td><td colspan="4"><table>
<tr><td>Comorbidities</td><td>Not reported</td><td>Not reported</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td colspan="4"><table>
<tr><td></td><td>PUFA</td><td>Placebo</td></tr>
<tr><td>N</td><td>55</td><td>55</td></tr>
<tr><td>Drop outs</td><td>7
Problems swallowing capsules (3)
Starting stimulant medication (2)
No compliance (1)

In addition:
Excluded from analysis because only took 57% of provided capsules (1)
Excluded from analysis because of no change in blood PUFA levels (1)</td><td>6
Problems swallowing capsules (2)
Starting stimulant medication (2)
No compliance (1)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="4">Two capsules per day containing 600mg Eicosapentaenoic acid and 120mg Docosahexaenoic acid and 15 mg Vitamin E (Merk Selbstmedikation)</td></tr>
<tr><td>Comparison</td><td colspan="4">Placebo: Two capsules per day of olive oil</td></tr>
<tr><td>Methods</td><td colspan="4">Following confirmation of inclusion criteria, participants were randomised to receive PUFAs or placebo for 16 weeks. Baseline measures were taken before the intervention and follow up measures at the end of the intervention period.</td></tr>
<tr><td>Length of follow up</td><td colspan="4">16 week treatment period</td></tr>
<tr><td>Location</td><td colspan="4">Germany, Secondary care setting (participants were recruited from a variety of sources including secondary care, by teachers, from community groups and from a newspaper advert)</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="4">ADHD symptoms
Parent – DISYPS-II total score<table>
<tr><td></td><td>PUFA</td><td>Placebo</td><td>Mean difference</td></tr>
<tr><td>Baseline</td><td>mean=1.68
se=0.08
sd=0.54*
n=45</td><td>mean=1.64
se=0.07
sd=0.49*
n=49</td><td></td></tr>
<tr><td>End -16 weeks treatment</td><td>mean=1.35</td><td>mean=1.34</td><td></td></tr>
</table></td></tr>
</table>

Bibliographic reference	Widenhorn-Muller K, Schwanda S, Scholz E et al. (2014) Effect of supplementation with long-chain omega-3 polyunsaturated fatty acids on behavior and cognition in children with attention deficit/hyperactivity disorder (ADHD): a randomized placebo-controlled intervention trial. Prostaglandins Leukotrienes & Essential Fatty Acids 91: 49-60

	se=0.08 sd=0.54* n=45	se=0.07 sd=0.48* n=47	
Change from baseline (end - baseline)**	mean=-0.33 sd=0.54 n=45	mean=-0.3 sd=0.49 n=47	**mean=-0.03* 95%CI=-0.25 to 0.19***

***calculated by reviewer**
****Imputed by reviewer**

Teacher – DISYPS-II total score

	PUFA	Placebo	Mean difference
Baseline	mean=1.31 se=0.09 sd=0.6* n=45	mean=1.31 se=0.08 sd=0.56* n=49	
End -16 weeks treatment	mean=1.04 se=0.10 sd=0.62* n=39	mean=1.11 se=0.08 sd=0.54* n=45	
Change from baseline (end - baseline)**	mean=-0.27 sd=0.61 n=39	mean=-0.2 sd=0.55 n=45	**mean=-0.12* 95%CI=-0.55 to 0.31***

***calculated by reviewer**
****imputed by reviewer**

Academic performance

Working memory index score (HAWIK-IV)

	PUFA	Placebo	Mean difference

<table>
<tr><td>Bibliographic reference</td><td>Widenhorn-Muller K, Schwanda S, Scholz E et al. (2014) Effect of supplementation with long-chain omega-3 polyunsaturated fatty acids on behavior and cognition in children with attention deficit/hyperactivity disorder (ADHD): a randomized placebo-controlled intervention trial. Prostaglandins Leukotrienes & Essential Fatty Acids 91: 49-60</td></tr>
<tr><td></td><td>
<table>
<tr><td>Baseline</td><td>mean=97.51
sd=10.04
n=46</td><td>mean=96.31
sd=9.48
n=49</td><td></td></tr>
<tr><td>End -16 weeks treatment</td><td>mean=101.78
sd=11.47
n=46</td><td>mean=96.92
sd=9.73
n=49</td><td>Time by treatment interaction ANOVA
F=5.54, p=0.019</td></tr>
<tr><td>Change from baseline (end – baseline)*</td><td>mean=-4.27
sd=10.83
n=49</td><td>mean=-0.61
sd=9.61
n=49</td><td>mean=-3.66**
95%CI=-7.71 to 0.39**</td></tr>
</table>
*imputed by reviewer
**calculated by reviewer

Number leaving study early
<table>
<tr><th>PUFA</th><th>Placebo</th><th>Relative risk (95%CI)**</th></tr>
<tr><td>7/55 (12.7%)</td><td>6/55 (10.9%)</td><td>1.17 (0.42 to 3.25)</td></tr>
</table>
**calculated by reviewer

Outcomes reported but not extracted: Erythrocyte membrane fatty acid composition, fish and seafood consumption, working memory scale subtests, child behaviour checklist (ADHD scale not reported), Teacher report form (ADHD scale not reported)</td></tr>
<tr><td>Source of funding</td><td>German Federal ministry of Education and Research</td></tr>
<tr><td>Comments</td><td>Randomisation: A computer-generated random sequence was used for allocation.
Allocation concealment: Not reported
Blinding: Participants, parents and those assessing outcome measures were blinded to group allocation.
Other: Per protocol analysis (did not take dropouts into account)</td></tr>
</table>

1

2

1

Appendix H: GRADE profiles

H.1 Question 1: Elimination/restriction diets for ADHD

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Few food diet	Control	Relative (95% CI)	Absolute	Quality
ADHD symptoms (Parent rated, up to 3 months) (Better indicated by lower values)											
2[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	65	62	-	SMD 1.92 lower (2.34 to 1.49 lower)	LOW
ADHD symptoms (Teacher rated, up to 3 months) (Better indicated by lower values)											
2[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	47	52	-	SMD 2.35 lower (2.87 to 1.82 lower)	LOW
Functional status (Parent rated, up to 3 months) (Better indicated by lower values)											
1[3]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	42	-	MD 8.70 lower (11.01 to 6.39 lower)	LOW
Functional status (Teacher rated, up to 3 months) (Better indicated by lower values)											
1[3]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	33	42	-	MD 3.20 lower (5.64 to 0.76 lower)	VERY LOW

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Few food diet	Control	Relative (95% CI)	Absolute	Quality
Number leaving study early											
2[1]	randomised trials	serious[5]	no serious inconsistency	serious[6]	very serious[7]	none	11/65 (16.9%)	9/62 (14.5%)	RR 1.18 (0.52 to 2.65)	26 more per 1000 (from 70 fewer to 240 more)	VERY LOW

[1] Pelsser 2009, Pelsser 2011
[2] Subjective outcome and studies were unblinded (parents, teachers, clinicians and children knew group allocation).
[3] Pelsser 2011
[4] Confidence intervals encompass clinically important benefit and no clinically important difference.
[5] Study was unblinded (considered less serious than for other outcomes as outcome is less subjective).
[6] Number leaving the study early is a surrogate measure for treatment acceptibility.
[7] Confidence intervals encompass clinically important benefit and harm.

H.2 Question 2: Polyunsaturated fatty acids (PUFAs) for ADHD

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PUFA	Placebo	Relative (95% CI)	Absolute	Quality
Change in ADHD symptoms (Parent reported, up to 3 months) (Better indicated by lower values)											
5[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	176	151	-	SMD 0.25 lower (0.6 lower to 0.1 higher)	LOW
Change in ADHD symptoms (Parent reported, 3-6 months) (Better indicated by lower values)											
5[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	233	183	-	SMD 0.21 lower (0.42 to 0.01 lower)	MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PUFA	Placebo	Relative (95% CI)	Absolute	
Change in ADHD symptoms (Parent reported, 12 or more months) (Better indicated by lower values)											
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[3]	none	30	30	-	SMD 0.45 lower (0.97 lower to 0.06 higher)	VERY LOW
Change in ADHD symptoms (Teacher reported, 3-6 months) (Better indicated by lower values)											
3[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	178	133	-	SMD 0.09 lower (0.32 lower to 0.14 higher)	HIGH
Functional status (Clinician reported, up to 3 months, clinical global impression) (Better indicated by lower values)											
2[9]	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[3]	none	64	60	-	MD 0.6 lower (0.95 to 0.25 lower)	LOW
Functional status (Clinician reported, 3 to 6 months, clinical global impression) (Better indicated by lower values)											
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[3]	none	30	30	-	MD 0.64 lower (1.07 to 0.21 lower)	VERY LOW
Functional status (Clinician reported, 6+ months, clinical global impression) (Better indicated by lower values)											
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[3]	none	30	30	-	MD 0.34 lower (0.77 lower to 0.09 higher)	VERY LOW
Academic performance - working memory (surrogate outcome, 3 to 6 months) (Better indicated by lower values)											
1[11]	randomised trials	no serious risk of bias	no serious inconsistency	serious[12]	serious[3]	none	49	49	-	MD 3.66 lower (7.71 lower to 0.39 higher)	LOW
Number leaving study early (up to 3 months)											
6[13]	randomised trials	no serious risk of	no serious inconsistency	serious[14]	very serious[15]	none	47/231 (20.3%)	41/199 (20.6%)	RR 0.98 (0.66 to 1.44)	4 fewer per 1000 (from 70 fewer to	VERY LOW

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PUFA	Placebo	Relative (95% CI)	Absolute	Quality
		bias								91 more)	
Number leaving study early (3 to 6 months)											
7[16]	randomised trials	no serious risk of bias	no serious inconsistency	serious[14]	very serious[15]	none	53/375 (14.1%)	41/295 (13.9%)	RR 0.94 (0.64 to 1.38)	8 fewer per 1000 (from 50 fewer to 53 more)	VERY LOW
Number leaving study early (6+ months)											
1[6]	randomised trials	very serious[7]	no serious inconsistency	serious[14]	serious[3]	none	3/30 (10%)	10/30 (33.3%)	RR 0.3 (0.09 to 0.98)	233 fewer per 1000 (from 7 fewer to 303 fewer)	VERY LOW
Adverse events - Headache											
2[17]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	57/167 (34.1%)	41/93 (44.1%)	RR 0.77 (0.52 to 1.15)	101 fewer per 1000 (from 212 fewer to 66 more)	MODERATE
Adverse events - Nausea											
2[18]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[15]	none	5/76 (6.6%)	7/76 (9.2%)	RR 0.75 (0.26 to 2.15)	23 fewer per 1000 (from 68 fewer to 106 more)	LOW
Adverse events - Dyspepsia											
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[19]	none	0/30 (0%)	0/30 (0%)	not estimable	not estimable	VERY LOW
Adverse events - Diarrhoea											
2[18]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[15]	none	3/76 (3.9%)	4/76 (5.3%)	RR 0.75 (0.18 to 3.17)	13 fewer per 1000 (from 43 fewer to 114 more)	LOW
Adverse events - Decreased appetite											
1[20]	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[15]	none	45/137 (32.8%)	21/63 (33.3%)	RR 0.99 (0.65 to	3 fewer per 1000 (from	LOW

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PUFA	Placebo	Relative (95% CI)	Absolute	Quality
		risk of bias							1.5)	117 fewer to 167 more)	
Adverse events - Stomach ache											
1[20]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[21]	none	63/137 (46%)	25/63 (39.7%)	RR 1.16 (0.81 to 1.65)	63 more per 1000 (from 75 fewer to 258 more)	MODERATE

[1] Assareh 2012, Barragan 2014, Johnson 2009, Vaisman 2008, Hariri 2012
[2] Confidence intervals are non-overlapping and test for heterogeneity is statistically significant (I2=58%)
[3] Confidence intervals incorporate clinically important benefit and no clinically important difference.
[4] Barragan 2014, Manor 2012, Gustafsson 2010, Bos 2015, Widenhorn-Muller 2014
[5] Includes unblinded study in which methylphenidate dose was adjusted by unblinded clinician and was difference across groups, and dropout rate was significantly higher in control group.
[6] Barragan 2014
[7] Single unblinded study. Methylphenidate dose was adjusted by unblinded clinician and differed between groups, and dropout rate was significantly higher in control group.
[8] Manor 2012, Gustafsson 2010, Widenhorn-Muller 2014
[9] Barragan 2014, Johnson 2009
[10] One of two studies unblinded and methylphenidate dose was adjusted by unblinded clinician and differed between groups, and dropout rate was significantly higher in control group..
[11] Widenhorn-Muller 2014
[12] Working memory is a surrogate outcome for academic performance.
[13] Johnson 2009, Dubnov-Raz 2014, Vaisman 2008, Hariri 2012, Bélanger 2009, Behdani 2013
[14] Number leaving the study early is a surrogate outcome for treatment acceptability.
[15] Confidence intervals incorporate clinically important benefits and harms.
[16] Stevens 2003, Perera 2012, Voigt 2001, Manor 2012, Gastafsson 2010, Bos 2015, Widenhorn-Muller 2014
[17] Manor 2012, Barragan 2014
[18] Gustafsson 2010, Barragan 2014
[19] Effect size not estimable.
[20] Manor 2012
[21] Confidence intervals incorporate clinically important harm and no clinically important difference.

Appendix I: Forest plots

I.1 Question 1: Elimination/restriction diets for ADHD

Figure 3: 'Few food' diet vs control. Parent-rated ADHD symptoms (up to 3 months)

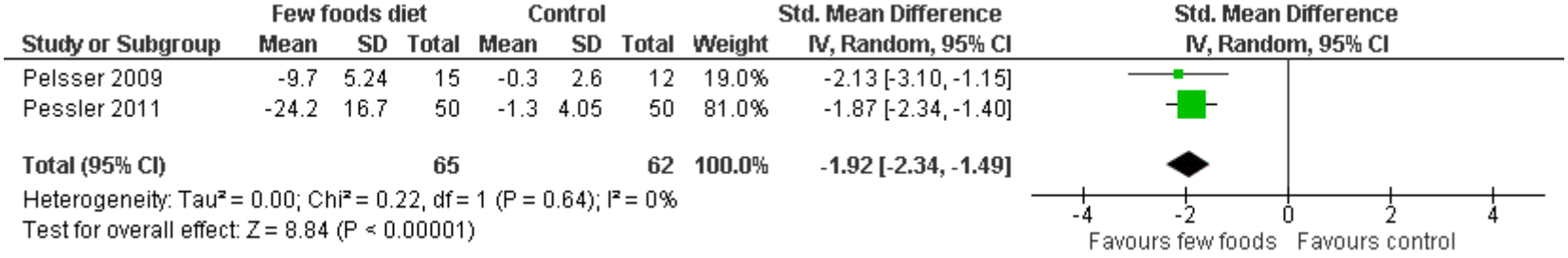

Figure 4: 'Few food' diet vs control. Teacher-rated ADHD symptoms (up to 3 months)

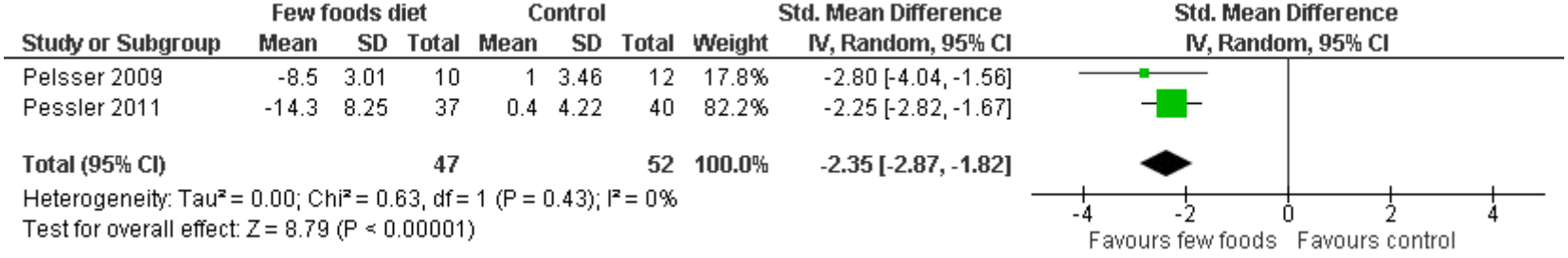

Figure 5: 'Few food' diet vs control. Parent-rated Functional status (up to 3 months)

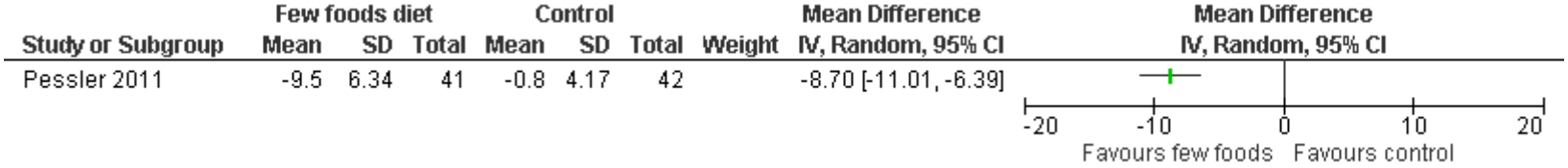

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Figure 6: 'Few food' diet vs control. Parent-rated Functional status (up to 3 months)

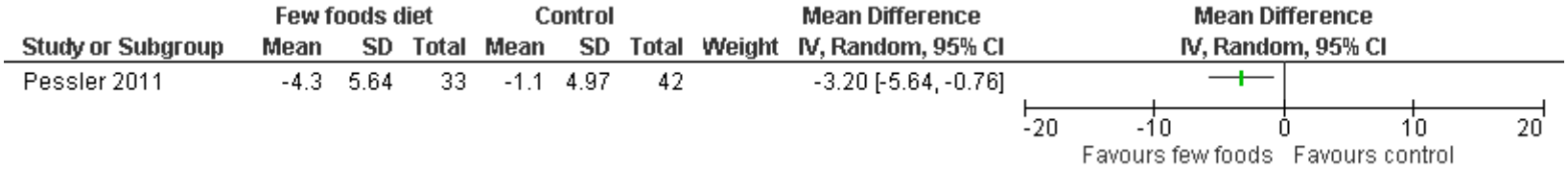

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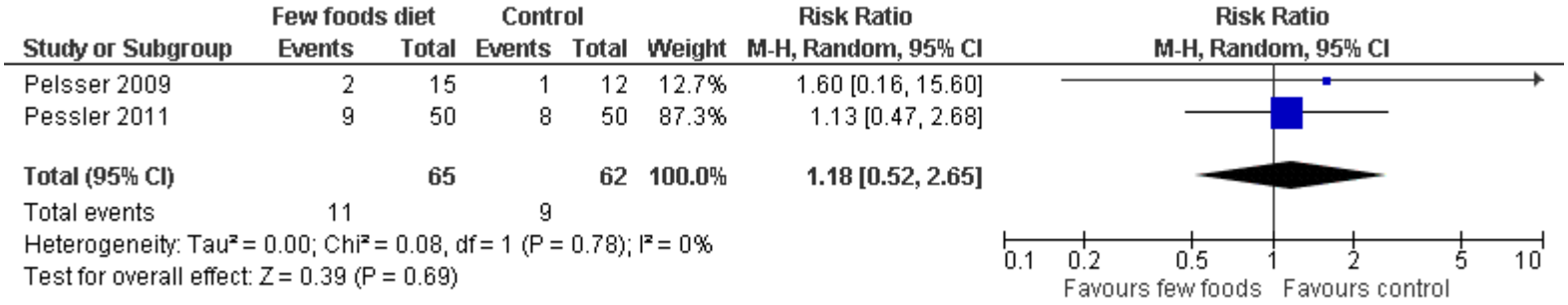
Figure 7: 'Few food' diet vs control. Number leaving study early (up to 3 months)



I.21 Question 2: Polyunsaturated fatty acids (PUFAs) for ADHD

Figure 8: PUFA vs control. Parent-rated ADHD symptoms (up to 3 months)

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Omega 3/6								
Assareh 2012, 274mg/d	-21	7.94	20	-24	6.56	20	16.4%	0.40 [-0.22, 1.03]
Barragan 2014, 732mg/d	-14.46	4.95	30	-13.83	4.68	30	20.1%	-0.13 [-0.64, 0.38]
Johnson 2009, 732mg/d	-3.78	7.14	34	-1.65	4.54	30	20.5%	-0.35 [-0.84, 0.15]
Subtotal (95% CI)			**84**			**80**	**56.9%**	**-0.06 [-0.47, 0.35]**
Heterogeneity: Tau² = 0.05; Chi² = 3.44, df = 2 (P = 0.18); I² = 42%								
Test for overall effect: Z = 0.30 (P = 0.77)								
1.1.2 Omega 3								
Vaisman 2008, 268mg/d	-4.03	7.15	39	-2.35	3.73	21	19.2%	-0.27 [-0.80, 0.26]
Hariri 2012, 900mg/d	-3.42	4.54	53	-0.1	4.57	50	23.9%	-0.72 [-1.12, -0.32]
Subtotal (95% CI)			**92**			**71**	**43.1%**	**-0.53 [-0.97, -0.09]**
Heterogeneity: Tau² = 0.05; Chi² = 1.80, df = 1 (P = 0.18); I² = 44%								
Test for overall effect: Z = 2.36 (P = 0.02)								
Total (95% CI)			**176**			**151**	**100.0%**	**-0.25 [-0.60, 0.10]**
Heterogeneity: Tau² = 0.09; Chi² = 9.64, df = 4 (P = 0.05); I² = 58%								
Test for overall effect: Z = 1.43 (P = 0.15)								
Test for subgroup differences: Chi² = 2.35, df = 1 (P = 0.13), I² = 57.4%								

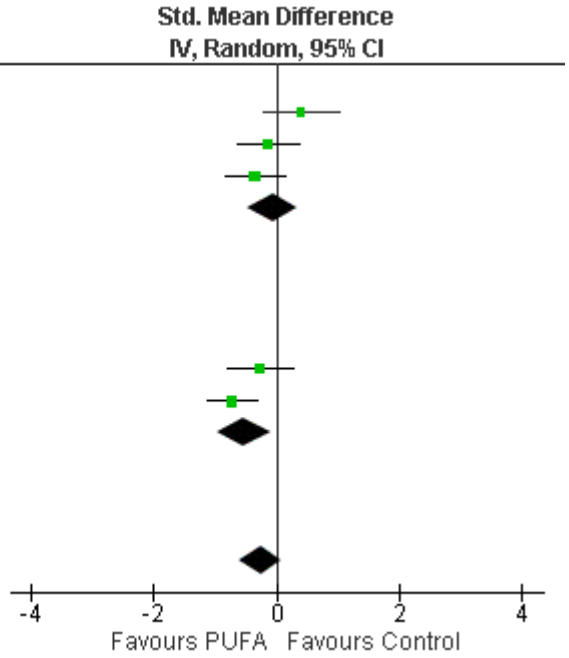


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Figure 9: PUFA vs control. Parent-rated ADHD symptoms (3 to 6 months)

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 Omega 3/6								
Barragan 2014, 732mg/d	-16.53	4.59	30	-15.2	4.51	30	15.6%	-0.29 [-0.80, 0.22]
Subtotal (95% CI)			**30**			**30**	**15.6%**	**-0.29 [-0.80, 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.11 (P = 0.27)								
1.2.2 Omega 3								
Manor 2012, 480mg/d	-5.36	9.46	98	-3.1	9.61	42	29.4%	-0.24 [-0.60, 0.13]
Gustafsson 2010, 503mg/d	-7.2	17.64	46	-6.6	17.14	46	23.6%	-0.03 [-0.44, 0.37]
Bos 2015, 1300mg/d	-1.2	3.05	20	1.1	2.76	20	9.9%	-0.78 [-1.42, -0.13]
W'horn-M'r 2014, 1440mg/d	-0.33	0.54	39	-0.3	0.49	45	21.5%	-0.06 [-0.49, 0.37]
Subtotal (95% CI)			**203**			**153**	**84.4%**	**-0.21 [-0.47, 0.05]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.14$, df = 3 (P = 0.25); $I^2 = 28\%$								
Test for overall effect: Z = 1.57 (P = 0.12)								
Total (95% CI)			**233**			**183**	**100.0%**	**-0.21 [-0.42, -0.01]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.25$, df = 4 (P = 0.37); $I^2 = 6\%$								
Test for overall effect: Z = 2.01 (P = 0.04)								
Test for subgroup differences: $Chi^2 = 0.08$, df = 1 (P = 0.78), $I^2 = 0\%$								

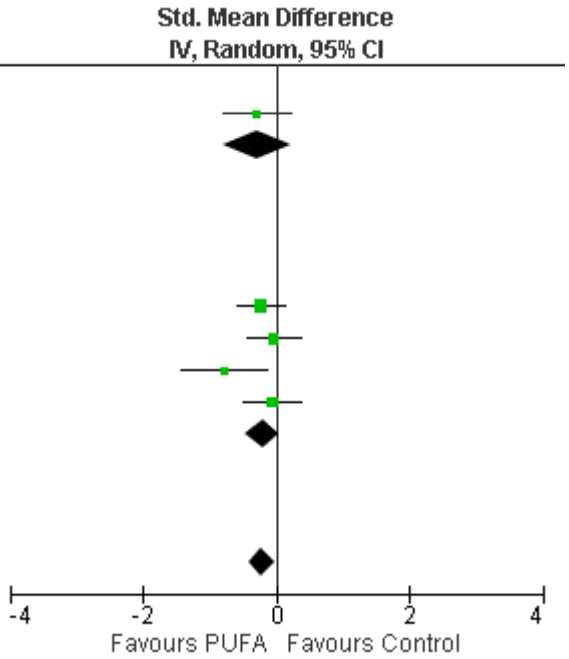

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Figure 10: PUFA vs control. Parent-rated ADHD symptoms (over 6 months)

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Control Mean	Control SD	Control Total	Std. Mean Difference IV, Random, 95% CI
1.3.1 Omega 3/6							
Barragan 2014, 732mg/d	-17.7	4.64	30	-15.6	4.5	30	-0.45 [-0.97, 0.06]

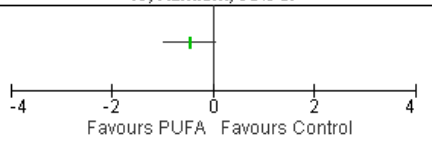

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Figure 11: PUFA vs control. Teacher-rated ADHD symptoms (3 to 6 months)

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.5.2 Omega 3								
Manor 2012, 480mg/d	-1.8	9.97	93	-2.21	11.29	42	39.8%	0.04 [-0.33, 0.40]
Gustafsson 2010, 503mg/d	-6.6	18.41	46	-2.8	16.6	46	31.5%	-0.21 [-0.62, 0.19]
W'horn-M'r 2014, 1440mg/d	-0.27	0.61	39	-0.2	0.55	45	28.7%	-0.12 [-0.55, 0.31]
Subtotal (95% CI)			**178**			**133**	**100.0%**	**-0.09 [-0.32, 0.14]**

Heterogeneity: Tau² = 0.00; Chi² = 0.86, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)

Test for subgroup differences: Not applicable

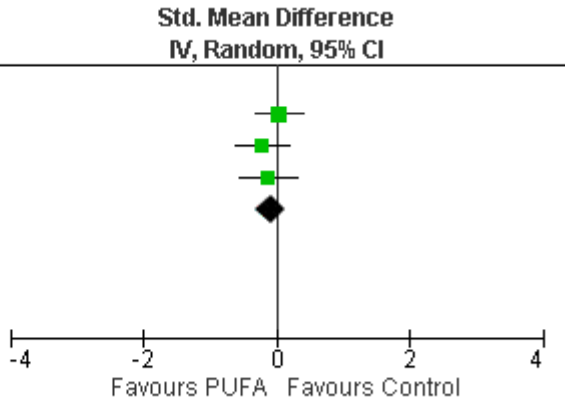

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Figure 12: PUFA vs control. Clinician-reported Functional status (up to 3 months)

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 Omega 3/6								
Barragan 2014, 732mg/d	-2.84	0.77	30	-2.03	0.99	30	41.6%	-0.81 [-1.26, -0.36]
Johnson 2009, 732mg/d	-0.58	0.87	34	-0.13	0.5	30	58.4%	-0.45 [-0.79, -0.11]
Subtotal (95% CI)			**64**			**60**	**100.0%**	**-0.60 [-0.95, -0.25]**

Heterogeneity: Tau² = 0.02; Chi² = 1.56, df = 1 (P = 0.21); I² = 36%
Test for overall effect: Z = 3.38 (P = 0.0007)

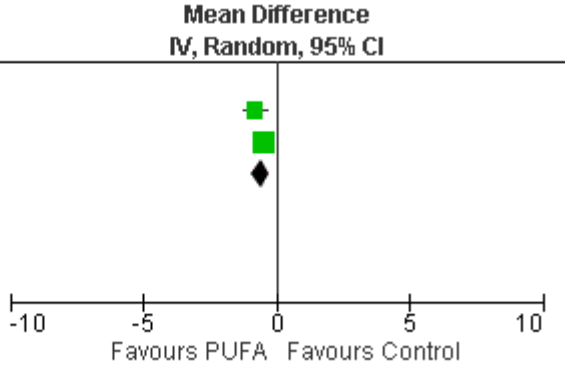

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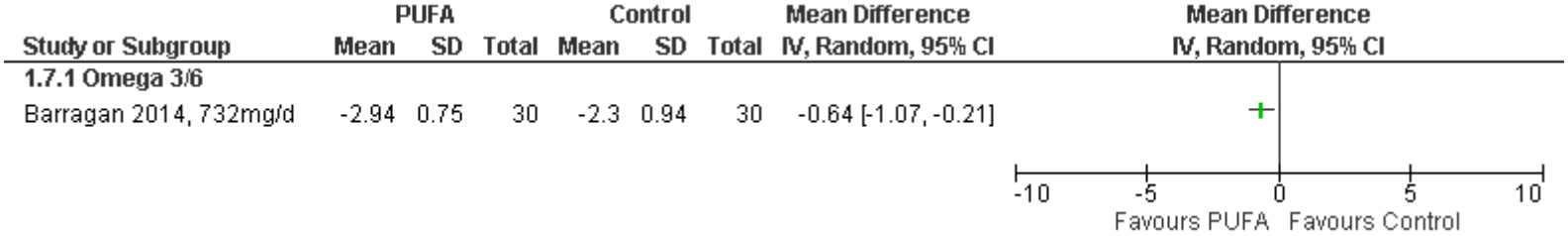
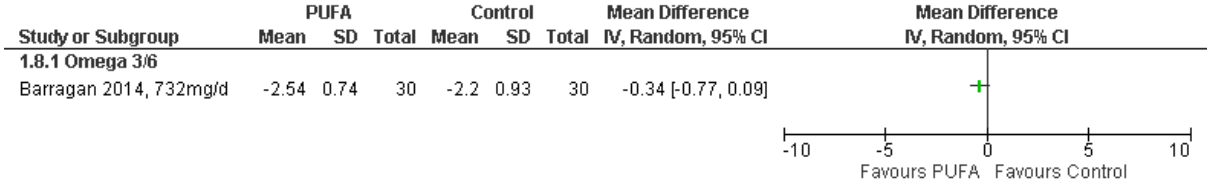
Figure 13: PUFA vs control. Clinician-reported Functional status (3 to 6 months)



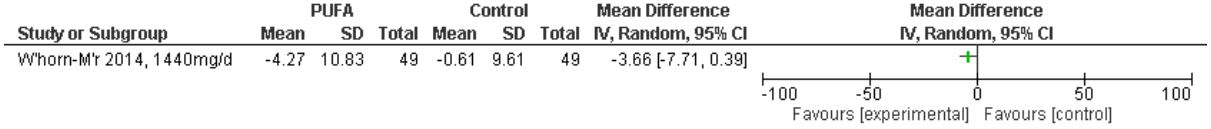
1

Figure 14: PUFA vs control. Clinician-reported Functional status (over 6 months)



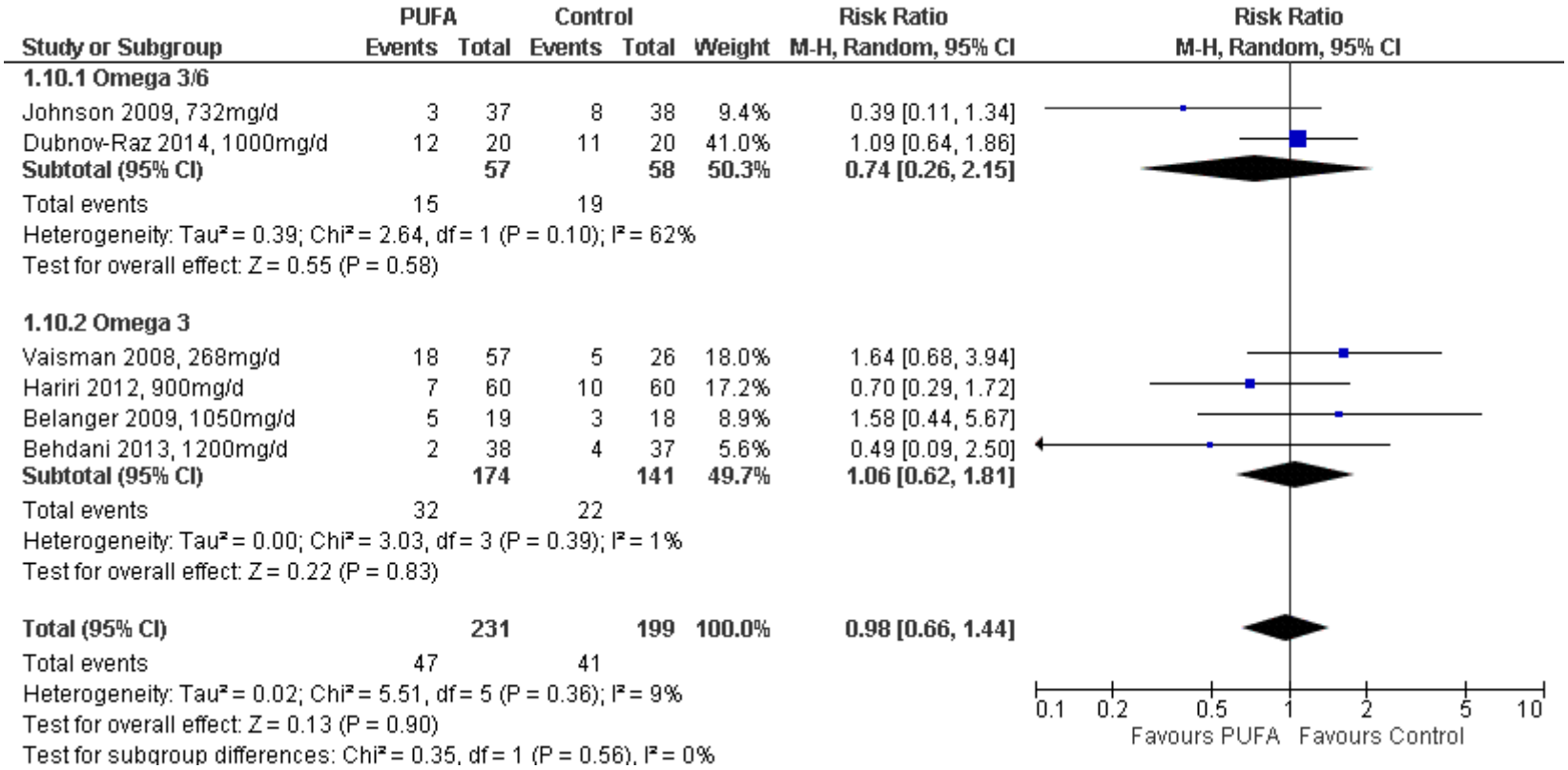
2

Figure 15: PUFA vs control. Academic performance – working memory (surrogate outcome) (3 to 6 months)



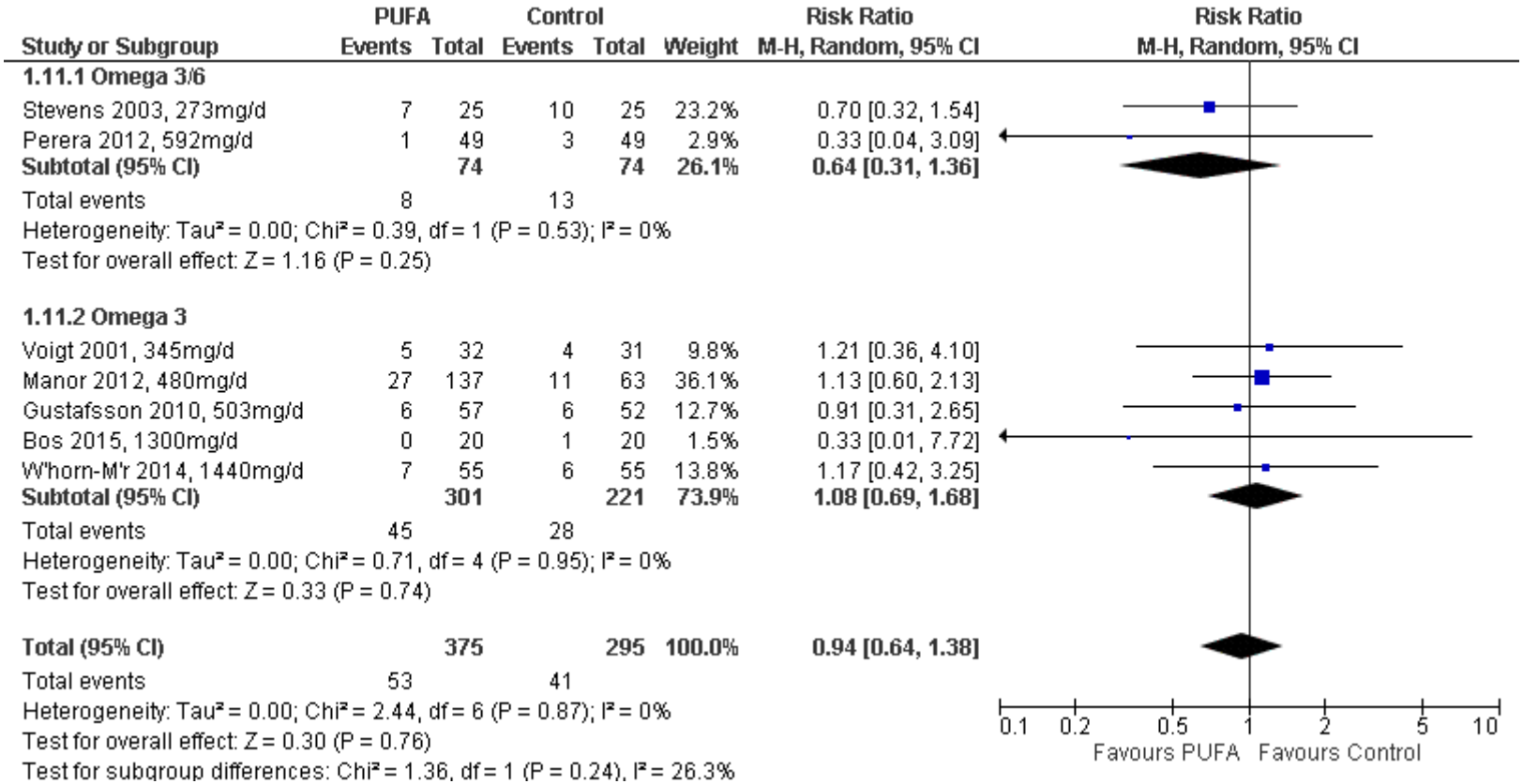
3

Figure 16: PUFA vs control. Treatment acceptability – number leaving study early (surrogate outcome) (up to 3 months)



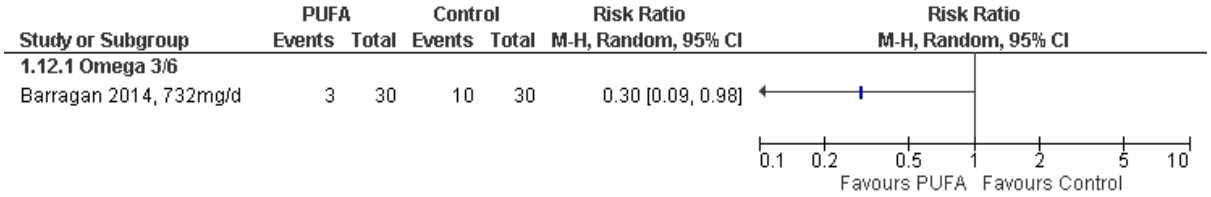
1

Figure 17: PUFA vs control. Treatment acceptability – number leaving study early (surrogate outcome) (3 to 6 months)



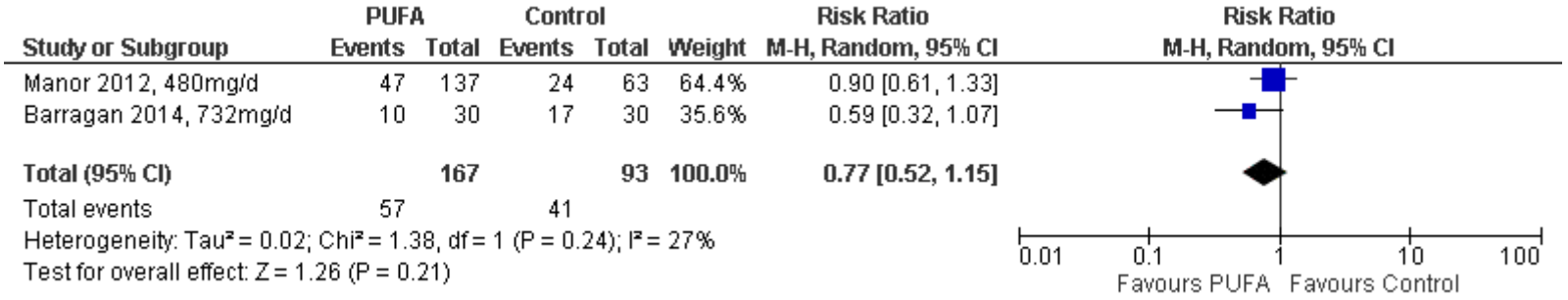
1

Figure 18: PUFA vs control. Treatment acceptability – number leaving study early (surrogate outcome) (over 6 months)



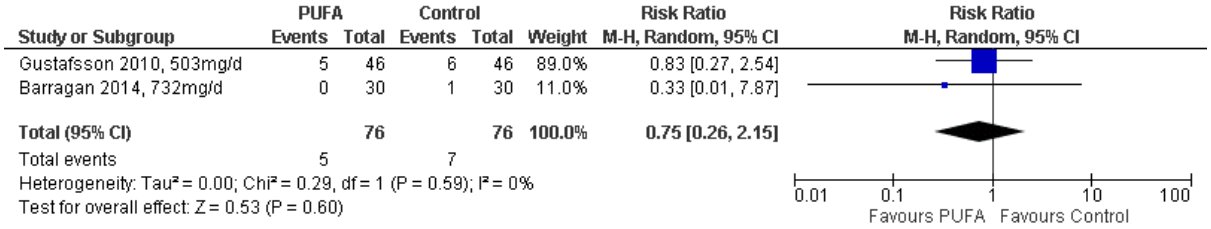
1

Figure 19: PUFA vs control. Adverse effects – headache



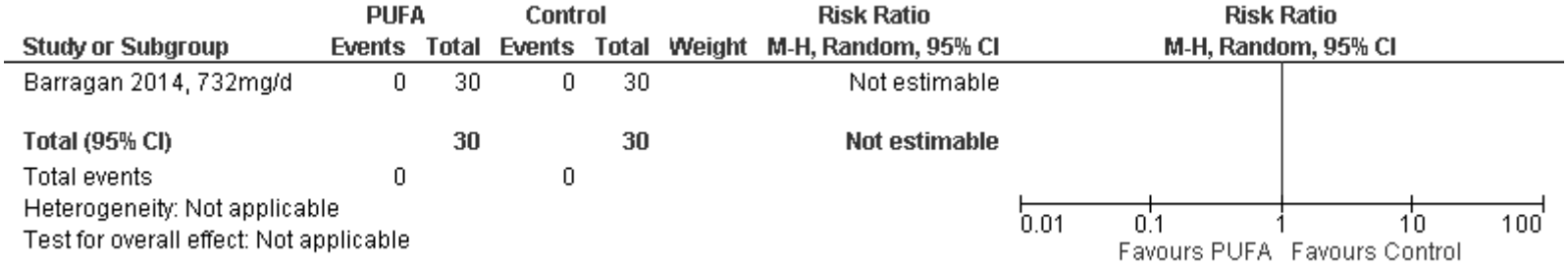
2

Figure 20: PUFA vs control. Adverse effects – nausea



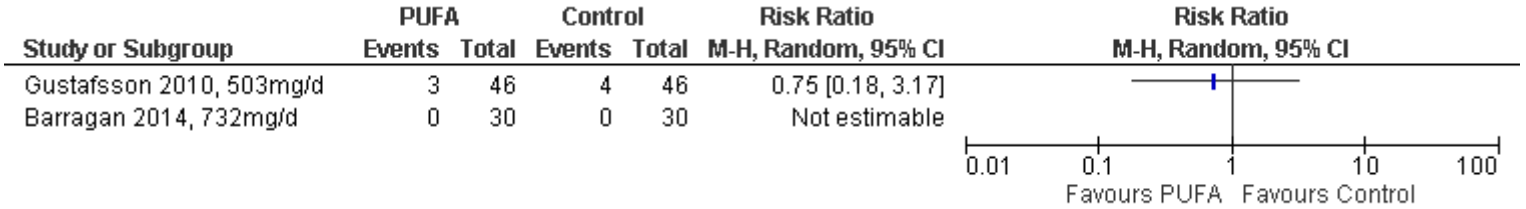
1

Figure 21: PUFA vs control. Adverse effects – dyspepsia



2

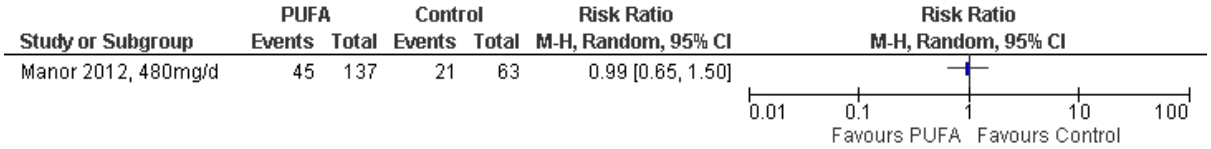
Figure 22: PUFA vs control. Adverse effects – diarrhoea



3

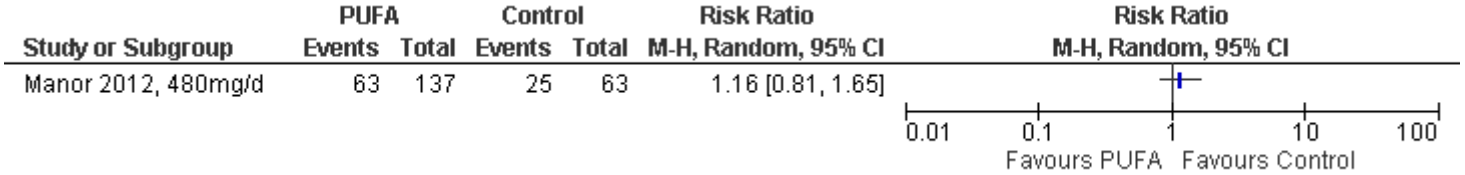
4

Figure 23: PUFA vs control. Adverse effects – decreased appetite



1

Figure 24: PUFA vs control. Adverse effects –stomach ache



Appendix J: Economic search strategy

A single economic search was conducted for both review questions. Databases that were searched, together with the number of articles retrieved from each database are shown in Table 24. The MEDLINE search strategy is shown in Table 25. The same strategy was translated for the other databases listed.

Table 24: Economic search summary

Economics	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	02/07/2015	1946 to June wk 4 2015	187
MEDLINE in Process (Ovid)	02/07/2015	July 1 2015	17
Embase (Ovid)	02/07/2015	1974 to 2015 July 01	519
NHS Economic Evaluation Database (NHS EED) (legacy database)	02/07/2015	2 of 4 April 2015	0
Health Technology Assessment (HTA Database)	02/07/2015	2 of 4 April 2015	2

Table 25: Economic search strategy

Database: Medline/MiP
Strategy used: 1 (attenti$ or disrupt$ or impulsiv$ or inattenti$).sh. 87309 2 Attention Deficit Disorder with Hyperactivity/ 21463 3 "attention deficit and disruptive behavior disorders"/ 2204 4 ((attenti* or disrupt*) adj3 (adolescen* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).tw. 44848 5 (disruptive* or impulsiv* or inattentiv*).tw. 20541 6 (adhd or addh or ad hd or ad??hd).tw. 14364 7 (attenti* adj3 deficit*).tw. 19685 8 Hyperkinesis/ 3762 9 (hyperkin* or hyperactiv*).tw. 41606 10 (hyper adj1 (activ* or kin*)).tw. 475 11 hkd.tw. 94 12 (minimal adj1 brain).tw.735 13 overactiv*.tw. not overactive bladder*.ti. 8714 14 (over adj1 activ*).tw. not overactive bladder*.ti. 6875 15 or/1-14 161794 16 Diet/ 115014 17 ((eliminat* or restrict*) adj4 (diet* or food* or nutriti*)).tw. 17935 18 exp Flavoring Agents/ 196857 19 (flavo* adj4 (food* or agent*)).tw. 2056 20 (flavo* adj1 (aroma or compound)).tw. 468 21 (sweeten* or sugar* or candy).tw. 82007 22 (acesulfam* or acetosulfam or sunette or alitame or aspart* or apm or canderel or hermesetas or equa or fliks or "mini d" or nutrasweet or sucrandel or "tri sweet" or milisucre or nozucar or (syrup adj1 (maize or corn)) or cyclamate* or "cyclamic acid" or ibiosuc or sucaryl or sukriso or fructose or dextrofructose or diabetin or laevoral or laevoran or laevosan or laevulose or levugen or levulos* or hernandulcin or calarose or insubeta or inversol or invertosteril or nulomoline or solinvert or travert or isomalt or palatinit or leucrose or maltitol or malbit or mannitol or cytal or sorbit*or monellin or neotame or saccharin* or goldswite or "benzoic sulfimide" or benzosulfimide or benzosulphimide or garantose or glu?id* or "ortho sulfobenzimide" or "ortho sulfobenzoic acid" or saccharod or

Database: Medline/MiP

saccharol or "sweet n low" or sweeta or sweetex or sweetnin or sykose or willosetten or cr?stallose or dagutan or kristallose or saxin or glucitol or glucohexitol or diakarman or glycitol or gulitole or karion or neosorb or sorbo* or stevia* or steviosi* or stevoside or sucralose or splenda or sucrose or microtal or saccharose or "saccharum album" or tabfine or (sweet adj2 protein) or thaumatin or xylit* or zerocal or sukrana or sucraplus or canys or cukren or nevella or glucose or isoglucose or lactose or maltose or osmitrol or osmofundin or molasse* or yal or sorbilax or medivac or sweetleaf* or ((rebaudianum adj1 eupatorium) or asugrin or saccharoid or nivitin or sionon or sorbelite)).tw. 486704

23 Caseins/ 13629

24 (casein* or phosphocasein).tw. 22399

25 exp Glutens/ 6805

26 (glute* or secalin* or hordein*).tw. 15061

27 exp Food additives/ 239057

28 ((food adj4 (additive* or preservative*)) or AFCE).tw. 4170

29 ((food or agent*) adj4 (colour* or color* or dye*)).tw. 2818

30 Tartrazine/ 315

31 (alkann* or anchus* or shikalkin or "allura red" or canthaxanthin* or orobronze or carmine or "carminic acid" or carmoisine or curcumin* or nanocurc or turmeric or demethoxycurcumin* or didemethoxycurcumin or bisdemethoxycurcumin or shikonin or tartrazine or "hydrazine yellow" or erioglaucine or alphazurine or indigotine).tw. 9050

32 Sodium Benzoate/ 251

33 (benzoate or benzoylate or carboxybenzene or "dracylic acid" or "phenylformic acid" or "benzoic acid").tw. 14373

34 exp Salicylates/ 62563

35 (salicylate* or salicylic).tw. 16278

36 exp Nitrites/ 17534

37 (nitrite* or "nitrous acid").tw. 24583

38 (((monosodium or sodium) adj2 (glutamate or monoglutamate)) or monosodiumglutamate or "glutamic acid" or "glutaminate sodium" or glutavene or sodiumglutamate or msg or vestin or accent).tw. 21900

39 exp Caffeine/ 20252

40 (caffein* or animine or cafein or coffe* or guaranine or guarin or methyltheobromine or "no doz" or nodoz or "pac compound" or thein or trimethylxanthine or vivarin or percoffedrinol or percutafeine or caffedrine or durvitan or dexitac or (quick adj1 pep)).tw. 29483

41 oligoantigenic.tw. 32

42 or/16-41 960754

43 exp Fatty Acids/ 388601

44 (fatty adj4 acid*).tw. 147394

45 (((polyunsaturated or unsaturated) adj4 (fat* or lipid*)) or (ufa* or pufa*)).tw. 30690

46 aliphatic acid*.tw. 327

47 ((omega or n) adj4 fatty).tw. 15599

48 ("omega 3" or "omega forte" or "bilantin omega" or "conchol 36" or "eicosa e" or eicosapen or epaisidin or epanova or sakana).tw. 7901

49 (((docosahexaenoic or docosahexenoic) adj1 acid*) or docosahexaenoate or dhasco).tw. 8280

50 (((linolenic or octadecatrienoic) adj1 acid*) or linolenate).tw. 6840

51 (((eicosapentaenoic or eicosapentanoic or timnodonic or icosapentaenoic) adj1 acid*) or eicosapentaeonate or icosapentaenoate).tw. 6116

52 ((hexadecatrienoic or stearidonic) adj1 acid*).tw. 206

53 (((eicosatrienoic or icosatrienoic) adj1 acid*) or eicosatrieonate or icosatrieonate).tw. 554

54 (((eicosatetraenoic or arachidonic or icosatetraenoic) adj1 acid*) or eicosatetraenoate).tw. 33179

55 ((heneicosapentaenoic or docosapentaenoic or tetracosapentaenoic or nisinic) adj1 acid*).tw. 638

56 "omega 6".tw. 2301

57 (((linoleic or octadecadienoic or linolelaidic or linoelaidic or linoic or linolic or dienoic) adj1 acid*)

Database: Medline/MiP

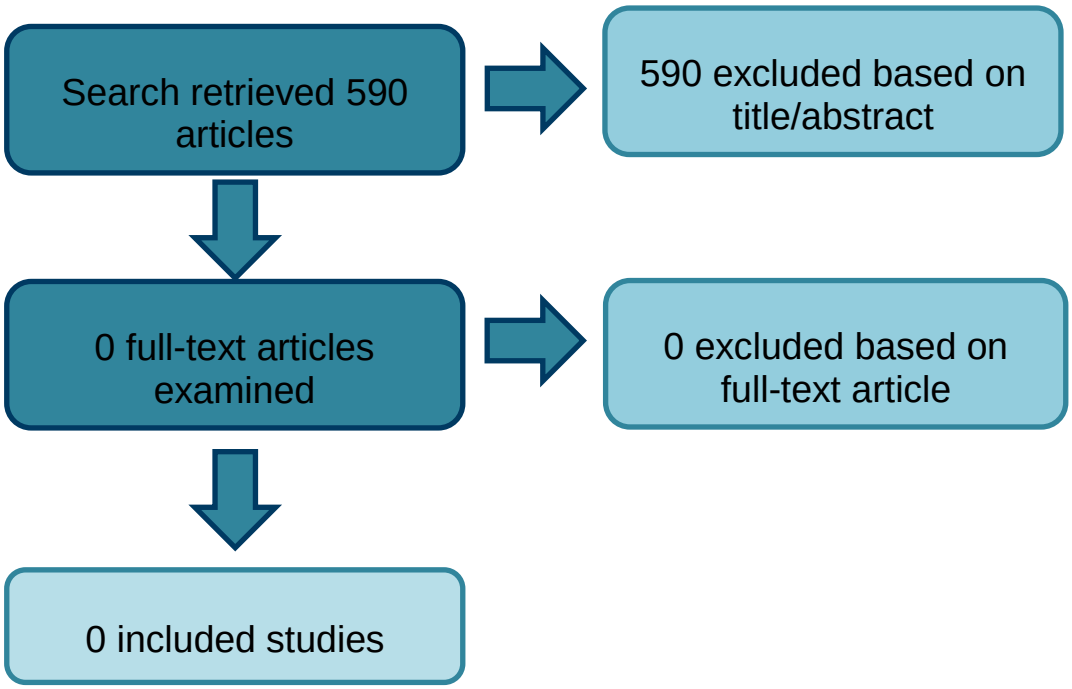
or linoleate or linolate).tw. 16291
58 ((linolenic or gamolenic) adj1 acid*).tw. 6287
59 ((calendic or eicosadienoic) adj1 acid*).tw. 124
60 ((gamma adj1 linolenic) or dhla or dihomogammalinolenic).tw. 1870
61 ((tetraenoic adj1 acid*) or arachidonate or "vitamin f").tw. 5927
62 ((docosadienoic or docosapentaenoic or tetracosatetraenoic) adj1 acid*).tw. 652
63 or/43-62 450895
64 42 or 63 1336759
65 15 and 64 7204
66 Economics/ 26629
67 exp "Costs and Cost Analysis"/ 188884
68 Economics, Dental/ 1861
69 exp Economics, Hospital/ 20355
70 exp Economics, Medical/ 13568
71 Economics, Nursing/ 3918
72 Economics, Pharmaceutical/ 2580
73 Budgets/ 9991
74 exp Models, Economic/ 10868
75 Markov Chains/ 10549
76 Monte Carlo Method/ 21257
77 Decision Trees/ 9141
78 econom$.tw. 164178
79 cba.tw. 8891
80 cea.tw.16811
81 cua.tw. 813
82 markov$.tw. 12380
83 (monte adj carlo).tw. 21998
84 (decision adj3 (tree$ or analys$)).tw. 8811
85 (cost or costs or costing$ or costly or costed).tw. 322314
86 (price$ or pricing$).tw. 24110
87 budget$.tw. 17924
88 expenditure$.tw. 36545
89 (value adj3 (money or monetary)).tw.1403
90 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. 2915
91 or/66-90 682549
92"Quality of Life"/ 127151
93 quality of life.tw. 147505
94 "Value of Life"/ 5451
95 Quality-Adjusted Life Years/ 7646
96 quality adjusted life.tw. 6465
97 (qaly$ or qald$ or qale$ or qtime$).tw. 5313
98 disability adjusted life.tw. 1298
99 daly$.tw. 1268
100 Health Status Indicators/ 20642
101 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 16140
102 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 1035
103 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 2869
104 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 21

Database: Medline/MiP
105 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. 336
106 (euroqol or euro qol or eq5d or eq 5d).tw. 4265
107 (qol or hql or hqol or hrqol).tw. 26548
108 (hye or hyes).tw. 54
109 health$ year$ equivalent$.tw. 38
110 utilit$.tw. 118417
111 (hui or hui1 or hui2 or hui3).tw. 895
112 disutili$.tw. 232
113 rosser.tw. 71
114 quality of wellbeing.tw. 5
115 quality of well-being.tw. 339
116 qwb.tw. 175
117 willingness to pay.tw. 2400
118 standard gamble$.tw. 667
119 time trade off.tw. 774
120 time tradeoff.tw. 208
121 tto.tw. 618
122 or/92-121 337398
123 91 or 122 974082
124 65 and 123 261
125 limit 124 to english language 245
126 animals/ not humans/ 3967288
127 125 not 126 187

1

Appendix K: Economic review flowchart

A single economic search was conducted for both review questions.



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