

Effects of oily fish/omega-3 fatty acids on the behavioural, cognitive and educational outcomes of normal school children: A systematic review

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**Effects of Oily Fish/Omega-3 Fatty Acids on the Behavioural,
Cognitive and Educational Outcomes of Normal School
Children: A Systematic Review**

**A WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT
COLLABORATION REPORT**

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WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION (WMHTAC)

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

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EXECUTIVE SUMMARY

Background

Omega-3 fatty acids are structural components of neuronal and other cell membranes and are essential for normal brain development and function as they cannot be synthesised de novo in humans and must therefore be provided by dietary source. It has also been proposed that the intake of omega-3 fatty acids and fish oil may be linked to children's behaviour and cognitive function.

Aim

To assess whether dietary or supplemental oily fish/omega-3 fatty acids alter the behavioural, cognitive and educational outcomes of normal school children.

Methods

Detailed searches of a number of electronic bibliographies were performed through to April 2006. Citation searches of included studies were undertaken and no language restrictions were applied. Randomised, quasi-randomised and non-randomised controlled studies were sought. Studies were assessed for inclusion according to predefined criteria. Data extraction and quality assessment were also undertaken.

Results

Two randomised controlled trials in Japanese and Thai school children were included. Both trials allocated children to receive fish oil-fortified foods or placebo. The doses and duration of intervention varied considerably across trials, i.e. trial 1 - omega-3 fatty acids at 1.3 g/day for 6-month period and trial 2 - 3.6 g/week for 3-months. Trial 1 reported no difference in examination performance between omega-3 and control. Trial 2 reported no differences in verbal aggression, anger, hostility, hyperactivity or inattention. Significant reductions seen in physical aggression and impulsivity were reported in girls receiving omega-3. This improvement was not seen in boys. Extra-aggression was increased in the omega-3 group but not the control group. Although double blind, given their limited methodological reporting, these trials were judged to be of poor to moderate quality.

Conclusions

There is insufficient evidence to either confirm or refute the hypothesis for the effect of omega-3 and fish oil on the behaviour, cognition and educational outcomes in normal school children. Well-conducted randomised controlled are therefore needed. Until such trials report their findings, there is no clear basis for changing the current recommendation of the consumption of at least two portions of fish per week, one of which should be oily, or the equivalent of 0.2g/day of omega-3 fatty acid.

Food Standards Agency (FSA) Systematic Review

In July 2006, after completion of the present review, the FSA published a systematic review that considered the effects of dietary supplementation with omega-3 fish oil upon the educational performance of UK school children. The FSA study included five randomised controlled trials that investigated the effects of supplemental fish oils in schoolchildren with various neuro-developmental disorders. The studies were small, the interventions and outcomes measures varied, and the reported results inconsistent. The reviewers concluded: *“All studies have been carried out in children with varying degrees of neuro-developmental disorder, findings were mixed and inconclusive; applicability of such data to mainstream children is questionable”*.

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1 AIM OF THE REVIEW

The aim of this systematic review is to assess whether dietary or supplemental oily fish or omega 3 fatty acids alter the behaviour, cognitive and education outcomes of normal school children.

The primary question to be answered by the review was:

- Do dietary or supplemental omega-3 fatty acids improve the behaviour, cognitive function and educational outcomes of children of school age?

Secondary questions included:

- Does any beneficial effect depend on the dose of omega-3 fatty?
- If there are any effects, do they differ between dietary or supplemental omega-3 fatty acid sources?
- Does any effect differ between fish and non-fish omega-3 fatty acid sources?
- Does any benefit depend on the nature of the comparator?
- Is any benefit stronger with longer trial duration?
- What are the side effects associated with increased omega-3 fatty acid intake, and what is their prevalence?

2 BACKGROUND

Fish oils and fatty fish contain high concentrations of long chain omega-3 polyunsaturated fatty acids. Dietary intake of fish and omega-3 fatty acids have been linked with a number of health benefits, most notably protection against cardiovascular disease.^{1,2}

In addition to their potential cardiovascular effects, omega-3 fatty acids are structural components of neuronal and other cell membranes and are essential for normal brain development and function as they cannot be synthesised de novo in humans and must therefore be provided by dietary source.³ Dietary

consumption of fish oil and omega-3 fatty acids has been linked with neuropsychiatric disorders and neurodevelopment in infancy. Epidemiological studies have suggested that high fish consumption is inversely associated with cognitive decline, and/or the development of dementia or Alzheimer's disease in middle age and the elderly.⁴ At the other end of the age scale, healthy pre-term infants randomised to receive dietary supplementation with long-chain polyunsaturated fatty acids, including omega-3, have been shown to have superior visual acuity than controls.⁵

It has also been proposed that the intake of omega-3 fatty acids and fish oil may be linked to children's behaviour and cognitive function. A number of studies have shown that common behavioural disorders of children including attention deficit hyperactivity disorder (ADHD), dyslexia and autistic spectrum disorders may involve functional deficiencies or imbalances in the omega-3 fatty acids.⁶⁻⁸ In addition, randomised double-blind controlled trials have shown the effect of omega-3 fatty acids and fish oil on the outcomes of children with previously diagnosed behavioural problems. Richardson and Puri compared supplements containing omega-3 fatty acids to placebo in 41 children with diagnosed ADHD aged 8-12 years. After 12-weeks, the mean scores for cognitive problems and general behaviour problems were significantly lower for the supplement group than for the placebo group.⁹ More recently, Richardson and Montgomery assessed the effects of fish oil supplements in school children of 5 to 12 years of age who met DSM-IV criteria for developmental coordination disorder. Although no effect of supplementation on motor skills was seen, significant improvements were found in reading, spelling and behaviour over a 3-month period.¹⁰

These observations have led to the hypothesis that enhancement of fish consumption and omega-3 fatty acids may have beneficial effects on the behaviour and cognitive and education outcomes of children without diagnosed behaviour disorders. No previous systematic review was identified that has addressed this hypothesis.

2.1 Omega-3 Fatty Acids and Their Dietary Sources

Polyunsaturated fatty acids (PUFAs) can be classified, on the basis of their chemical structure, into two groups: omega-3 (n-3) and omega-6 (n-6) fatty acids. Omega-3 means that the first double bond in this family of PUFAs is three carbons from the methyl end of the molecule. Omega-3 and 6 fatty acids cannot be synthesised in the human body, yet these are necessary for proper physiological functioning and are thus called 'essential fatty acids'. Principle members of the omega-3 fatty acid family include alpha-linolenic acid (ALA; 18:3, n-3), eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3) and docosapentaenoic acid (DPA, 22:5 n-3).

Fish and fish oil are rich sources of omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are present in fatty fish and algae. Alpha-linolenic acid (ALA) is an omega-3 fatty acid present in seeds and oils, green leafy vegetables, and nuts and beans (such as walnuts and soyabeans). Fish and fish oil are preferred sources of omega-3 fatty acid as they provide EPA and DHA directly, therefore avoiding the competition for enzymes to convert ALA to EPA. Levels of EPA and DHA in fish are summarised in table 1. For those who do not like fish, supplements containing very long-chain n-3 fatty acids (either fish oil or algal oil) or foods fortified with them are an option.

2.2 UK Population Intake of Omega-3 Fatty Acids and Fish Oils

It is generally accepted that the majority of the UK population does not consume enough fish, particularly oily fish, for health.¹¹ The National Diet and Nutrition Survey shows that at most a third of people in the UK eat oil-rich fish on a regular basis and the average amongst these consumers is only 200g (i.e. one portion per week).^{11,12} Amongst children, only 5 to 10 percent consume fish with an average of 100mg per portion (i.e. one small portion per week) (see Table 2). It is becoming clear that the balance between intakes of the n-3 and n-6 fatty

acids may be more important for health than the actual amounts in the diet. This is because of accumulating knowledge of how these two families interact metabolically. The n-6 fatty acid content of the UK diet has risen substantially over the past couple of decades as the food industry have replaced traditional sources of fat (e.g. lard and butter) with vegetable oils (e.g. sunflower oil, corn oil), in response to research concerning heart disease. However, to some extent, very recently, the balance may have been partially redressed with the increased availability of rapeseed oil (rich in omega 3 alpha-linolenic acid), which is now widely used in the UK.

2.3 Current Dietary Guidelines

Individuals with CHD are encouraged to eat at least one daily meal that includes a fatty fish or take a daily fish oil supplement to achieve a recommended level of 0.9g per day of EPA.¹³ For adults and children without CHD, current UK guidelines advise at least two portions a week of fish, one of which should be oily fish, increasing in the population average consumption of long-chain n-3 PUFA from about 0.1g/day to about 0.2g/day. A maximum of four portions of oily fish per week for adults is recommended given hypothetical concerns about toxic contaminants, particularly mercury.¹¹ Children under 16 years of age and women before and during pregnancy are advised to avoid consumption of large predatory fish such as swordfish, which have accumulated a considerable concentration of mercury. High-quality fish oil supplements usually do not contain these contaminants. Most commercial fish oil capsules (1 g) contain 180 mg of EPA and 120 mg of DHA (see Table 1).

The 2001 census estimates 913,878 children in the West Midlands of school age (5 to 17 years). Based on a consumption of one fish oil capsule per day at a cost of about £30 per year child¹, the cost of providing supplementation to this group would be about £2.7 million per annum.

¹ <http://www.google.co.uk/search?hl=en&q=fish+oil+capsules&meta> [last searched 6th July]

Table 1 Amounts of EPA+DHA in Fish and Fish Oils and the Amount of Fish Consumption Required to Provide 1 g of EPA+DHA

	EPA+DHA Content, g/3-oz Serving Fish (Edible Portion) or g/g Oil	Amount Required to Provide ~1 g of EPA+DHA per Day, oz (Fish) or g (Oil)
Fish		
Tuna		
Light, canned in water, drained	0.26	12
White, canned in water, drained	0.73	4
Fresh	0.24–1.28	2.5–12
Sardines	0.98–1.70	2–3
Salmon		
Chum	0.68	4.5
Sockeye	0.68	4.5
Pink	1.09	2.5
Chinook	1.48	2
Atlantic, farmed	1.09–1.83	1.5–2.5
Atlantic, wild	0.9–1.56	2–3.5
Mackerel	0.34–1.57	2–8.5
Herring		
Pacific	1.81	1.5
Atlantic	1.71	2
Trout, rainbow		
Farmed	0.98	3
Wild	0.84	3.5
Halibut	0.4–1.0	3–7.5
Cod		
Pacific	0.13	23
Atlantic	0.24	12.5
Haddock	0.2	15
Catfish		
Farmed	0.15	20
Wild	0.2	15
Flounder/Sole	0.42	7
Oyster		
Pacific	1.17	2.5
Eastern	0.47	6.5
Farmed	0.37	8
Lobster	0.07–0.41	7.5–42.5
Crab, Alaskan King	0.35	8.5
Shrimp, mixed Species	0.27	11
Clam	0.24	12.5
Scallop	0.17	17.5
Capsules		
Cod liver oil	0.19	5
Standard fish body Oil	0.30	3
Omega-3 fatty acid concentrate	0.50	2

From: <http://www.healthyhearts.com/fishoilomega.htm>

Table 2 UK population levels of fish intake

Age (years)	Sex	Sample	Portion size (grams)			Percent of sample consuming fish
			Minimum	Mean	Maximum	
1.25 to 4.5	M&F	1675	2	47	170	6
4 to 6	M	184	21	57	78	5
	F	8	8	68	162	10
7 to 10	M	256	40	85	178	8
	F	226	14	84	170	8
11 to 14	M	237	48	137	237	7
	F	138	18	137	196	6
15 to 18	M	179	49	114	354	8
	F	210	18	97	198	7
18 to 64	M	766	10	148	340	20
	F	958	4	143	350	21

Adapted from [11]

3 METHODS

3.1 Search Strategy

The following databases were searched:

- MEDLINE (Ovid) 1966 to March Week 5 2006
- EMBASE (Ovid) 1980 to 2006 Week 14
- Cochrane Library (CENTRAL) (Wiley internet version) 2006 Issue 1
- Science Citation Index (Web of Science) 1970 – April 2006
- PsycINFO (Ovid) 1967 to April week 1 2006
- ERIC (CSA Illumina) 'Earliest to current' (searches carried out April 2006)

Searches included text words and index terms, which encompassed: *fish oils, fatty acids, omega 3, essential fatty acids; children, teenagers, adolescents; and learning, educational measurement, behaviour, concentration*. Search strategies are listed in Appendix 1. Bibliographies of identified trials were checked. No language or date restrictions were applied.

3.2 Inclusion & exclusion criteria

Studies were included if they met the following criteria:

- *Study design*: Systematic reviews, randomised or quasi-randomised controlled trials (RCTs), or non randomised comparative studies
- *Population*: Normal children (see below) aged 4 to 18 years. Studies with children with a pre-diagnosed behavioural disorder (e.g. ADHD) were excluded from this review.
- *Intervention*: Dietary advice or supplementation to increase fishy oil and/or omega-3 intake.
- *Comparator*: Placebo, no supplementation or usual diet.

Study selection was carried out by a single reviewer (RST) and checked by a second (MJC).

“Normal children” in the present context means that the study sample populations must not be selected because they satisfy some definition of behavioural and or cognitive deficit. “Normal populations” of schoolchildren would be members of non-specialised schools. The inclusion criteria do not imply that studies have to have actively identified and excluded children with cognitive or behavioural deficit.

3.3 Data extraction strategy & quality assessment

Data extraction and quality assessment was undertaken by a single reviewer (RST) and checked by a second (MJC). The methodological quality of included studies was assessed on the basis of the adequacy of the method of allocation of children to intervention or control group, adequacy of concealment of allocation, level of blinding, use of intention-to-treat-analysis, and description of loss to follow up. An overall quality (Jadad) score was assigned to RCTs.¹⁴

3.4 Data handling and analysis

The characteristics (i.e. patient population, interventions, comparators and outcomes) and methodological quality of each study were summarised in tabular form. Differences between intervention and control arms of studies are reported. Given the limited body of evidence that met the inclusion criteria, pooling of data across studies with meta-analysis did not prove possible.

4 RESULTS

4.1 Quantity of research available

Sensitive rather than specific search strategies were used and therefore a large number of citations were identified. The majority were excluded on the basis of title or abstract. Although a number of RCTs of omega-3/fish oil were identified, many of these were undertaken in children with prior behavioural disorders, in particular attention deficit hyperactivity disorder (ADHD) (Figure 1).

Two RCTs fulfilled the inclusion criteria, one was only available in abstract form.^{15,16} and the other as a full paper¹⁶ No non-randomised comparative studies or systematic reviews of omega-3 intake were identified. Details of the studies excluded on the basis of full paper are listed in Appendix 2; these included five studies identified in a Food Standards Agency review briefly described below.

4.2 FSA report, 2006

During the later stages of the preparation of this report it came to our attention that the Food Standards Agency (FSA) was undertaking a systematic review entitled “ *A systematic review of the effect of nutrition, diet and dietary change on learning, education and performance of children of relevance to UK schools* ” . This review included analysis of research on fish oils/omega-3. The report was made available on the FSA website (<http://www.food.gov.uk/multimedia/pdfs/systemreview.pdf>) in early July 2006. It examined five studies of the impact of fish oil/omega-3 supplementation in children with various neuro-developmental problems but failed to identify any RCT or non RCT of omega 3 supplementation in a general population of schoolchildren. The characteristics and findings of the five omega 3 studies reported by authors of the FSA review are summarised at the end of this report.

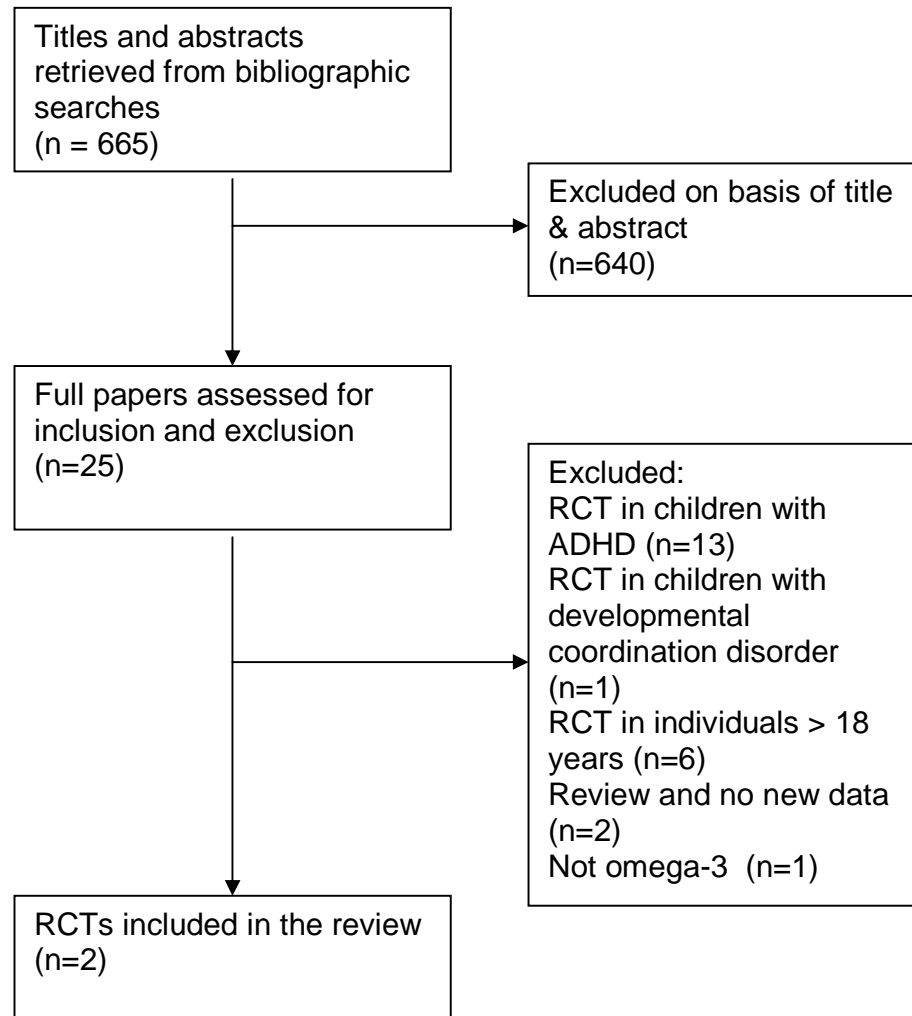


Figure 1. Flow diagram for identified trials

4.3 Characteristics of included studies

Thienprasert et al¹⁵ randomised 64 Thai school children aged to 8 to 12 years to receive food fortified with a total of 1g DHA and 308 mg EPA per day (n=33) or the same food without supplements (n=31) for six months. These foods included milk, bread and sauces. A number of outcomes were assessed including physical performance. Only the outcomes of school absenteeism and educational attainment (as assessed by exam performance) were relevant to this report (Table 3).

Table 3 Main characteristics of included studies

Author (year) Country	Population (% male) Age (yr)	Intervention	Control	Outcomes relevant to report	Follow Up (months)
Theinprasert et al (2002) ¹⁵ Thailand	N = 64 (%Not reported) Range 8-12	DHA-rich fish oil: 1g ω 3 DHA & 303mg ω 3 EPA per day (fortified foods)	Control foods (PUFA content not reported)	1] School academic performance; 2] School absenteeism	6
Itomura et al (2005) ¹⁶ Japan	N = 166* 49% Mean 10.4 (SD 0.9)	DHA-rich fish oil: 3.6g ω 3 DHA, 0.84mg ω 3 EPA & 3.6g ω 6 linoleic per week (fortified foods)	Control-oil: Low ω 3 DHA & ω 3 EPA; 7.8 g ω 6 linoleic per week (fortified foods)	1] Hostility- Agression Questionnaire. 2] Rosenzweig Picture- Frustration test. 3] ADHD DSM-IV criteria.	3

SD: standard deviation PUFA polyunsaturated fatty acid. * 179 randomised

The RCT of Itomura et al¹⁶ was undertaken in 166 Japanese school children aged 9 to 12 years (Table 3). The children of the fish oil group (n=83) took fish oil-fortified foods (bread, sausage and spaghetti). These foods were provided in amounts such that each subjects in the fish oil group had an intake of 3600mg of DHA and 840mg of EPA per week for 3-months. The controls took foods that were supplemented with 50% soya bean and 50% rapeseed oils instead of fish oils so that control diet contained much larger amounts (7.8 g /week) of omega 6 linoleic (C18:2 fatty acid) than the intervention diet (3.6 g / week) and was almost free of EPA and of DHA (long chain omega 3 fatty acids). Children were assessed at baseline (first day of dietary manipulation) and at 3-months.

Outcomes measures included the Japanese version of two validated outcomes – Hostility-Aggression Questionnaire for Children and Rosenzweig Picture-Frustration test, assessing verbal aggression, physical aggression, anger and hostility. In addition, attention deficit, hyperactivity and impulsivity were assessed using the diagnostic criteria for ADHD of DSM-IV. Changes in RBC phospholipid fatty acid profiles were used to determine if dietary manipulation had been successful.

Table 4 Quality of included studies

Author	Randomisation method	Concealment	Blinding	Loss to follow up/drop outs	ITT analysis	Jadad score
Theinprasert <i>et al</i> (2002) ¹⁵	Not stated	Not stated	Double blind	Not stated	Not stated	1/5
Itomura <i>et al</i> (2005) ¹⁶	Not stated	Not stated	Double blind	13/179 166 analysed	No	2/5

4.4 Quality of included studies

Results of the assessment of study quality are summarised in Table 4. Given the limited details available in the abstract of the Thienprasert trial,¹⁵ it was judged to be of poor quality (Jadad score: 1/5). Details of the method of generating and concealing the random number sequence were not reported. However, the authors reported the children in the two groups did not differ by weight, height, gender, physical examination or medical history records. The randomised trial was described as a 'double-blind', all outcome assessments being blinded to treatment group. No details of masking procedures or losses follow up were provided.

The Itomura trial¹⁶ was judged to be of moderate quality (Jadad score: 2/5). The authors failed to provide details of the method for the generation of random numbers, concealment and masking of intervention and control foods. Because fish oils-containing foods are likely to smell and taste differently, the authors judged the quality of blinding by asking the parent/guardians to guess the

randomisation status of their child. There was evidence that masking was not effective, based on results of a post-study questionnaire asking participants' which food they had been allocated. One hundred and seventy nine children were randomised and 166 provided outcomes at follow up with 13 losses being accounted for.

4.5 Findings

Thienprasert *et al*¹⁵ analysed their outcomes using repeated measures ANOVA and group analyses. The number of days absent from school were lower in the DHA/EPA group (mean 1.7, standard deviation 2.0) compared to the control group (5.8, 3.6) ($P < 0.04$). This reduction was due to a lower number of children sick per month in the DHA/EPA group (1.5, 1.6) compared to the control group (4.2, 2.4) ($P < 0.05$) (Table 5). No difference between groups was found in exam performance.

Table 5 Main findings of included studies

Thienprasert et al 2002¹⁵	
Outcome	Result
School academic performance;	<i>No treatment effect observed.</i>
School absenteeism	<i>Days off school: 1.7 ± 2.0 vs 5.3 ± 3.6 p <0.04 in favour of fish oil Pupils sick / month: 1.5 ± 1.6 vs 4.2 ± 2.4 p <0.05 in favour of fish oil</i>
Itomura et al (2005)¹⁶	
Outcome	Result
Hostility-Aggression Questionnaire. a) verbal aggression b) anger c) hostility d) physical aggression	<i>a) No treatment effect observed. b) No treatment effect observed. c) No treatment effect observed. d) Boys: NS small decrease both groups; Girls: Increase in control group (p 0.0004) no change in fish oil group (girls inter-group difference p 0.008).</i>
Rosenzweig Picture-Frustration test.	<i>Extra-aggression increased in fish oil group (score 4 to score 5; p <005) did not change in control group (score 5 to score 5).</i>
ADHD DSM-IV criteria. a) attention deficit b) hyperactivity c) impulsivity	<i>a) No treatment effect observed. b) No treatment effect observed. c) Boys: no treatment effect. Girls: decrease fish oil group only (p 0.02)</i>

The Itomura trial¹⁶ compared the behavioural scores of fish-oil and control groups at 3-months using analysis of covariance adjusting for baseline outcome values. Analysis of variance analysis was used to assess the change in outcome with treatment groups and gender as factors. Where gender was found to be statistically significant, the authors reported the outcome results for boys and girls separately (Table 5). There was no significant difference in verbal aggression, anger or hostility as assessed by the Hostility-Aggression Questionnaire between control and fish oil groups. Physical aggression as assessed by the Hostility-Aggression Questionnaire for Children in girls increased significantly (median: 13 to 15, n = 42) in the control group and did not change (13 to 13, n = 43) in the fish oil group (P = 0.008). In contrast, there were no significant changes in physical aggression in boys or differences between fish oil and control groups. Aggression against others ('extra-aggression') assessed by the Picture Frustration Test did not change in the control group (median: 5 to 5), but increased significantly in the fish oil group (4 to 5) (P = 0.02). The authors propose that changes in extra-aggression might be explained partly by significantly lower baseline values of extra-aggression in the fish oil group than in control group (P = 0.02). Impulsivity of girls assessed by parent/guardians using the diagnostic criteria for ADHD of DSM-IV was significantly reduced in the fish oil group (1 to 0) (P = 0.008). There was no between group difference in impulsivity boys. Hyperactivity and inattention did not differ between treatment groups.

5 DISCUSSION

5.1 Principle findings

Two small RCTs^{15,16} of low to moderate quality found no consistent benefit of omega-3 fatty acids and fish oils on the behaviour, cognition or educational outcomes of healthy Japanese and Thai school children. There is, therefore, insufficient evidence to either confirm or refute the hypothesis that increased intake of fish oils and omega-3 fatty acids affects behavioural, cognitive or educational outcomes of normal children. Furthermore, it is not possible to comment on the importance of either the dose or source (i.e. fish versus non-fish) of the relative balance of benefits and harms of omega-3 fatty acids.

5.2 Strengths and limitations

The principle strengths of this report were its comprehensiveness and its specific focus. Searches were undertaken across a number of bibliographic databases that spanned health, psychology and education literature. The review focused on randomised or quasi-randomised controlled studies and therefore sought to identify high quality evidence of the effect of omega-3 fatty acids in normal children. We may, therefore, have failed to identify observational evidence, such as cohort, case control and before and after studies, that addresses this question. Some of the bibliographic databases searched (in particular MEDLINE and EMBASE) were limited (by study design filters) so as identify RCTs. However, this was not possible for others (i.e. ERIC, PsychInfo and Ovid In process). That search yield of these latter databases failed to identify observational studies is indicative that the amount of missing non-RCT evidence in this case is small.

It could be argued that the consideration of lower levels of evidence and studies undertaken in other populations may have helped to inform this report. For example, we identified from searches RCTs of omega-3 fatty acids in normal young adults¹⁷⁻¹⁹ and children with ADHD, or other behavioural problems.^{6,8,20-29}

Both the risk of bias and questionable generalisability of such evidence support the case for the focus of this systematic review.

5.3 Implications for future research

This report identifies a need for further RCTs. Such trials face some specific methodological challenges that include: the choice of appropriate dose(s) of omega-3 or fish oil, adequate blinding of an intervention that may have a characteristic taste or smell and the selection of appropriate and validated measures for what are complex and interrelated outcomes. Future studies also need to be of sufficient follow up to fully assess the balance of the potential benefits and harms of omega-3 fatty acids.

The searches for this review identified a fairly substantial evidence base (13 RCTs) for the use of omega-3 fatty acids in children with ADHD. A systematic review of this evidence base would assist inform future policy of the role of omega-3 fatty acids in this specific population of children.

A press release on 6th September 2006 (see Appendix 3) announced that a large trial of omega 3 supplementation was to be undertaken in a general population of school children. The proposed trial aims to recruit 5000 year eleven school children in County Durham who would be offered “eye Q” capsules as omega 3 fish oil-enriched supplements. The outcome measures include performance in mock GCSE and actual GCSE examinations. Study design was not detailed but the comparison to be made in order to test efficacy of the intervention appears to be between the present cohort of year eleven school children and those representing previous years’ cohorts. The press release stated “*All of our research, both published and unpublished, shows that the eye q formula can really help enhance achievement in the classroom*”; we twice e-mailed the contact address provided in the press release requesting further details regarding the published and unpublished research quoted but no response was elicited (see Appendix 3).

6 CONCLUSIONS

There is insufficient evidence to either confirm or refute the hypothesis for the effect of omega-3 and fish oil on the behaviour, cognition and educational outcomes of normal children. Well-conducted RCTs are, therefore, needed. Until such trials report their findings, there is no clear basis for changing the current recommendation of the consumption of at least two portions of fish per week, one of which should be oily, or the equivalent of 0.2g/day of omega-3 fatty acid.

7 FSA SYSTEMATIC REVIEW: NATURE, FINDINGS & CONCLUSIONS

In July 2006 The Food Standards Agency (FSA) published a report entitled “A systematic review of the effect of nutrition, diet and dietary change on learning, education and performance of children of relevance to UK schools ”.

(<http://www.food.gov.uk/multimedia/pdfs/systemreview.pdf>) Its focus on the effect of dietary intervention on educational performance of school children was the same as the present review but the remit was much broader in that many dietary interventions were considered beside w 3-fatty acid/ oily-fish supplementation. Further differences were that the FSA review allowed inclusion of studies on populations of school children with learning or other deficits and excluded studies performed in countries which fell below a specified level of economic development commensurate with that in the UK (“population criterion”).

The FSA search strategy identified approximately 24,000 studies that yielded 29 included studies of which five investigated the effects of dietary supplementation with w3-enriched fish oil in children with various neuro-developmental disorders. The search strategy implemented for the present review also identified these five studies; they were obtained as full papers but were excluded on the basis of inappropriate population (see list Appendix 2 studies numbered 13, 17, 20, 21, 23). The two studies included for the present review were not mentioned in the FSA review. Unfortunately no list of papers excluded on full paper was provided

in the FSA report and so it is not possible to determine exactly why the studies of Thienprasert et al 2002¹⁵ and Itomura et al 2005¹⁶ were excluded. It is possible the former did not satisfy the “population criterion” while the latter may not have been indexed in electronic data-bases at the time of the FSA search (22 December 2005), or these studies may have been missed amongst the 24000 titles retrieved from searching.

The FSA reviewers summarised the characteristics of this group of five fish oil studies as follows:

- Population sizes small
- Study periods short
- Interventions various with regard to type and dose of fatty acid supplements
- Outcome measures various
- Study quality medium to high

Further details of the included studies and main study results are provided here in tables 6, 7 and 8. These tables are adapted from those published in the FSA report and are not the result of independent scrutiny of the five primary studies.

Table 6 FSA studies: study design and populations.

Author YEAR Country	Design Control N (% drop out)	Population: Age (years), Neuro-developmental condition (gender)
Voigt et al.2001 ²⁹ USA	RCT Placebo 63 (14.3%)	6-12 All ADHD (♀ & ♂)
Richardson & Puri.2002 ⁹ UK	RCT Placebo 41 (22%)	8-12 ADHD-related symptoms (♀ & ♂)
Stevens et al. 2003 ²⁸ USA	RCT Placebo 50 (34%)	6-13 Inattention, disruptive behaviours (♀ & ♂)
Hirayama et al. 2004 ²⁷ JAPAN	RCT Placebo 40 (NR)	6-12 ADHD symptoms (♀ & ♂)
Richardson & Montgomery 2005 ¹⁰ UK	RCT (cross over) Placebo 117 (6.0%)	5-12 all met criteria for dyspraxia (♀ & ♂)

Table 7 FSA studies: study settings, durations and interventions

Author YEAR Country	Duration Setting	Intervention (mg / day)	Comparator
Voigt et al. 2001 ²⁹ USA	4 months Home	Fish oil: ω 3 DHA = 345	<i>Placebo not reported.</i>
Richardson & Puri 2002 ⁹ UK	12 weeks Special school	Fish oil: ω 3 EPA = 186, ω 3 DHA = 480, ω 6 γ -linolenic = 96, ω 6 linoleic = 864, ω 6 arachidonic = 42, (thyme oil at 8mg/d)	<i>Placebo: ω9 olive oil (18:1)</i>
Stevens et al. 2003 ²⁸ USA	4 months Community	Fish oil: ω 3 DHA = 480, ω 3 EPA = 80, ω 6 arachidonic = 40, ω 6 γ -linolenic = 96	<i>Placebo: ω9 olive oil (18:1)</i>
Hirayama et al. 2004 ²⁷ JAPAN	2 months Summer camp	Fish oil: ω 3 DHA = 510, ω 3 EPA = 100 [in bread and milk]	<i>Placebo: ω9 olive oil (18:1)</i>
Richardson & Montgomery 2005 ¹⁰ UK	3 months State schools.	80% fish oil and 20% evening primrose oil: ω 3 EPA = 558; ω 3 DHA = 17.	<i>Placebo: ω9 olive oil (18:1)</i>

Table 8 FSA Review studies: main outcome measures and results

Author YEAR Country	Measurements	Results
Voigt et al 2001 ²⁹ USA	Test of ADHD symptoms. Two parental tests. <i>Plasma phospholipids.</i>	NO significant group differences in objective or subjective ADHD measures by the study end. Intervention: plasma phospholipid DHA \uparrow 2.5 fold ($p < 0.001$), no correlation to changes in assessed behaviours.
Richardson & Puri 2002 ⁹ UK	Conners CPRS-L–behaviour assessment (parental)	Three out of 14 scales significant reductions ($p = 0.05, 0.03, 0.05$ respectively)
Stevens et al 2003 ²⁸ USA	TESTS: (Conners, Woodcock-Johnson, Conners Teacher & parental questionnaire & disruptive-behaviour disorder rating) <i>Plasma & RBC EFA.</i>	After ITA (34% Drop Out) two of the 16 outcome measures significantly improved in fish oil group ($p = 0.05$ & $P = 0.03$). Significant correlations between change in RBC EPA / DHA content & parent- teacher-observed behaviors ($p < 0.05$).
Hirayama et al 2004 ²⁷ JAPAN	TESTS: Frostig; Miller; Beery ; Corkum & Siegel. Parent & teacher assessments.	No significant group difference between changes in test scores. 'Visual short term memory' & 'continuous performance' significantly improved in control group only ($p = 0.02$ and 0.001).
Richardson & Montgomery 2005 ¹⁰ UK	TESTS: Henderson; Conners ADHD; Wechsler Objective.	Significant improvements in reading and spelling ($p = 0.04$ & < 0.01) in fish oil arm. CTRS-L global scale improvements ($p < 0.05$) and subscale improvements ($p < 0.05$) except for perfectionism and social problems in fish oil group. No significant group differences for motor skills.

On the basis of their analysis of the results published in the five RCTs of n-3 fish oil supplements (see Table 8) the FSA reviewers came to the following conclusion:

“All studies have been carried out in children with varying degrees of neuro-developmental disorderfindings were mixed and inconclusive.....applicability of such data to mainstream children is questionable.”

These conclusions are essentially concordant with those of the present review. It should be born in mind that the reviews were conducted and conclusions reached in mutual ignorance of the existence of the other review.

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Appendix 1 Search Strategies

Source - Cochrane Library (CENTRAL) 2006 Issue 1

#1 fish next oil* in All Fields in all products
913
#2 fatty next acid* in All Fields in all products
5194
#3 omega3 in All Fields in all products
239
#4 omega next 3 in All Fields in all products
143
#5 omega6 in All Fields in all products
14
#6 omega next 6 in All Fields in all products
26
#7 pufa OR pufas in All Fields in all products
309
#8 MeSH descriptor Fish Oils explode all trees in MeSH products
998
#9 MeSH descriptor Fatty Acids, Essential, this term only in MeSH products
128
#10 MeSH descriptor Fatty Acids, Omega-6 explode all trees in MeSH products
302
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
5591
#12 child OR children OR infant* OR teen* OR adolescent* OR adolescence in All Fields in all products
92335
#13(#11 AND #12)
954
#14 learning OR attention OR behavior* OR education* OR hyperactive OR hyperactivity OR concentrate OR concentration in All Fields in all products
85566
#15 MeSH descriptor Educational Measurement explode all trees in MeSH products
1073
#16 MeSH descriptor Child Behavior explode all trees in MeSH products
518
#17 (#14 OR #15 OR #16)
85792
#18
(#13 AND #17)
380

Source - Ovid MEDLINE(R) 1966 to March Week 5 2006

1 fish oil\$.mp. (5275)
2 fatty acid\$.mp. (118627)
3 (omega3 or omega 3).mp. (5360)
4 (omega6 or omega 6).mp. (1965)
5 (pufa or pufas).mp. (3276)
6 exp fish oils/ (9724)
7 Fatty Acids, Essential/ (3526)
8 exp Fatty Acids, Omega-6/ (9045)
9 or/1-8 (124148)
10 (child or children or infant\$ or teen\$ or adolescent\$ or adolescence\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2082751)

Effects of Oily Fish/Omega-3 Fatty Acids on the Performance of Normal School Children

- 11 adolescent/ or child/ (1535665)
- 12 10 or 11 (2082751)
- 13 9 and 12 (9046)
- 14 (learning or attention or behavior or behaviour or education\$ or hyperactive or hyperactivity or concentrate or concentration).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1685128)
- 15 exp educational measurement/ (60202)
- 16 exp child behavior/ (8687)
- 17 or/14-16 (1708875)
- 18 13 and 17 (1347)
- 19 limit 18 to "reviews (optimized)" (168)
- 20 from 19 keep 1-168 (168)
- 21 limit 18 to "therapy (optimized)" (166)

Source - EMBASE 1980 to 2006 Week 14

- 1 fish oil\$.mp. (6084)
- 2 fatty acid\$.mp. (82356)
- 3 (omega3 or omega 3).mp. (6032)
- 4 (omega6 or omega 6).mp. (1872)
- 5 (pufa or pufas).mp. (3138)
- 6 fish oil/ (5331)
- 7 Essential Fatty Acid/ (1450)
- 8 omega 3 fatty acid/ or omega 6 fatty acid/ (5130)
- 9 or/1-8 (84758)
- 10 (child or children or infant\$ or teen\$ or adolescent\$ or adolescence).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (890558)
- 11 Child/ (311792)
- 12 or/10-11 (890558)
- 13 9 and 12 (5041)
- 14 (learning or attention or behaviour or behavior or education\$ or hyperactive or hyperactivity or concentrate or concentration).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1252890)
- 15 academic achievement/ (11069)
- 16 child behavior/ (8847)
- 17 or/14-16 (1256014)
- 18 13 and 17 (978)
- 19 limit 18 to "reviews (1 term min difference)" (165)
- 20 limit 18 to "treatment (2 or more terms min difference)" (164)
- 21 from 20 keep 1-164 (164)

Source - PsycINFO 1967 to April Week 1 2006

- 1 fish oil\$.mp. (26)
- 2 fatty acid\$.mp. (995)
- 3 (omega3 or omega 3).mp. (134)
- 4 (omega6 or omega 6).mp. (19)
- 5 (pufa or pufas).mp. (55)
- 6 fatty acids/ (620)
- 7 or/1-6 (1008)
- 8 (child or children or infant\$ or teen\$ or adolescent\$ or adolescence).mp. [mp=title, abstract, subject headings, table of contents, key concepts] (364605)
- 9 7 and 8 (94)
- 10 (learning or attention or behaviour or behavior or education\$ or hyperactive or hyperactivity or concentrate or concentration).mp. [mp=title, abstract, subject headings, table of contents, key concepts] (598589)

Effects of Oily Fish/Omega-3 Fatty Acids on the Performance of Normal School Children

- 11 educational measurement/ (7116)
- 12 exp behavior/ (513491)
- 13 or/10-12 (913506)
- 14 9 and 13 (49)
- 15 from 14 keep 1-49 (49)

Source – Science Citation Index (Web of Science)1970 – April 2006

(fish oil* OR fatty acid* OR omega 3 OR omega 3 OR omega6 OR omega 6 OR pufa OR pufas)
AND (child OR children OR infant* OR teen* OR adolescent* OR adolescence) AND (learning
OR attention OR behavior OR behaviour OR education* OR hyperactive OR hyperactivity OR
concentrate OR concentration) AND (trial)

Source – ERIC (CSA Illumina), 'earliest to current'

(fish oil* or fatty acid* or omega 6 or omega 3 or pufa
or pufas)

Appendix 2 Studies excluded on full paper.

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in adults with attention deficit hyperactivity disorder. *Reprod Nutr Dev.*
2005;45:549-58. [ADHD population]

Appendix 3 Press release of September 6 2006.

ADVANCE DIARY NOTE

EMBARGOED: Not for broadcast or publication before 10am on Wednesday September 6, 2006

LARGEST EVER BACK-TO-SCHOOL FISH OIL TRIAL COULD BOOST GCSE PASS RATE

County recruits 5,000 Year 11 pupils for unique study

Education chiefs in County Durham are to mount a unique back-to-school initiative next month which they believe could result in record GCSE pass levels next summer.

All Year 11 pupils at Durham County Council's 36 comprehensive schools are to be offered omega-3 fish oil supplements to see whether the proven benefits it has already brought children and young people in earlier trials can boost exam performances too.

It is hoped that around 5,000 Year 11 pupils will be signing-up in September to begin taking the supplement eye q, which was used in all the previous studies and has been offered free of charge by the manufacturer Equazen.

The initiative – the largest-ever programme using fatty acids in the classroom - is the brainchild of Dave Ford, the Council's Chief Schools Inspector, who has followed the progress of children involved in earlier studies in the County with the omega-3 fish oil supplement.

He is convinced that the same improvements in concentration and learning, if applied to Year 11 pupils, could have a direct impact on their GCSE results.

The County-wide trial will continue until the pupils complete their GCSE examinations next June, and the first test of the supplement's effectiveness will be when they sit their 'mock' exams this December.

"We are able to track pupils' progress and we can measure whether their attainments are better than their predicted scores," said Mr Ford.

The trial has won the backing of Durham County Councillors, who are committed to making a difference to children's outcomes and improving their life chances.

Councillor Claire Vasey, the Authority's Cabinet Member for Children and Young People's Services said : " We have been leading the way in researching the effects of omega-3 supplementation on children's behaviour and learning.

" If we can improve the concentration of some of our children with this initiative, then they will benefit even more from the opportunities presented to them in our schools.

" These are the valuable experiences that will have a great impact on determining their future."

Adam Kelliher, Managing Director of supplement manufacturer Equazen, said : "All of our

research, both published and unpublished, shows that the eye q formula can really help enhance achievement in the classroom.

(More...2/.)

-2-

“ That is why we are supporting Durham County Council in this initiative to move beyond research and into practical implementation.”

The Durham Schools trial (www.durhamtrial.org) saw 12 schools offer the eye q supplement to pupils aged 6-12 in 2002 as part of a double blind, placebo controlled study. Significant improvements were seen in attention, hyperactivity and short term memory and achievements in reading and spelling were also highly significant. Since then, teenagers from Greenfield Community College also saw improvements in behaviour and attention after taking the supplement and infants attending three Sure Start Early Years settings saw gains far beyond expectation in behaviour, concentration and language developments. As a result of these projects, the County has built a unique relationship with Equazen and felt able to approach the company for this much larger scale initiative.

- *Over the last four years, the level of GCSE attainment at five or more A* - C grade passes in County Durham has improved by more than 15 per cent – far ahead of the national average increase.*

This year, the percentage of pupils gaining five or more A-C grades topped 56 per cent, 5.5% up on last year and the biggest increase ever in a single year in the County. It is likely to bring the County's pass rate very close to - or even on a par with - the national average pass rate.*

Eye q is commercially available through retailers such as Boots and Superdrug. For more information 0870 241 5621 or go to www.equazen.com

(Ends)

NOTE TO NEWS EDITORS:

You will be invited to send a reporter and/or photographer to a media launch of the trial at a County Durham school on the morning of September 6 where key players in the initiative, including pupils, will be available for interview.

Further details will be released once arrangements are finalised.

Press enquiries: Hannah Carter 020 7243 7102 / 07795 630258 / hannah@equazen.com

E-mail requests (see below) for further information regarding the published and unpublished research referred to in the press release failed to illicit a response.

Dear Hannah,

We have almost finished a systematic review of the effectiveness of dietary or supplementary omega 3 fish oil for cognitive and educational outcomes in normal children.

It was therefore with great interest that we read the recent press release about the impending Durham schools trial.

In the press release Adam Kelliher, Managing Director of supplement manufacturer Equazen is quoted *“All of our research, both published and unpublished, shows that the eye q formula can really help enhance achievement in the classroom.”*

Since we are eager to consider all the available evidence relevant to this important topic we would be most grateful if you could supply a list of the published papers alluded to (preferably with copies of same) , and also the titles and or study protocols of any unpublished trials that you have undertaken.

Thank you for any time you can spare for this

Best regards

Martin Connock

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