Omega-3 for Child Behaviour and Learning

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A Rotten Way to Feed the Children

16 Apr 2004 - Times Educational Supplement
By Stephanie Northern

"The physical risks to children from a nutritionally poor diet are now acknowledged, but the damage being done to their behaviour, learning abilities and mood is not."

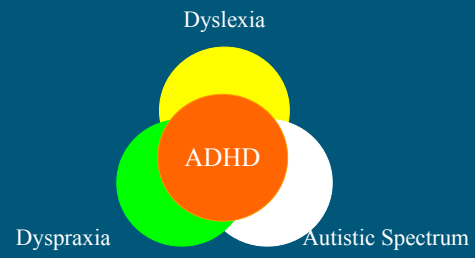
- The UK Government has been forced to pump £342 million into school behaviour improvement programmes.
- The WHO predicts a 50 per cent rise in child mental disorders by 2020.
- Dyslexia, hyperactivity, autism and related conditions all appear to be on the increase.

ADHD, Dyslexia, Dyspraxia and Autism – core defining features

ADHD	Hyperactivity / Impulsivity Attentional difficulties (ADD)
Dyslexia	Poor reading, spelling, writing (&working memory) Specific Reading Difficulties (SRD)
Dyspraxia	Poor movement, planning & organisational skills Developmental Co-ordination Disorder (DCD)
Autism	(ASD) Social & communication deficits, stereotyped / obsessional behaviour, restricted interests

- Dimensional element to difficulties in each case
  - 20% of UK school children are affected to some degree
- Diagnoses are only descriptions – not explanations

Childhood behavioural and learning difficulties – the Overlap

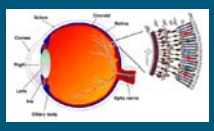


High comorbidity (30-50% for any two of these conditions) compounds heterogeneity

Omega-3 and Vision

Omega-3 fatty acids from fish oils are absolutely essential to the visual system

- 30-50% of the retina should be made of the omega-3 DHA
- At the earliest stages of visual processing, DHA deficiency can reduce retinal signalling by more than a thousand-fold
- Omega-3 deficiency is associated with poor night vision and other problems with visual, spatial and attentional processing.



Which fats really are essential?

- Essential Fatty Acids (EFA)

  Two fatty acids are called 'essential', because humans can't make them – so they must come from the diet

  - Linoleic acid (LA) (omega-6)
  - Alpha-linolenic acid (ALA) (omega-3)

- **Highly Unsaturated Fatty Acids (HUFA)**

  These are the ones that the brain really needs.

  They aren't always called 'essential' because in theory, humans can synthesise them from the 'parent' EFAs.

Synthesis of Highly Unsaturated Fatty Acids (HUFA) from 'Essential' Fatty Acids (EFA)

	omega-6		omega-3	
EFA	LA (Linoleic)	18:2	ALA (A-linolenic)	18:3
	GLA	18:3		18:4
	DGLA	20:3 *		20:4
HUFA	AA (Arachidonic)	20:4 *	EPA	20:5 *
	Adrenic	22:4	DPA(n-3)	22:5
	DPA(n-6)	22:5	DHA	22:6

Conversion of EFA to HUFA is poor, and is further blocked by:

Diet and Lifestyle

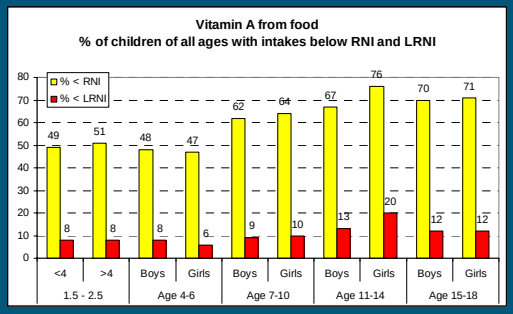
- Saturated fats
- Hydrogenated fats
- Trans fatty acids
- Lack of co-factors *(e.g. Zinc, magnesium, manganese, Vitamins A, B3, B6, C etc.)*
- 'Stress' hormones
- Viral infections

NB: Excess alcohol & smoking: both destroy HUFA via oxidative stress

Constitutional factors

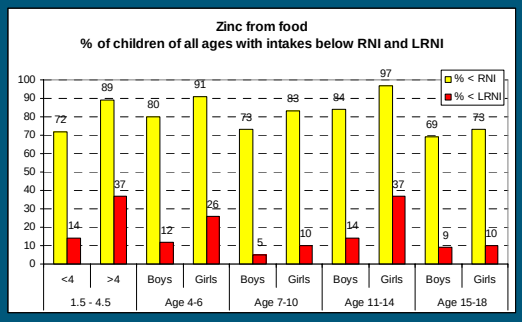
- Ageing
- Atopic eczema (& other allergies?)
- Diabetes
- Being male
  - *Testosterone blocks conversion*
  - *Oestrogen helps to protect HUFA from breakdown*
- Genetic predisposition to a spectrum of developmental and psychiatric disorders?

Vitamins and Minerals – Vitamin A



* Gregory et al 2000. National Diet and Nutrition Surveys, HMSO

Vitamins and Minerals – Zinc



* Gregory et al 2000. National Diet and Nutrition Surveys, HMSO

Dietary Sources of Omega-6

	omega-6		
EFA	LA (Linoleic)	18:2	← Vegetable oils, nuts, seeds, grains
	GLA	18:3	← Evening primrose oil
	DGLA	20:3 *	
HUFA	AA (Arachidonic)	20:4 *	← Meat, eggs and dairy products (milk, yogurt, butter, cheese)
	Adrenic	22:4	
	DPA(n-6)	22:5	

Dietary Sources of Omega-3

omega-3

Green leafy vegetables, seaweed, & some nuts & seeds - flax, walnut, canola (rapeseed) oils → ALA (α-linolenic) 18:3 (EFA)

18:4

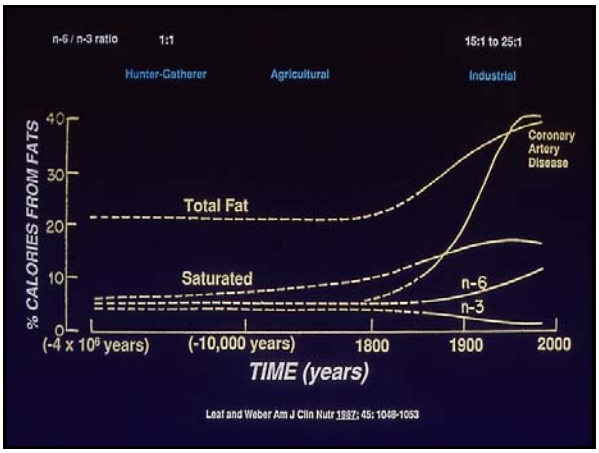
20:4

Fish and seafood  → EPA 20:5 *

DPA(n-3) 22:5

→ DHA 22:6

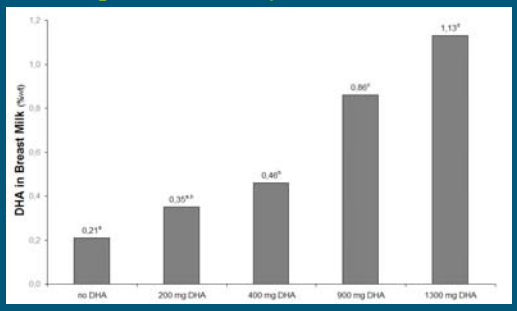
(HUFA)



What are fatty acids essential for?

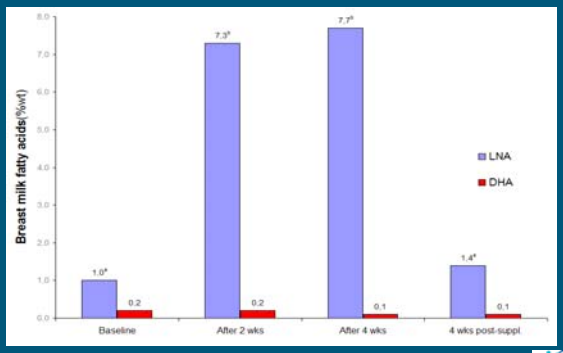
1. The structure of all cell membranes
   - Omega-3 (and omega-6) increase membrane fluidity, essential for optimal cell signalling
2. Brain development
   - Fatty acids make up around 20% of dry brain mass, and affect brain growth and connectivity
   - Supplementing infant formula with HUFA (found naturally in breastmilk) can improve visual and cognitive development

DHA concentrations in breast milk depend on dietary DHA intake



Makrides M et al. Eur J Clin Nutr 1996;50(6):352-357

Supplementing lactating women with flaxseed oil (20 g/d with 10.7 g LNA) does not increase DHA in their milk



What are fatty acids essential for?

1. The structure of all cell membranes
   - Omega-3 and omega-6 increase the flexibility of membranes, which is necessary for proper cell signalling
2. Brain development
   - Fatty acids make up around 20% of dry brain mass, and affect brain growth and connectivity
   - Supplementing infant formula with HUFA (found naturally in breastmilk) can improve visual and cognitive development
3. Maintenance of optimal brain function throughout life
   - Cell signalling depends on membrane fluidity
   - Omega-3 and omega-6 fatty acids and their derivatives have very powerful effects on many aspects of cell signalling.
   - The substances we make from them can profoundly affect hormone balance, blood flow and immune function

Fatty acid deficiency in childhood disorders of behaviour and learning

What's the Direct Evidence?

Fatty acid abnormalities and behaviour and learning difficulties (1)

Clinical signs consistent with omega 3/6 deficiency

- Excessive thirst, frequent urination, rough dry skin & hair, soft or brittle nails, hard dry 'bumpy' skin
  - ADHD *(Colquhoun and Bunday 1981; Stevens et al, 1995, 1996, Sinn et al 2006)*
  - Dyslexia *(Baker, 1985; Richardson et al, 2000; Taylor et al, 2000)*
  - Autism *(Bell et al, 2000, Ross and Riordan, 2001)*

Fatty acid abnormalities and behaviour and learning difficulties (2)

Blood biochemical evidence

- Deficiencies of omega-3 / omega-6 fatty acids
  - ADHD *(Bekaroglu et al 1986; Mitchell et al 1987; Stevens et al, 1995, 1996, 2006 – but NB not 2003; Chen et al 2004; Young et al 2004)*
  - Dyslexia *(Baker, 1985, Ross et al 2004, Cyhlarova et al 2007)*
  - Autism *(Bell et al, 2000, 2004; Vancassel et al 2001)*
- Enzyme abnormalities (PLA2) consistent with increased loss of omega-3 / omega-6 fatty acids
  - Dyslexia *(MacDonell et al, 2000)*
  - Autism *(Bell et al, 2003)*

Can treatment with omega-3 fatty acids help?

Evidence from
Randomised Controlled Trials

Omega-3 for physical & mental health

- Randomised controlled trials have already shown that omega-3 (notably EPA) in adults can be beneficial for:
  - Cardiovascular function
  - Inflammatory disorders

  And:
  - Schizophrenia (4/5 trials)
  - Bipolar disorder (manic depression) (2/3 trials)
  - Major depression (5/6 trials)
  - Borderline Personality Disorder (1/1 trial)
  - Preventing stress-induced aggression (1/1 trial)
  - Reducing violence in Young Offenders* (1/1 trial)
  - Slowing decline in early-stage Alzheimers' (1/1 trial)

* Active treatment also included vitamins, minerals and omega-6 fatty acids

RCTs of Omega-3 for Child Behaviour and Learning - overview

- Two negative studies
  - No benefits from treatment primarily or exclusively with DHA in two studies of ADHD *(Voigt, 2001, Hirayama et al, 2004)*
- Three positive studies
  - Significant benefits from fish oils, providing both EPA and DHA in three studies of children with dyslexia, dyspraxia and ADHD *(Richardson & Puri, 2002; Stevens et al 2003; Richardson & Montgomery 2005)*

Can HUFA treatment reduce ADHD symptoms in dyslexic children?

A randomised controlled trial

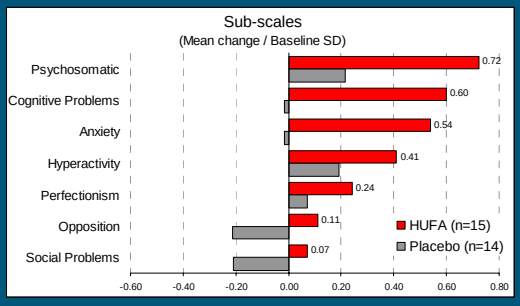
Richardson and Puri (2002) Prog. Neuropsychopharm Biol Psychiat. 26:233-9

School study: 29 children aged 8-11

- All showed specific reading difficulties (dyslexia) and
- Children were pre-selected for ADHD symptoms (>1SD above population means on parent ratings via CPRS-L), a criterion met by 74% of the initial sample.
- Treatment for 3 months in parallel groups

Treatment effect sizes 0-3 months

Richardson and Puri (2002) Prog. Neuropsychopharm. Biol. Psychiat. 26:233-9



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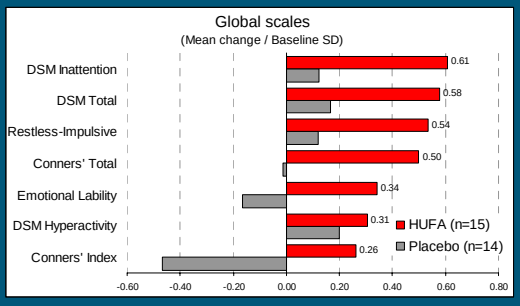


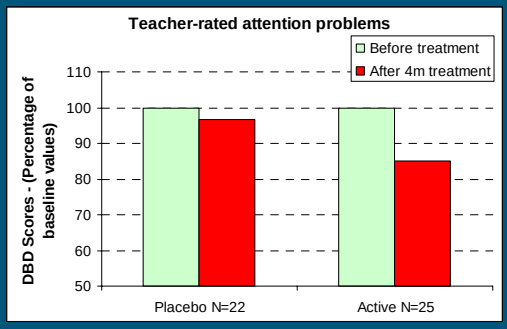
EFA supplementation in children with inattention, hyperactivity and other disruptive behaviours

Stevens et al (2003) Lipids, 38(10) 1007-21

RCT involving 50 children aged 6-13

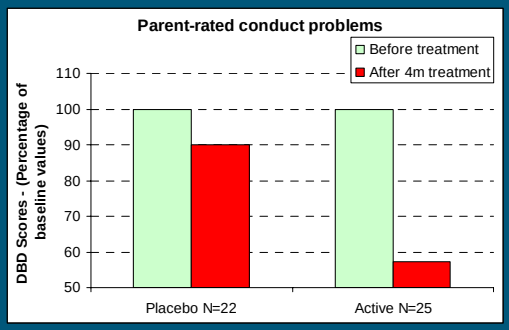
- All were under treatment for ADHD-type difficulties and
- Children were pre-selected for physical signs consistent with EFA deficiency
  - 75% of initial sample met this criterion, but NB: later blood tests contradicted this)
- Treatment for 4 months in parallel groups

Stevens et al (2003) Lipids, 38(10) 1007-21



Group difference (ITT) $p < 0.03$

Stevens et al (2003) Lipids, 38(10) 1007-21



Group difference (ITT) $p < 0.05$

THE OXFORD-DURHAM STUDY:

A randomised controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder.

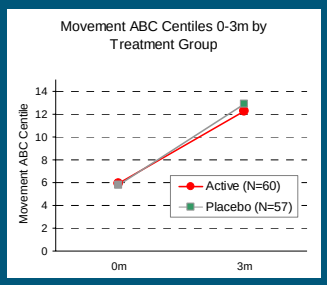
Richardson AJ & Montgomery P. *Pediatrics*, 2005, 115:1360-6

117 underachieving children aged 5-12 years from mainstream schools

- All showed specific difficulties in motor coordination (DSM-IV DCD)
- 40% were behind expected achievement in reading and spelling
- Over 30% scored in the clinical range for ADHD-type symptoms (>2SD above population means)

Motor skills

Richardson AJ & Montgomery P. *Pediatrics*, 2005, 115:1360-6



This shows why a placebo control group is simply essential

Reading and Spelling

Richardson AJ & Montgomery P. *Pediatrics*, 2005, 115:1360-6

Active treatment

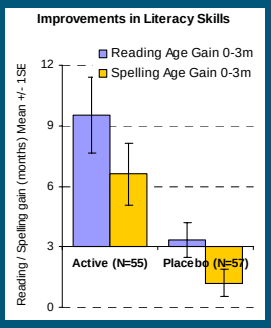
- Compared with expected progress for normal children, gains were > 3 x normal rate for reading, > 2 x for spelling

Placebo

- Gains were 1 x normal rate for reading, < 0.5 x for spelling

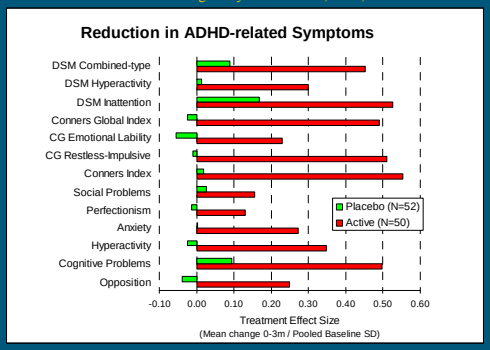
Group Differences

- Reading $p < 0.004$
- Spelling $p < 0.001$

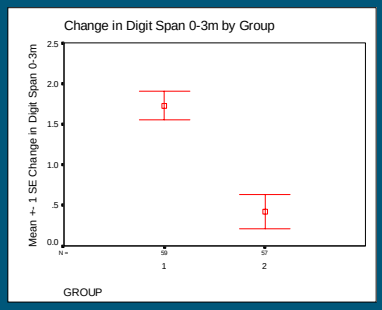


Behaviour Ratings

Richardson AJ & Montgomery P. *Pediatrics*, 2005, 115:1360-6



Improvements in Working Memory



Dietary need for Omega-3

- Scientific and medical experts recommend a daily intake of at least 500mg/day EPA+DHA* simply to maintain cardiovascular health. *(ISSFAL Statement 2004; UK JHCI 2005)*
- In the UK, average daily intakes are more like 100-150mg (most children consume less)
- Requirements for optimal brain function have never been investigated.
  - Successful trials for child behaviour and learning have used 550 - 750mg EPA+DHA

*Conversion of ALA from vegetable sources is not always reliable

Summary

- Omega-3 from fish and seafood (EPA and DHA) are essential for optimal brain development and function (as well as physical health), but lacking from UK diets.
  - Nutrition is not 'alternative': it is a medical fundamental.
  - Diet affects gene expression throughout life – and it also affects future generations.
- Controlled trials show that treatment with omega-3 from fish oils can:
  - reduce symptoms of depression and other mental health conditions in adults (and probably in children)
  - improve behaviour and learning in children with ADHD, dyslexia or dyspraxia
  - Large-scale studies (ideally with general population samples) are urgently needed to confirm and extend these findings

Conclusions and Recommendations

- Optimal intakes of omega-3 (and other nutrients) must be assessed in relation to brain and behaviour
  - UK diets have changed dramatically, and the role of dietary fats is crucial, but seriously misunderstood
- Better education for professionals and the public on nutrition and health is essential
  - Evidence-based information, independent of vested interests
- Fish oils for behaviour and learning in the general school population? For children with special needs?
  - Controlled trials are needed to evaluate benefits vs costs, but supplementation of risk groups could lead to huge savings for education, health, social services and criminal justice.

Further Information

For details of this and related research see

Food And Behaviour Research
www.fabresearch.org

and the book
theyarewhatyoufeedthem.com

Associated features common to ADHD, Dyslexia, Dyspraxia and Autism – (1)

- Genetic risk
- Neurodevelopmental anomalies
  - Pregnancy and birth complications, low birth weight
  - Minor physical anomalies
- Excess of males affected
- Allergies / auto-immune problems
- Other physical complaints (digestion etc)
- Delayed /atypical motor & language development

Associated features common to ADHD, Dyslexia, Dyspraxia and Autism – (2)

- Sleep problems - settling, waking, nightmares
- Mood disorders - depression, anxiety, mood swings
- Behavioural problems - stress-susceptibility, conduct disorder, low frustration tolerance
- Perceptual and cognitive abnormalities
  - visual and auditory problems
  - attention / working memory & language problems

Nutrition for behaviour, learning and mood – key issues

1. Blood sugar regulation problems?
2. Micronutrient deficiencies / imbalances?
   - Omega-3 / Omega-6 balance
   - Vitamins & essential minerals
3. Anti-nutrients and toxicity issues?
4. Food allergies or intolerances?
5. Enzymes / gut flora / digestion & absorption

RCTs of Omega-6 Fatty Acids for Child Behaviour and Learning

- Two studies only
  - Two small early studies using evening primrose oil showed little if any benefit in ADHD *(Aman et al, 1987, Arnold et al, 1989)*
  - Study design limitations in each case
  - Zinc status a possible moderator of treatment with either EPO or d-amphetamine *(Arnold et al, 2000)*

Evening primrose oil – no clear benefits shown for brain function, but can help to relieve symptoms of atopic eczema
(Horrobin, 2000; Morse and Clough 2006)

RCT of Omega-3 for Child Behaviour and Learning (Richardson 2006, Int Rev Psychiatry)

Investigators	Diagnosis (+ Source)	N (M,F)	Active Treatment	Trial Design	Duration	Outcome
Voigt et al, 2001	DSM-IV ADHD with minimal or no comorbidity (Psychiatric clinic, USA)	54 (42,12)	DHA 345mg (from algae)	RCT, double-blind, parallel groups; adjunctive to Pharmacotherapy	4 months	No effect of treatment on a wide range of behavioural and computerized measures of ADHD-related symptoms
Richardson & Puri 2002	Dyslexia + ADHD features (Special school, UK)	29 (25,4)	EPA 186 mg DHA 480 mg (from fish oil) Omega-6 (GLA 96 mg, AA 42 mg) Vitamin E 60 IU	RCT, double-blind, parallel groups (+ one-way placebo active crossover); Monotherapy	12 weeks (+12 weeks)	Active > placebo for changes in parent ratings of ADHD-related symptoms
Stevens et al 2003	ADHD-type difficulties + physical signs consistent with EFA deficiency (Community-based sample, USA)	47 (41,6)	EPA 80mg, DHA 480mg (from fish oil) Omega-6 (GLA 96mg, AA 40mg) Vitamin E 56 IU	RCT, double-blind, parallel groups; adjunctive to Pharmacotherapy	16 weeks	Active > placebo for changes in teacher-rated attention, parent-rated conduct, and % meeting clinical criteria for ODD
Hirayama et al 2004	ADHD (Special summer camp, Japan)	40 (32,8)	EPA 100mg approx DHA 510mg approx (from fish oil & fermented soybean oil)	RCT, double-blind, parallel groups; adjunctive to Pharmacotherapy	2 months	No effect of treatment on a wide range of behavioural and psychometric measures
Richardson & Montgomery 2005	DSM-IV DCD (mainstream schools in one UK geographical region)	117 (78,39)	EPA 558mg DHA 174 mg (from fish oil) Omega-6 (GLA 60 mg) Vitamin E 15 IU	RCT, double-blind, parallel groups (+ one-way placebo active crossover); monotherapy	12 weeks (+12 weeks)	Active = Placebo for changes in motor function Active > Placebo for changes in teacher-rated ADHD,- reading and spelling achievement

Implications for Research

- Populations studied
  - Age and sex
  - Clinical diagnosis (and comorbidity issues?)
  - Other selection criteria (fatty acid status?)
- Omega-3 treatment formulations & dosages
  - EPA vs DHA?
  - Omega-6 and antioxidant components?
  - Dosage issues
  - Comparison treatments? (Choice of placebo)
- Outcome Measures
  - Behaviour (ADD / Hyperactivity/ Impulsivity? Mood? Sleep?)
  - Academic achievement (Reading, spelling?)
  - Cognitive function (Working memory? Executive function?)
- Mechanisms of action?

Populations studied

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Hirayama et al 2004	ADHD *(Special summer camp, Japan)*	40 (32,8)
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Formulations and Dosages

Investigators	Diagnosis	N	Active Treatment
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Stevens et al 2003	ADHD-type difficulties + physical signs of EFA deficiency	47	EPA 80mg, DHA 480mg (from fish oil) *Omega-6 (GLA 96mg, AA 40mg) Vitamin E 56 IU*
Hirayama et al 2004	ADHD-type difficulties	40	EPA 100mg, DHA 510mg approx (from fish oil & fermented soybean oil)
Richardson & Montgomery 2005	DSM-IV DCD	117	EPA 558mg, DHA 174 mg (from fish oil) *Omega-6 (GLA 60 mg) Vitamin E 15 IU*

Appropriate Dosage?

- Will vary between individuals
  - 600-800 mg / day of EPA+DHA has been used in successful trials of dyslexia / dyspraxia / ADHD
  - For ADHD / ASD – severe cases may need at least 1g day? (this dosage has been found effective for mood disorders)
  - Dosages of 2g - 4g / day of EPA have been used with success in Depression, Bipolar Disorder, Schizophrenia
  - The profile of other fatty acids provided by the diet or supplement may be important.
    - Ratio of EPA / DHA?
    - Need for omega-6 (GLA)?
    - Antioxidants / other micronutrients?

Possible predictors of a good response to supplementation with EPA/DHA

(1) Physical signs of fatty acid deficiency / allergies

(2) Attentional / organisational problems (ADD)

(3) Emotional lability / mood swings / impulsivity

(4) Anxiety / tension / social withdrawal

(5) Sleep problems (difficulty settling and waking)

(6) Visual symptoms (and visuo-motor problems?)

Implications for Clinical Practice?

- Safety and tolerability
- Adjunctive treatment or monotherapy?
- Treatment regime?
  - What formulations and dosages will be most effective?
  - Duration of treatment?
- Which individuals are most likely to benefit?
  - Trait / feature / symptom-based approach makes more sense than reliance on current (descriptive) diagnostic categories
  - Would increasing dietary intake show benefits for behavour and learning in the general population?

Side effects?

- Wide benefits for general physical health, including:
  - Benefits for cardiovascular function
  - Anti-inflammatory actions (benefits for allergies, arthritis)
  - Improvements in health / strength of skin, hair, nails
  - Protection against some forms of cancer?
  - Improved blood sugar regulation and weight control?
  - Higher (and more balanced) energy levels?
- Good tolerability. Only known negative side-effect* is digestive intolerance
  - Affects < 3%, and can depend on supplement quality + other aspects of diet / general health.

* A few individuals are genuinely allergic to particular fish proteins
* Anticoagulant medication should be monitored, as omega-3 can have similar effects
* Possible interactions with other drugs merit further study

Supplements- practicalities

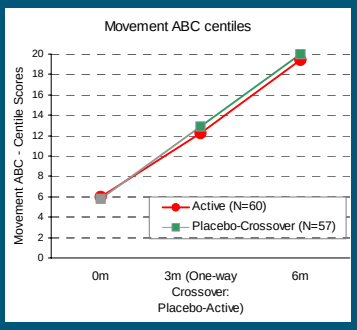
- Omega-3 rather than omega-6 supplements are likely to be more effective for difficulties in behaviour, learning and mood
- EPA appears more important than DHA in improving brain function, although both are crucial for health.*
- Quality of oils is crucial (but high prices are not a guide to this!)
- Fish liver oils in *large quantities* should be avoided because these are rich in Vitamin A (toxic in excess).
- Anti-oxidants (notably Vitamin E) will help to protect HUFA. Multivitamins and minerals will help in synthesis.
- Always consult with your medical practitioner about dietary supplements (especially if any medical treatment is ongoing)

* To maintain heart health, at least 500mg/day EPA+DHA is recommended by experts. *(ISSFAL 2004; UK JHCI 2005)*

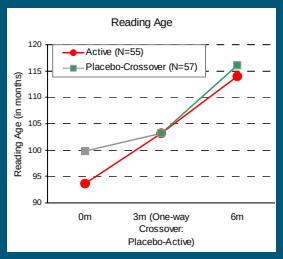
Oxford-Durham Study 3-month follow-up period

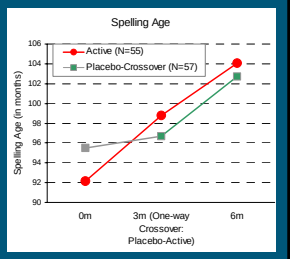
- Children crossing over from placebo to active treatment made gains similar to those of children receiving active treatment in the first 3 months
- Children continuing on active treatment maintained or improved on their earlier progress

Motor skills

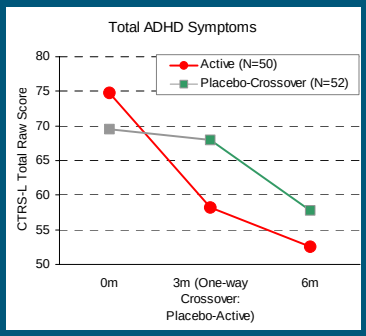


Reading and Spelling





ADHD



Children with Severe ADHD symptoms: 0-3 month period – Active vs Placebo

- Before treatment, 32 children (approx 30%) scored in the clinical range for ADHD-type symptoms on teacher ratings
- After treatment:
  - In the active treatment group, 7/16 children no longer had scores in the clinical range
  - Of the children on placebo, only 1/16 imrpoved in this way