British Journal of Nutrition (2012), **107**, S261–S270
doi:10.1017/S000711451200164X

Effects of omega 3 fatty acids supplementation in behavior and non-neurodegenerative neuropsychiatric disorders

R. M. Ortega[1,2]*, E. Rodríguez-Rodríguez[2,3] and A. M. López-Sobaler[1,2]

[1]*Departamento de Nutrición, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain*
[2]*Research group UCM-920030, Departamento de Nutrición, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain*
[3]*Sección Departamental de Química Analítica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain*

Abstract

This work provides a systematic review of all published randomised, controlled clinical trials (RCT) investigating the effects of *n*-3 PUFA intake on the prevention and treatment of non-neurodegenerative neuropsychiatric disorders. Five databases (PubMed, EMBASE, LILACS, CINAHL and The Cochrane Database) were searched for RCT in this area published up to April 2011. The selected studies all involved human participants and included a comparison group. Thirty eight studies were identified, which examined the influence of *n*-3 PUFA supplementation on the prevention/treatment of depression (non-perinatal) (*n* 23), perinatal depression (*n* 6) and attention deficit hyperactivity disorder (ADHD) (*n* 9). Great heterogeneity was noticed in terms of study design, the doses of *n*-3 PUFA administered, and study duration. Some benefit was noted with respect to the treatment of hyperactivity and depression in over half the examined studies, although the evidence was not conclusive. For any firm conclusions to be drawn, further studies will be needed that take into account the initial *n*-3 PUFA status of the subjects. Excessive *n*-3 PUFA intakes might be associated with a greater risk of peroxidation events and therefore neuropsychiatric deterioration. Indeed, some studies only recorded benefits when lower doses were administered. It is therefore important that the dose required to achieve any potential benefit be determined.

Key words: **Omega 3: Behaviour: Neuropsychiatric disorders: Systematic review**

There is biochemical evidence that *n*-3 polyunsaturated fatty acids (*n*-3 PUFA) play an important role in neural structure and function. The brain and central nervous system contain high concentrations of *n*-3 PUFA and several studies suggest a role for them in nervous system activity, the neuroplasticity of nerve membranes, synaptogenesis, synaptic transmission and neurotransmitter uptake[(1)]. In fact, reduced blood levels of *n*-3 PUFA have been associated with a number of neuropsychiatric conditions, including attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, schizophrenia and depression[(2,3)].

n-3 PUFA are available from dietary sources only; an insufficient intake may therefore be associated with psychiatric effects[(4)]. Some evidence exists that suggests supplementation with individual *n*-3 PUFA or their combinations can reduced the intensity of the symptoms associated with certain neuropsychiatric conditions[(5)].

Nevertheless, although some studies find positive effects associated with supplementation, others do not find this benefit[(6–8)]. It is worth mentioning that messages which recommend the use of *n*-3 PUFA supplements to prevent and reduce the risk of various diseases such as depression have spread rapidly among the population based on studies that find positive results[(9)]. However, some aspects must be taken into account before releasing a general recommendation: if the effects are valid for both healthy and sick subjects and what doses and time of treatment are required to achieve the effects.

The aim of the present systematic review was to examine all published RCT investigating the effects of dietary supplementation with *n*-3 PUFA on the prevention and treatment of non-neurodegenerative neuropsychiatric conditions.

Experimental method

A computerized search was conducted for clinical trials in the Medlars Online International Literature (MEDLINE, via PubMed), the EMBASE®, the Latin American and Caribbean Heath Sciences Literature (LILACS), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane databases. The search terms and equations used for the PubMed search were: "Fatty Acids, Omega-3"[Mesh] AND ("Depression"[Mesh] OR "Mood disorders" [Mesh] OR "Attention Deficit Disorder with Hyperactivity"[Mesh]), limited to 'clinical trials' and 'humans' (Fig. 1). Similar equations were

* **Corresponding author:** R. M. Ortega, fax +34 91 394 18 10, email rortega@farm.ucm.es

used with the other databases. The references in these returned articles were checked manually for further studies.

Report inclusion and data extraction

The titles and abstracts of the articles detected (*n* 182 detected by the 1st April 2011) were inspected independently by two researchers (AMLS and ERR) to select those relevant to the present work. Initial discrepancies between these researchers' decisions were either resolved or a third reviewer (RMO) was called to make a judgement. Duplicates, review articles and non-relevant articles were excluded (*n* 122). Twenty two of the remaining 60 articles were rejected for the reasons shown in Fig. 1, which summarizes the inclusion/exclusion criteria of the work. The data of the 38 remaining articles were tabulated by all three of the above researchers. When data were incomplete, the corresponding authors were contacted and asked to provide the missing information. Tables 1–3 summarise the design of and the results provided by the 38 articles finally selected.

Because pregnancy is a specific physiological situation, data from studies about perinatal depression are presented separately from studies examining the effect of *n*-3 PUFA supplementation in depression at other stages of life (Table 2).

Results

Twenty three RCT (published since May 1999) examined the effect of *n*-3 PUFA supplementation on the prevention and treatment of non-perinatal depression (Table 1). The studies were heterogeneous in terms of sample size (which ranged from 14[10] to 302 subjects[11]). Two studies involved only women[12,13], and two only children[14,15]. The diagnosis of the study subjects also varied, from major depressive disorder (MDD)[13,15–23], to bipolar disorder (BD)[10,14,24–26], depression but not MDD[12,27], depression with other pathologies[28–31] and healthy volunteers[11,32]. The type and quantity of *n*-3 PUFA administered varied too, from 0·4 g/d[11] to 9·6 g/d[26]. Six studies involved the administration of EPA (20 : 5*n*-3) only, employing doses of 1 g/d[16,19,21,24,28] to 6·6 g/d[14]. Two studies involved the administration of DHA (22 : 6*n*-3) only[17,18]. The remaining studies involved the administration of both EPA and DHA in varying quantities, with the EPA/DHA ratio ranging from 0·25[22] to 7[12,32]. In some studies the subjects received no pharmacological treatment as part of the study[11–14,16,18,19,27,32], while in others[10,29] some drug was administered. In the majority of studies[15,20–26,28,30,31], however, the subjects continued with their normal treatment.

Six RCT (published since May 2003) examined the effect of *n*-3 PUFA supplementation on the prevention and treatment of perinatal depression (Table 2). Again, these were heterogeneous in terms of sample size, which ranged from 26[33] to 2399 subjects[34]. Three studies were performed on pregnant women with MDD[4,33,35], analysing the effect of *n*-3 PUFA supplementation on the course of disease. The remaining trials all examined healthy women to determine the preventive effects of supplementation when given postpartum[36], pre-partum[34] and over both periods[37]. The type and quantity of *n*-3 PUFA administered also differed widely. In one study only DHA[36] was given, in three studies different quantities of DHA + EPA[34,35,38] were given, in one[33] DHA + EPA and an *n*-6 PUFA were given, and in one[37] DHA + AA (20 : 4*n*-6) or DHA alone was given. The doses of *n*-3 PUFA given ranged from 0·2 g/d[36] to 3·4 g/d[35].

Nine RCT (published since August 2001) examined the effect of *n*-3 PUFA supplementation on the prevention and treatment of ADHD (Table 3). Again, the sample size was heterogeneous, with a range of 37[39] to 129[40] subjects. Five studies involved supplementation with *n*-3 and *n*-6 PUFA. Generally, supplementation with EPA and/or DHA was provided, except in one study[41] that involved supplementation with LA (18 : 2*n*-6) and ALA (18 : 3*n*-3). The dose of *n*-3 PUFA administered ranged from 0·345 g/d[42] to 1·4 g/d[39].

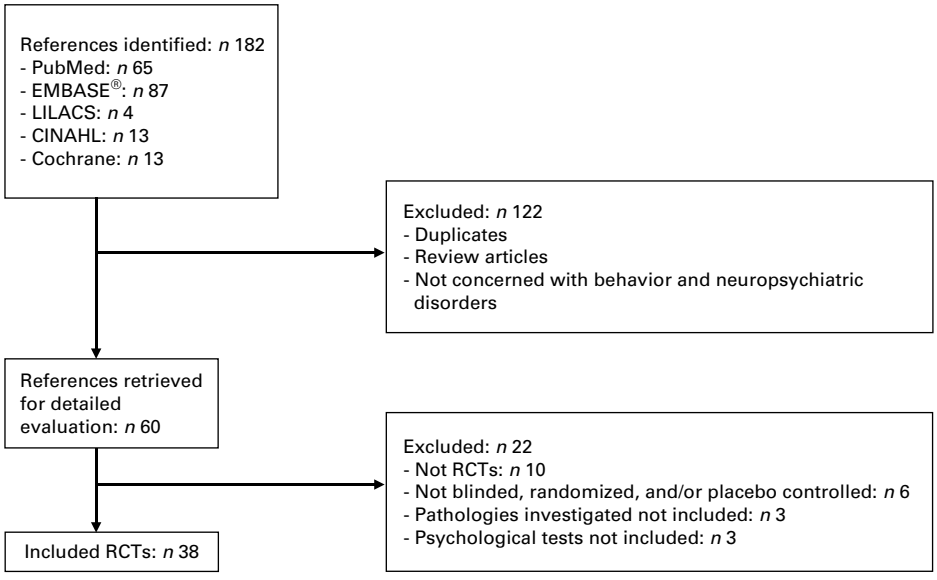

Fig. 1. Literature search flow chart.

Table 1. Randomised controlled clinical trials of supplementation with *n*-3 PUFA in subjects with depression and related disorders

Reference	Diagnosis	*n* (age, years)	Daily dose of *n*-3	Placebo	Drug Treatment	Length of trial (weeks)	Outcome
Antypa *et al.*, 2009[32]	Healthy	56 (22·4 ± 3·8)	1740 mg EPA + 250 mg DHA	olive oil	None	4	Few effects on cognitive reactivity, risky decision-making or control/ perfectionism score.
Bot *et al.*, 2010[28]	MDD in diabetic patients	25 (18-75)	1000 mg EPA	rapeseed oil + medium chain triglycerides	Adjunct	12	No effect
Carney *et al.*, 2009[29]	MDD in coronary heart disease	122 (58,3 ± 8,9)	930 mg EPA + 750 mg DHA	corn oil	50 mg sertraline	10	No effect
Chiu *et al.*, 2005[10]	BD (acute manic phase)	14 (NR)	2200 mg EPA + 1200 mg DHA	olive oil	20 mg/kg/d valproate	4	No effect
da Silva *et al.*, 2008[30]	MDD in Parkinson's disease	29 (49-78)	720 mg EPA + 480 mg DHA	mineral oil	Adjunct in Parkinson's disease, none in healthy	12	Improvement in depression symptoms
Frangou *et al.*, 2006[24]	BD I and II	75 (18-70)	1000 mg EPA / 2000 mg EPA	paraffin oil	Adjunct	12	Significant improvement with EPA. No difference between 1 g and 2 g of EPA
Freund-Levi *et al.*, 2008[31]	Depression in Alzheimer disease	204 (74 ± 9)	600 mg EPA + 1700 DHA	corn oil	ongoing usual treatment	26	No effect
Gracious *et al.*, 2010[14]	BD I and II	51 (6-17)	6600 mg ALA	olive oil	None	16	No effect on sample as a whole, but a significant effect in the subgroup in which EPA blood levels improved
Jazayeri *et al.*, 2008[16]	MDD	60 (20-59)	1000 mg EPA / 1000 mg EPA + 20 mg fluoxetine	rapeseed oil	None	8	Significant effect of EPA, similar to fluoxetine. EPA + fluoxetine combination was superior to either of the above alone.
Keck *et al.*, 2006[25]	BD	116 (20-73)	6000 mg EPA	paraffin oil	Adjunct	16	No effect
Lucas *et al.*, 2009[12]	PD and depression in menopause	120 women (40-55)	1050 mg EPA + 150 mg DHA	sunflower oil	None	8	Improvement in women with PD but without MDD at baseline
Marangell *et al.*, 2003[17]	MDD	36 (18-65)	2000 mg DHA	NR	None	6	No effect
Mischoulon *et al.*, 2008[18]	MDD	35 (18-80)	1000 mg DHA / 2000 mg DHA / 4000 mg DHA	corn and soy oil	None	12	Positive effect at lower doses
Mischoulon *et al.*, 2009[19]	MDD	57 (18-80)	1000 mg EPA	paraffin oil	None	8	No effect
Nemets *et al.*, 2002[20]	MDD	20 (18-75)	2000 mg EPA	not specified	Adjunct	4	Significant effects after 3 week of treatment
Nemets *et al.*, 2006[15]	MDD	28 (6-12)	380-400 mg EPA + 180-200 mg DHA	olive oil or safflower oil	Adjunct in 5 children, none in the rest	16	Highly significant effects of omega-3
Peet and Horrobin, 2002[21]	MDD	70 (18-70)	1000 mg EPA / 2000 mg EPA / 4000 mg EPA	paraffin oil	Adjunct	12	Clear effect with 1000 mg EPA
Rogers *et al.*, 2008[27]	Mild to moderate depression	218 (18-70)	630 mg EPA + 850 mg DHA	olive oil	None	12	No effect

https://doi.org/10.1017/S0007114512001640x Published online by Cambridge University Press

British Journal of Nutrition

Table 1. *Continued*

Reference	Diagnosis	*n* (age, years)	Daily dose of *n*-3	Placebo	Drug Treatment	Length of trial (weeks)	Outcome
Rondanelli *et al.*, 2010[13]	MDD or dysthymia	46 women (65-90)	1670 mg EPA + 830 mg DHA	paraffin oil	None	8	Significant improvement with supplementation
Silvers *et al.*, 2005[22]	MDD	77 (18-65)	600 mg EPA + 2400 mg DHA	olive oil	Adjunct	12	No effect
Stoll *et al.*, 1999[26]	BD I and II	30 (18-65)	6200 mg EPA + 3400 mg DHA	olive oil	Adjunct	16	Significant symptom reduction and better outcome
Su *et al.*, 2003[23]	MDD	28 (18-60)	4400 mg EPA + 2200 DHA	olive oil	Adjunct	8	Significant improvement with supplementation
van de Rest *et al.*, 2008[11]	Healthy	302 (≥65)	1800 mg EPA + DHA/400 mg EPA + DHA	sunflower oil high in oleic acid	None	26	No effect

MDD = major depression disorder; BD = bipolar disorder; PD = psychological distress; NR = not reported

In five studies[39–41,43,44] the subjects received no pharmacological treatment, in one a stimulant medication[42] was provided, and in two[45,46] the subjects continued with their normal medication.

Discussion

n-3 PUFA and depression disorders

Depression is very common – one in five people become depressed at some point in their lives[47]. A significant proportion (10–20 %) of patients do not respond at all or respond poorly to therapy[48]; useful prevention and treatment strategies are therefore a priority.

Although observational studies have indicated that depression is associated with lower levels of total *n*-3 PUFA and those of both EPA and DHA[49], only two studies were found that analysed the role of *n*-3 PUFA supplements in healthy persons, the results of which were not conclusive.

Van de Rest *et al.*[11] reported no effect on mental well-being for either of two doses of *n*-3 PUFA administered (0·4 g/d and 2·0 g/d) compared to a placebo. In contrast, Antipa *et al.*[32] reported a positive effect of supplementation on cognitive reactivity, risky decision-making and control/perfectionism score. The dose of *n*-3 PUFA used in the latter work was also 2 g/d, although the EPA/DHA ration was higher (7·0 compared to 1·3).

The majority of studies, which employed doses of up to 2·5 g/d, performed on patients with depression, MDD or BD who received no pharmacological treatment, recorded a positive effect for EPA supplementation[10,12], DHA supplementation,[18] and their combination[12,13]. Gracious *et al.*[14] also reported a positive effect, but for a dose of 6·6 g/d EPA. Those studies that found no difference in effect between the administration of *n*-3 PUFA and placebo also employed low/moderate doses of *n*-3 PUFA[17,19,27] (up to 2 g/d). However, the EPA/DHA ratio was much higher in those that found positive effects (EPA/DHA = 2·0[13]-7·0[12]) compared to those that found no effect (EPA/DHA = 0·70)[27].

More trials report a positive effect for *n*-3 PUFA supplementation as an adjunct therapy[15,20,21,23,24,26] than those that found no effect[22,25]. As in those studies that involved *n*-3 PUFA supplementation only, those that found this positive effect involved lower doses of EPA (< 2·0 g/d[22,25]) or a higher EPA/DHA ratio[15,23,26] (2·0 *vs.* 0·25[22] in positive and negative trials respectively). Carney *et al.*[29] (who administered sertraline) and Chiu *et al.*[10] (who used valproate) found no evidence that *n*-3 PUFA increased the effect of medication on depression or manic phase BD symptoms.

The trials that involved *n*-3 PUFA administration with and without pharmacological treatment found EPA to produce more promising results with respect to the improvement of depression symptoms than DHA monotherapy[50,51]. A specific ratio of EPA/DHA might be the most effective[28]. However, whereas increased *n*-3 PUFA intake might alleviate depressive symptoms, there is little evidence it is of any benefit in the treatment of mania[10,52].

British Journal of Nutrition

Table 2. -Randomized controlled clinical trials of supplementation with *n*-3 PUFA in patients with perinatal depression

Reference	Diagnosis	*n* (age, years)	Daily dose of PUFA	Placebo	Drug Treatment	Length of trial (weeks)	Outcome
Doornbos *et al.*, 2009[37]	Healthy	119 (NR)	220 mg DHA / 220 mg DHA + 220 mg AA	soy bean oil	NR	From enrolment (14-20 w of pregnancy) until 3 months after delivery	No effect
Freeman *et al.*, 2008[38]	MDD in pregnancy	59 (18-45)	1100 mg EPA + 800 mg DHA	corn oil + 1 % fish oil	none	8	No effect
Llorente *et al.*, 2003[36]	Healthy	119 (NR)	~ 200 mg DHA	not specified	none	16 (after delivery)	No effect
Makrides *et al.*, 2010[34]	Healthy	2399 (28·9 ± 5·6)	100 mg EPA + 800 mg DHA	rapeseed, sunflower, palm	none	From enrolment (< 21 w of pregnancy) until birth.	No effect
Rees *et al.*, 2008[33]	MDD or dysthymia in pregnancy	26 (> 21 y)	414 mg EPA + 1638 mg DHA + 198 *n*-6	Sunola oil	none	6	No effect
Su *et al.*, 2008[35]	MDD in pregnancy	36 (18-40 y)	2200 mg EPA + 1200 mg DHA	olive oil	none	8	Improvement of depression symptoms by week 6

MDD = major depression disorder; NR = not reported

Depression is a common co-morbid disorder in both type 1 and type 2 diabetes mellitus[28], but a considerable percentage of diabetic subjects receiving antidepressant drugs does not achieve full remission[53]. Depression is also frequent in patients with Parkinson Disease[54,55], but antidepressant treatment given in addition to Parkinson's medication can often result in collateral effects and adverse reactions[56]. Depression may also occur in the early stages of Alzheimer disease[57]. However, very few studies have been performed in such patients. Bot *et al.*[28] found no evidence of a therapeutic effect of 1·0 g/d ethyl–EPA as an add-on to antidepressant medication compared to placebo in diabetic patients with depression, and Freund-Levi *et al.*[31] observed no positive effect on depression symptoms in patients with Alzheimer disease. However, in these trials, patients continued with their usual treatment for depression, and this may have masked small effects of treatment with *n*-3 PUFA. Certainly, da Silva *et al.*[30] found that an EPA/DHA ratio of 1·5 improved depressive symptoms in patients with Parkinson disease, even in those who had already been taking antidepressant medication for over a year but still suffered major depression diagnosis.

n-3 PUFA supplementation and perinatal depression

Pregnancy leads to several changes in *n*-3 PUFA status, including a depletion of maternal plasma DHA under normal dietary conditions, that persist after delivery[58]. Mothers may be at higher risk of post-partum depression when they become depleted in *n*-3 PUFA, especially DHA, and certainly, depression is quite common in the post-partum period[59]. The studies described in Table 2 all investigate the possible effects of *n*-3 PUFA supplementation on the prevention and treatment of perinatal depression.

In studies involving healthy women, supplementation was found not to be associated with any effect on the prevention of depression during[37] or after[34,36,37] pregnancy. Llorente *et al.*[36] used supplements of DHA at a dose of 200 mg/d with no other treatment, and observed no effect on the incidence of postpartum depression, while Doornbos *et al.*[37] used supplements of DHA (220 mg/d) or DHA + AA (220 mg/d each), and found them to have no effect either (Table 2). This may have been because no EPA was provided in these studies, or simply because of their small sample sizes. Makrides *et al.*[34] overcame some of the limitations of these studies, such as the low dose of DHA given, the absence of EPA in supplements, and small sample size. However, even when 800 mg/d DHA were provided, along with 100 mg/d EPA, no reduction in the prevention of postpartum depression was seen.

In pregnant women diagnosed with perinatal depression, supplementation was associated with no improvement in symptoms in some studies[33,35,38](Table 2). For example, Freeman *et al.*[38] reported no improvements with a dose of EPA + DHA of 1·9 g/d, and Rees *et al.*[33] observed none after providing 6 g/d of fish oil (414 mg EPA + 1638 mg DHA). The only study to report some improvement in symptoms was that of Su *et al.*[35]. The main difference between

Table 3. Randomised controlled clinical trials of supplementation with *n*-3 PUFA in children with ADHD

Reference	Diagnosis	*n* (age, years)	Daily dose of PUFA	Placebo	Drug Treatment	Length of trial (weeks)	Outcome
Bélanger *et al.*, 2009[39]	DSM-IV ADHD	37 (6 -12)	500-1000 mg EPA + 200-400 mg DHA (according to body weight)	sunflower oil	none	8 + 8	No effect of treatment
Gustafsson *et al.*, 2010[43]	DSM-IV ADHD	92 (7-12)	500 mg EPA + 2·7 mg DHA	rapeseed oil + medium-chain triglycerides	none	15	No significant effect on sample as a whole, but improvement in sub-group of children with opposi tional behaviour and less impulsi-veness/hyperactivity
Hirayama *et al.*, 2004[45]	DSM-IV ADHD + ADHD-suspected	40 (6-12)	500 mg DHA + 100 mg EPA (added to foods)	Non-enriched foods	Ongoing usual treatment	8·5	No effect of treatment
Johnson *et al.*, 2009 (phase 1)[44]	DSM-IV ADHD	82 (8-18)	558 mg EPA + 174 mg DHA + 60 mg GLA	olive oil	none	12	No significant effect on sample as a whole, but improvement in sub-group of children with ADHD inat-tentive subtype and comorbid neurodevelopmental disorders
Raz y col., 2009[41]	AFA and DSM-IV ADHD	73 (7-13)	480 mg of LA + 120 mg of ALA	1000 mg Vit C	none	7	No effect of treatment
Richardson and Puri., 2002[46]	ADHD-like symptoms + learning disabilities	41 (8-12)	186 mg EPA +480 mg DHA + 96 mg GLA + 864 mg LA + 42 mg AA	olive oil	none	12	Significant effect on symptoms
Sinn and Bryan., 2007 (phase 1)[40]	Score ≥ 2 SD above average Conners ADHD Index.	129 (7-12)	LC-PUFA (558 mg EPA + 174 mg DHA + 60 mg GLA)	Palm oil	none	15	Improvement in parent ratings of ADHD-related symptoms; no improvements in teacher reports
Stevens *et al.*, 2003[62]	ADHD-like symptoms + EFA deficiency	47 (6-13)	480 mg DHA + 80 mg EPA + 40 mg AA + 96 mg GLA	olive oil	ongoing usual treatment	17·5	Significant improvements only in 2 of 16 outcome measures
Voigt *et al.*, 2001[42]	DSM-IV ADHD	63 (6-12)	345 mg DHA	Not specified	Adjunctive	17·5	No effect

GLA: gamma linolenic acid

this and the previous two studies was that the dose of *n*-3 PUFA administered and the EPA/DHA ratio (1·8) were higher, and that the Hawthorn effect (a high response in the control group)[60] was avoided by not including those individuals in the randomisation procedure who, after a single-blind placebo run-in of 1 week, showed a strong placebo response.

Although the use of *n*-3 PUFA supplements in depressed pregnant women at the above doses does not appear to improve symptoms, there is insufficient evidence to confirm this at present. New trials should be undertaken in which the consumption of fish is controlled since this has the potential to confound the results. In such trials, depressed pregnant women should be provided an *n*-3 PUFA supplement with an adequate EPA/DHA ratio, and an adequate control group should be present. The involvement of depressed pregnant women with an inadequate *n*-3 PUFA status might also be useful. Certainly, future studies should examine the improvement in gestational diabetes since, in the general population, diabetes is associated with a greater risk of depression[28].

n-3 PUFA supplementation and ADHD

The link between ADHD and *n*-3 PUFA deficiency was first proposed by Colquhoun & Bunday[61]. Since then, a number of researchers have reported lower *n*-3 PUFA levels in children with ADHD than in healthy controls[62–66], and different studies have been carried out to determine whether *n*-3 PUFA supplementation can improve symptoms.

Some authors have reported improvements with *n*-3 PUFA supplements[40,43,44,46,62], although even the best have been modest. Further, the applicability of these studies to children with ADHD is questionable since some of studies focused on children not properly diagnosed with ADHD (DSM-IV)[40,46,62], others were unable to demonstrate clinical improvements in more than one setting[40,46,62], and some found positive results only when comparing certain subgroups of children[43,44,46].

A number of studies report no effect of supplementation on ADHD[39,41,42,45]; in all these studies the children had been properly diagnosed with ADHD (DSM-IV).

A number of limitations could have conditioned the results obtained in these studies on children with ADHD. The majority had a small sample size as a result of a high dropout rate. Although some studies found that children with ADHD had a less adequate *n*-3 PUFA status than the controls[39,43,62], virtually none tried to determine whether the baseline status was adequate and none indicated, when effects of supplementation on ADHD were seen, whether the children involved had any starting deficiency. This poor design quality might explain the results obtained in many of these studies: while the initial status of a subject might be improved by supplementation, if a deficiency remains uncorrected no improvement in symptoms might occur.

The lack of positive results observed in the examined studies might also be due to their short-term nature (none lasted longer than four months) and the low *n*-3 PUFA doses employed. Although the fatty acid composition of the plasma and erythrocytes could change over such short periods, the turnover of fatty acids in the brain is likely to be quite low in children. Longer periods of supplementation and/or larger supplements might be required for any change in the fatty acid content of the central nervous system to be seen.

Given the above, and in agreement with that stated in a recent review by Raz & Gabis[67], support for the use of essential fatty acids (EFA) supplements in children with ADHD will require further studies with more rigorous methodologies, proper ADHD diagnosis, known baseline fatty acid status, behavioural assessment in more than one setting, to be blinded (unfortunately problematic with fish oil supplements), and to involve adequate sample sizes and supplementation periods.

Omega 3 and other neuropsychiatric and behavioral disorders

Although initially 3 papers were excluded because they did not fit the inclusion criteria, we find interesting the topics addressed and deserve to be mentioned. The first study is a research conducted in 30 women with borderline personality disorder[68]. The main finding is that those women who received 1 g of ethyl-EPA (E-EPA) daily for 8 weeks experienced a greater decrease in depressive and aggressive symptoms than those receiving placebo (mineral oil). In other study, the effect of *n*-3 PUFA was analyzed in eleven patients with current obsessive-compulsive disorder, who were randomly allocated to 6 weeks of placebo (2 g/day of liquid paraffin) followed by 6 weeks of 2 g/day of EPA, or to EPA followed by placebo[69]. The authors didn't find significant effect of the supplement. According with the author's conclusion, one of the reasons for its ineffectiveness could be a low EPA dose. The last work studied the effect of *n*-3 on the Developmental Coordination Disorder[70]. In this study, 117 children aged 5 to 12 years were given a supplement with an omega 3:6 ratio of 4:1 or a placebo for 3 months, followed by a period for 3 months in which all participants received the supplement. Although there were not improvements on motor skills, improvements for active treatment versus placebo were found in reading, spelling, and behaviour over the 3 months of treatment. After the crossover, similar changes were seen in the placebo-active group, whereas children continuing with active treatment maintained or improved their progress. In view of these results is interesting to note the possible use of *n*-3 in the treatment of some neuropsychiatric and behavioural disorders, yet little studied.

Conclusions

In conclusion, the results of the articles examined in the present work regarding the effect of *n*-3 PUFA supplementation on the prevention and treatment of non-neurodegenerative neuropsychiatric disorders are inconclusive, although it would seem plausible that such supplementation could provide some benefit.

Having in mind the data of the present review, most of the existing studies do not meet important requirements to elucidate the effect of *n*-3 PUFA on the prevention and treatment of non-neurodegenerative neuropsychiatric disorders. Future studies should include: a sample size justified by an adequate sample size predetermination (specific to the group under study); the assessment of basal situation in *n*-3 PUFA in order to include only those patients with a status that could be improved; an appropriate selection criteria (healthy or sick subjects, with or without drug treatment...); control of dietary intake during the intervention, since changes in other nutrients may modify the results of the intervention; and the study of changes in erythrocytes *n*-3 PUFA levels in order to determine whether dietary intervention corresponds with changes in biochemical parameters. In addition, according with the studies included in the present review, the ratio EPA/DHA should be higher than 1·5-2 and future studies should be long enough to ensure that biochemical changes lead to a functional change (in both behavior or neuropsychiatric disorders). Thus, improving the design of future studies is essential to reach conclusive results.

Acknowledgements

R. M. O. and A. M. L. S. contributed to the planning of the search of this review, A. M. L. S. and E. R. R. decided the analysis and presentation of the results and created the quality assessment tool of the articles. All authors were involved in the analyses of the articles. A. M. L. S. and E. R. R. wrote the introduction and methodology of the first manuscript. All authors wrote the results section and revised and discussed all drafts and approved the final manuscript. There are no conflicts of interest to report. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

1. Chang CY, Ke DS & Chen JY (2009) Essential fatty acids and human brain. *Acta Neurol Taiwan* **18**, 231–241.
2. Horrobin D (2002) Cardiovascular disease, affective disorders and impaired fatty acid and phosopholipid metabolism. In *Vascular disease and affective disorders*, pp. 332–352 [AD Chiu E and C Katona, editors]. London: United Kingdom.
3. Young G & Conquer J (2005) Omega-3 fatty acids and neuropsychiatric disorders. *Reprod Nutr Dev* **45**, 1–28.
4. Freeman MP, Hibbeln JR, Wisner KL, *et al.* (2006) Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry* **67**, 1954–1967.
5. Bourre JM (2005) Dietary omega-3 Fatty acids and psychiatry: mood, behaviour, stress, depression, dementia and aging. *J Nutr Health Aging* **9**, 31–38.
6. Silvers KM, Woolley CC, Hamilton FC, *et al.* (2005) Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukot Essent Fatty Acids* **72**, 211–218.
7. Grenyer BF, Crowe T, Meyer B, *et al.* (2007) Fish oil supplementation in the treatment of major depression: a randomised double-blind placebo-controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry* **31**, 1393–1396.
8. Raz R, Carasso RL & Yehuda S (2009) The influence of short-chain essential fatty acids on children with attention-deficit/hyperactivity disorder: a double-blind placebo-controlled study. *J Child Adolesc Psychopharmacol* **19**, 167–177.
9. Appleton KM, Rogers PJ & Ness AR (2010) Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. *Am J Clin Nutr* **91**, 757–770.
10. Chiu CC, Huang SY, Chen CC, *et al.* (2005) Omega-3 fatty acids are more beneficial in the depressive phase than in the manic phase in patients with bipolar I disorder. *J Clin Psychiatry* **66**, 1613–1614.
11. van de Rest O, Geleijnse JM, Kok FJ, *et al.* (2008) Effect of fish-oil supplementation on mental well-being in older subjects: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr* **88**, 706–713.
12. Lucas M, Asselin G, Merette C, *et al.* (2009) Ethyl-eicosapentaenoic acid for the treatment of psychological distress and depressive symptoms in middle-aged women: a double-blind, placebo-controlled, randomized clinical trial. *Am J Clin Nutr* **89**, 641–651.
13. Rondanelli M, Giacosa A, Opizzi A, *et al.* (2010) Effect of omega-3 fatty acids supplementation on depressive symptoms and on health-related quality of life in the treatment of elderly women with depression: a double-blind, placebo-controlled, randomized clinical trial. *J Am Coll Nutr* **29**, 55–64.
14. Gracious BL, Chirieac MC, Costescu S, *et al.* (2010) Randomized, placebo-controlled trial of flax oil in pediatric bipolar disorder. *Bipolar Disord* **12**, 142–154.
15. Nemets H, Nemets B, Apter A, *et al.* (2006) Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *Am J Psychiatry* **163**, 1098–1100.
16. Jazayeri S, Tehrani-Doost M, Keshavarz SA, *et al.* (2008) Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder. *Aust N Z J Psychiatry* **42**, 192–198.
17. Marangell LB, Martinez JM, Zboyan HA, *et al.* (2003) A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry* **160**, 996–998.
18. Mischoulon D, Best-Popescu C, Laposata M, *et al.* (2008) A double-blind dose-finding pilot study of docosahexaenoic acid (DHA) for major depressive disorder. *Eur Neuropsychopharmacol* **18**, 639–645.
19. Mischoulon D, Papakostas GI, Dording CM, *et al.* (2009) A double-blind, randomized controlled trial of ethyl-eicosapentaenoate for major depressive disorder. *J Clin Psychiatry* **70**, 1636–1644.
20. Nemets B, Stahl Z & Belmaker RH (2002) Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry* **159**, 477–479.
21. Peet M & Horrobin DF (2002) A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry* **59**, 913–919.
22. Silvers KM, Woolley CC, Hamilton FC, *et al.* (2005) Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukot Essent Fatty Acids* **72**, 211–218.
23. Su KP, Huang SY, Chiu CC, *et al.* (2003) Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. *Eur Neuropsychopharmacol* **13**, 267–271.

24. Frangou S, Lewis M & McCrone P (2006) Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. *Br J Psychiatry* **188**, 46–50.
25. Keck PE Jr, Mintz J, McElroy SL, *et al.* (2006) Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol Psychiatry* **60**, 1020–1022.
26. Stoll AL, Severus WE, Freeman MP, *et al.* (1999) Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* **56**, 407–412.
27. Rogers PJ, Appleton KM, Kessler D, *et al.* (2008) No effect of n-3 long-chain polyunsaturated fatty acid (EPA and DHA) supplementation on depressed mood and cognitive function: a randomised controlled trial. *Br J Nutr* **99**, 421–431.
28. Bot M, Pouwer F, Assies J, *et al.* (2010) Eicosapentaenoic acid as an add-on to antidepressant medication for co-morbid major depression in patients with diabetes mellitus: a randomized, double-blind placebo-controlled study. *J Affect Disord* **126**, 282–286.
29. Carney RM, Freedland KE, Rubin EH, *et al.* (2009) Omega-3 augmentation of sertraline in treatment of depression in patients with coronary heart disease: a randomized controlled trial. *JAMA* **302**, 1651–1657.
30. da Silva TM, Munhoz RP, Alvarez C, *et al.* (2008) Depression in Parkinson's disease: a double-blind, randomized, placebo-controlled pilot study of omega-3 fatty-acid supplementation. *J Affect Disord* **111**, 351–359.
31. Freund-Levi Y, Basun H, Cederholm T, *et al.* (2008) Omega-3 supplementation in mild to moderate Alzheimer's disease: effects on neuropsychiatric symptoms. *Int J Geriatr Psychiatry* **23**, 161–169.
32. Antypa N, Van der Does AJ, Smelt AH, *et al.* (2009) Omega-3 fatty acids (fish-oil) and depression-related cognition in healthy volunteers. *J Psychopharmacol* **23**, 831–840.
33. Rees AM, Austin MP & Parker GB (2008) Omega-3 fatty acids as a treatment for perinatal depression: randomized double-blind placebo-controlled trial. *Aust N Z J Psychiatry* **42**, 199–205.
34. Makrides M, Gibson RA, McPhee AJ, *et al.* (2010) Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. *JAMA* **304**, 1675–1683.
35. Su KP, Huang SY, Chiu TH, *et al.* (2008) Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* **69**, 644–651.
36. Llorente AM, Jensen CL, Voigt RG, *et al.* (2003) Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. *Am J Obstet Gynecol* **188**, 1348–1353.
37. Doornbos B, van Goor SA, Dijck-Brouwer DA, *et al.* (2009) Supplementation of a low dose of DHA or DHA + AA does not prevent peripartum depressive symptoms in a small population based sample. *Prog Neuropsychopharmacol Biol Psychiatry* **33**, 49–52.
38. Freeman MP, Davis M, Sinha P, *et al.* (2008) Omega-3 fatty acids and supportive psychotherapy for perinatal depression: a randomized placebo-controlled study. *J Affect Disord* **110**, 142–148.
39. Belanger 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. *Paediatr Child Health* **14**, 89–98.
40. Sinn N & Bryan J (2007) Effect of supplementation with polyunsaturated fatty acids and micronutrients on learning and behavior problems associated with child ADHD. *J Dev Behav Pediatr* **28**, 82–91.
41. Raz R, Carasso RL & Yehuda S (2009) The influence of short-chain essential fatty acids on children with attention-deficit/hyperactivity disorder: a double-blind placebo-controlled study. *J Child Adolesc Psychopharmacol* **19**, 167–177.
42. 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. *J Pediatr* **139**, 189–196.
43. Gustafsson PA, Birberg-Thornberg U, Duchen K, *et al.* (2010) EPA supplementation improves teacher-rated behaviour and oppositional symptoms in children with ADHD. *Acta Paediatr* **99**, 1540–1549.
44. 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. *J Atten Disord* **12**, 394–401.
45. Hirayama S, Hamazaki T & Terasawa K (2004) Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder - a placebo-controlled double-blind study. *Eur J Clin Nutr* **58**, 467–473.
46. Richardson AJ & Puri BK (2002) 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. *Prog Neuropsychopharmacol Biol Psychiatry* **26**, 233–239.
47. Olfson M, Shea S, Feder A, *et al.* (2000) Prevalence of anxiety, depression, and substance use disorders in an urban general medicine practice. *Arch Fam Med* **9**, 876–883.
48. McIntyre RS & O'Donovan C (2004) The human cost of not achieving full remission in depression. *Can J Psychiatry* **49**, 10S–16S.
49. Lin PY & Su KP (2007) A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *J Clin Psychiatry* **68**, 1056–1061.
50. Pouwer F, Nijpels G, Beekman AT, *et al.* (2005) Fat food for a bad mood. Could we treat and prevent depression in Type 2 diabetes by means of omega-3 polyunsaturated fatty acids? A review of the evidence. *Diabet Med* **22**, 1465–1475.
51. Martins JG (2009) EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. *J Am Coll Nutr* **28**, 525–542.
52. Hegarty BD & Parker GB (2011) Marine omega-3 fatty acids and mood disorders - linking the sea and the soul: 'Food for Thought' I. *Acta Psychiatr Scand* **124**, 42–51.
53. Lustman PJ & Clouse RE (2002) Treatment of depression in diabetes: impact on mood and medical outcome. *J Psychosom Res* **53**, 917–924.
54. Nuyen J, Schellevis FG, Satariano WA, *et al.* (2006) Comorbidity was associated with neurologic and psychiatric diseases: a general practice-based controlled study. *J Clin Epidemiol* **59**, 1274–1284.
55. Wichowicz HM, Slawek J, Derejko M, *et al.* (2006) Factors associated with depression in Parkinson's disease: a cross-sectional study in a Polish population. *Eur Psychiatry* **21**, 516–520.
56. Vajda FJ & Solinas C (2005) Current approaches to management of depression in Parkinson's Disease. *J Clin Neurosci* **12**, 739–743.
57. McKeith I & Cummings J (2005) Behavioural changes and psychological symptoms in dementia disorders. *Lancet Neurol* **4**, 735–742.

British Journal of Nutrition

58. Al MD, van Houwelingen AC & Hornstra G (2000) Long-chain polyunsaturated fatty acids, pregnancy, and pregnancy outcome. *Am J Clin Nutr* **71**, 285S–291S.
59. Jans LA, Giltay EJ & Van der Does AJ (2010) The efficacy of n-3 fatty acids DHA and EPA (fish oil) for perinatal depression. *Br J Nutr* **104**, 1577–1585.
60. Walsh BT, Seidman SN, Sysko R, *et al.* (2002) Placebo response in studies of major depression: variable, substantial, and growing. *JAMA* **287**, 1840–1847.
61. Colquhoun I & Bunday S (1981) A lack of essential fatty acids as a possible cause of hyperactivity in children. *Med Hypotheses* **7**, 673–679.
62. Stevens L, Zhang W, Peck L, *et al.* (2003) EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. *Lipids* **38**, 1007–1021.
63. Mitchell EA, Aman MG, Turbott SH, *et al.* (1987) Clinical characteristics and serum essential fatty acid levels in hyperactive children. *Clin Pediatr (Phila)* **26**, 406–411.
64. Arnold LE, Kleykamp D, Votolato NA, *et al.* (1989) Gamma-linolenic acid for attention-deficit hyperactivity disorder: placebo-controlled comparison to D-amphetamine. *Biol Psychiatry* **25**, 222–228.
65. Burgess JR, Stevens L, Zhang W, *et al.* (2000) Long-chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder. *Am J Clin Nutr* **71**, 327S–330S.
66. Chen JR, Hsu SF, Hsu CD, *et al.* (2004) Dietary patterns and blood fatty acid composition in children with attention-deficit hyperactivity disorder in Taiwan. *J Nutr Biochem* **15**, 467–472.
67. Raz R & Gabis L (2009) Essential fatty acids and attention-deficit-hyperactivity disorder: a systematic review. *Dev Med Child Neurol* **51**, 580–592.
68. Zanarini MC & Frankenburg FR (2003) Omega-3 Fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *Am J Psychiatry* **160**, 167–169.
69. Fux M, Benjamin J & Nemets B (2004) A placebo-controlled cross-over trial of adjunctive EPA in OCD. *J Psychiatr Res* **38**, 323–325.
70. Richardson AJ & Montgomery P (2005) The Oxford-Durham study: a randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics* **115**, 1360–1366.

British Journal of Nutrition