Prostaglandins, Leukotrienes and Essential Fatty Acids ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

journal homepage: www.elsevier.com/locate/plefa

Which polyunsaturated fatty acids are active in children with attention-deficit hyperactivity disorder receiving PUFA supplementation? A fatty acid validated meta-regression analysis of randomized controlled trials

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ARTICLE INFO

Article history:
Received 25 August 2013
Received in revised form
31 December 2013
Accepted 27 January 2014

Keywords:
ADHD
DPA
EPA
GLA
Meta-analysis
Meta-regression

ABSTRACT

Concerns about growth retardation and unknown effects on long-term brain development with stimulants have prompted interest in polyunsaturated fatty acid supplementation (PUFA) as an alternative treatment. However, randomized controlled trials (RCTs) and meta-analyses of PUFA supplementation in ADHD have shown marginal benefit, and uncertainty exists as to which, if any, PUFA might be effective in alleviating symptoms of ADHD. We conducted an updated meta-analysis of RCTs in ADHD together with multivariable meta-regression analyses using data on PUFA content obtained from independent fatty acid methyl ester analyses of each study PUFA regimen. The PubMed, Embase and PsycINFO databases were searched with no start date and up to 28th July 2013. Study inclusion criteria were: randomized design, placebo controlled, PUFA preparation as active intervention, reporting change scores on ADHD rating-scale measures. Rating-scale measures of inattention and hyperactive-impulsive symptoms were extracted, study authors were contacted to obtain missing data, studies not reporting negative findings had these data imputed, and study quality was assessed using the Jadad system plus other indicators. Random-effects models were used for pooled effects and for meta-regression analyses. Standardized mean differences (SMD) in inattention, hyperactive-impulsive and combined symptoms were assessed as rated by parents, teachers or all raters. The influence of study characteristics and PUFA regimen content was explored in multivariable meta-regression analyses. The overall pooled estimate from 18 studies showed that combined ADHD symptoms rated by all raters decreased with PUFA supplementation; SMD −0.192 (95% CI: −0.297, −0.086; $P<0.001$). However, when analyzed by rater, only parent-rated symptoms decreased significantly. Multivariable meta-regression showed that longer study duration, γ-linolenic acid (GLA), and the interaction between GLA and eicosapentaenoic acid (EPA) were associated with significant decreases in inattention; however, PUFA regimen content was unrelated to changes in hyperactive-impulsive symptoms. Certain fatty acids present in placebo preparations may potentially have been psychoactive. This meta-analysis provides modest evidence of PUFA effectiveness in ADHD, especially GLA and EPA for inattention symptoms; however, evidence of reporting bias, publication bias, variable methodological quality, and use of potentially psychoactive placebos limit the generalizability of these findings.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is relatively common and increasing in importance; recent prevalence estimates in childhood are 8.7–10.6% [1]. The burden associated with childhood and adolescent ADHD includes diminished quality of life for patients and their families [2], increased economic costs [3], and if inadequately managed, an increased risk for the development of long-term academic underachievement [4], conduct disorder [5–7], alcohol dependence during adulthood in males [8], and later antisocial personality and/or criminality [9–11].

During the 1990s, the multi-site collaborative randomized trial known as the Multimodal Treatment Study of Children with ADHD (MTA) was set up by the National Institute of Mental Health to examine comparative long-term treatment effectiveness of medication management (involving carefully crafted methylphenidate titration followed by monthly visits) versus behavioral treatment versus combined methylphenidate and behavioral treatment versus routine

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http://dx.doi.org/10.1016/j.plefa.2014.01.004
0952-3278

community care [12]. At 14-month follow-up, the medication arm was superior to both behavioral treatment (parent, school, and child components, with therapist involvement gradually reduced over time) and routine community care (which included medication in two-thirds of cases) [13]. However, intent-to-treat analyses showed that the benefit of medication management was completely lost at three-year follow-up, with no significant differences in ADHD symptoms apparent between the four groups [14]; furthermore, pharmacotherapy was associated with growth retardation [15].

There is anxiety among parents and professionals alike [16–18] about the side-effects of long-term stimulant pharmacotherapy, including effects on brain development and the subsequent risk of substance abuse. In juvenile rats, methylphenidate induces lipid and protein damage in the prefrontal cortex [19], and decreases anterior cingulate cortical intra-network functional connectivity, striatal myelination, striatal volume, and increases corpus callosal fractional anisotropy [20]. Of relevance to the concern about future vulnerability to drug abuse, early exposure to methylphenidate increases responsiveness to cocaine in adult male rats [21]. In addition, non-stimulant medication for ADHD such as atomoxetine is associated with troublesome side-effects such as nausea, loss of appetite, dry mouth, insomnia and fatigue [22]. Therefore, there is an ongoing search for alternative effective ADHD treatments with good tolerability and safety.

In their seminal study, Stevens and colleagues reported that boys with ADHD had lower concentrations than controls of certain plasma polar lipids (20:4$n-6$, 20:5$n-3$, and 22:6$n-3$) and erythrocyte lipids (20:4$n-6$ and 22:4$n-6$) [23]. Furthermore, children with lower compositions of total omega-3 fatty acids had more behavioral problems, temper tantrums, and learning, health and sleep problems than did those with high proportions of omega-3 fatty acids [23,24]. In 1981, Colquhoun and Bunday put forward the hypothesis that many of the clinical features of ADHD could be explained on the basis of an underlying abnormality of fatty acid metabolism, and further hypothesized that treatment with poly-unsaturated fatty acids (PUFAs) may be of therapeutic value [25]. This fatty-acid model might also explain the co-morbidity of ADHD with dyslexia, developmental coordination disorder, and autism spectrum disorders [26].

There have been several randomized controlled PUFA trials in children and adolescents with ADHD in recent years with meta-analytic investigations beginning to appear in the literature [27–29]. Given that these meta-analyses have drawn different conclusions on overall effectiveness of PUFAs [27–29], the differential efficacy of eicosapentaenoic acid (EPA) versus docosahexaenoic acid (DHA) [27], the role of combined omega-6 and omega-3 PUFA supplementation [28], and the influence of symptom rater blinding [29], we carried out an exploratory meta-regression analysis of ADHD trials examining the role of PUFAs with no *a priori* assumption concerning which PUFA might or might not be effective in alleviating symptoms of ADHD. To achieve this we performed a meta-analysis of rating scale outcomes adjusted for reporting bias in combination with meta-regression analyses using data from independent fatty acid content analyses of study regimens, which to our knowledge has not previously been undertaken.

2. Methods

2.1. Search strategy

Articles were identified for inclusion in the meta-analysis using the following search strategy with no specific start date. The PubMed database was searched using the following MeSH and free terms:

((“Attention Deficit Disorder with Hyperactivity”[Mesh] OR “attention deficit”[All Fields] OR “hyperactivity”[All Fields] OR “inattention”[All Fields] OR “impulsivity”[All Fields] OR “ADHD”[All Fields]) AND (“Fatty Acids, Essential”[Mesh] OR “Fatty Acids, Omega-3”[Mesh] OR “Fish Oils”[Mesh] OR “Eicosapentaenoic Acid”[Mesh] OR “Docosahexaenoic Acids”[Mesh] OR “fatty acids”[All Fields] OR “essential fatty acids”[All Fields] OR “fish oil”[All Fields] OR “polyunsaturated”[All Fields] OR “eicosapentaenoic”[All Fields] OR “docosahexaenoic”[All FIelds])) AND (“Clinical Trial”[Publication Type] OR “treatment”[All Fields] OR “administration”[All Fields] OR “randomized”[All Fields] OR “randomised”[All Fields] OR “placebo”[All Fields] OR “trial”[All Fields] OR “study”[All Fields]) AND (“children”[All Fields] OR “adolescents”[All Fields] OR “child”[All Fields] OR “adolescent”[All Fields])

The Ovid platform was also employed to search the EMBASE and psycINFO databases using the following terms:

(attention deficit OR hyperactivity OR impulsivity OR ADHD) AND (treatment OR administration OR randomized OR randomised OR placebo OR trial OR study) AND (children OR adolescents OR child OR adolescent) AND (fatty acids OR essential fatty acids OR fish oil OR polyunsaturated OR eicosapentaenoic OR docosahexaenoic).

As of the 28th July 2013, 146 abstracts were identified from the PubMed search, and 1259 abstracts were identified from the EMBASE and psycINFO databases, giving a total of 1129 abstracts after duplicates were removed.

From the combined PubMed and Ovid searches, 32 abstracts were selected for examination of the full citation on the basis of the following inclusion criteria: (i) randomized design; (ii) placebo controlled; (iii) use of a PUFA preparation as active intervention; and (iv) reporting sufficient statistical results on changes in scores of a validated rating-scale measure of ADHD symptoms in response to intervention. Studies were included if they reported changes in ADHD symptoms in children and/or adolescents with a formal diagnosis of ADHD or without (for example, dyslexia, developmental coordination disorder, or reading impairment in otherwise normal children). Studies examining changes in ADHD symptoms in children and/or adolescents with autistic spectrum disorders were excluded.

Of these 32 full citations, 18 citations were identified that described studies that could be subjected to meta-analytic review (one placebo-controlled trial, although not described as randomized in the study report, was confirmed as randomized by the author [30] and was therefore included) and 14 citations were excluded (see PRISMA flow diagram in Supplementary eFig. 1). Reasons for exclusion were as follows; 1, not randomized [31]; 1, not placebo-controlled [32]; 3, open-label [33–35]; 2, letters related to primary publication [36,37]; 1, results reported as median values and despite contacting the corresponding author no mean and standard deviation values could be obtained [38]; 1, in adults [39]; 2, reported cognitive function tests only [40,41]; 1, no rating of hyperactivity or inattention [42]; 1, reporting fatty acid profiles related to an earlier randomized controlled trial [43]; and 1, no data presented for numbers of patients in each treatment group [44]. Of note, our selection strategy identified all studies included in a recent Cochrane systematic review [28], which employed a more extensive search strategy of multiple databases. Therefore, despite the simplicity of the present search strategy, it is unlikely that significant studies have been missed. The characteristics of the final 18 included studies are shown in Table 1.

2.2. Outcome measures

ADHD rating scales were chosen as meta-analytic outcomes rather than neuropsychological tests of attention or impulsivity, because neuropsychological tests were employed less frequently and more variably than rating scales to have allowed for reliable

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Table 1
Characteristics of the 18 included studies listed chronologically according to e-publication date or publication date, whichever was earlier.

Study [reference]	Clinical disorder	Number, total (FA/placebo)	Mean age (y)	% Male	Fatty acid preparation (manufacturer)	Reported daily fatty acid regimen(s) (use as adjunctive, monotherapy or mixed)	Placebo content	Duration (days)	Outcome measure	Rater (missing)	Quality score	Trial registration
Aman et al. [30]	ADHD	31 (31/31)[a]	8.9	87.1	Efamol (Efamol Ltd, UK)	2.160 g LA+0.270 g GLA (monotherapy)	Liquid paraffin	28	ACTeRS Conners[b] RBPC	Teacher Teacher Parent	4	No
Arnold et al. [54]	ADHD	18 (18/18)[a]	9	100	Efamol (Efamol Ltd, UK)	2.800 g LA+0.320 g GLA (monotherapy)	Liquid paraffin	28	Conners[c]	Teacher (Parent)	3	No
Voigt et al. [56]	ADHD	63 (32/31)	9.3	77.7	DHASCO (Martek Biosciences Inc., USA)	0.345 g DHA (adjunctive)	Not stated	120	CBCL Conners[c]	Parent (Parent)	7	No
Richardson and Puri [65]	Dyslexia	41 (22/19)	10.3	85.4	Efalex (Efamol Ltd, UK)	0.186 g EPA+0.480 g DHA+0.096 g GLA+0.864 g LA+0.042 g AA (monotherapy)	Olive oil	84	Conners[d]	Parent	8	No
Stevens et al. [66]	ADHD	47 (25/22)	9.8	87.2	Efalex (Efamol Ltd, UK)	0.080 g EPA+0.480 g DHA +0.096 g GLA+0.040 g AA (mixed)	Olive oil	120	Conners[e] DBD	Parent Teacher Parent Teacher	9	No
Hirayama et al. [45]	ADHD	40 (20/20)	9.0	80.0	DHA-enriched food	0.100 g EPA+0.514 g DHA (mixed)	Non-enriched food	60	DSM-IV symptom count	Parent/ Teacher[f]	6	No
Richardson and Montgomery [63]	DCD	117 (60/57)	8.8	66.7	eye q (Equazen, UK)	0.558 g EPA+0.174 g DHA +0.060 g GLA (monotherapy)	Olive oil	90	Conners[g]	Teacher	8	No
Sinn and Bryan [55]	ADHD	104 (77/27)	9.4	74.0	eye q (Equazen, UK)	0.558 g EPA+0.174 g DHA+0.060 g GLA (monotherapy)	Palm oil	105	Conners[h]	Parent (Teacher)	4	No
Johnson et al. [67]	ADHD	75 (37/38)	12.0	85.3	eye q (Equazen, UK)	0.558 g EPA+0.174 g DHA+0.060 g GLA (monotherapy)	Olive oil	90	ADHD-RS	Clinician	8	Yes NCT01219309
Vaisman et al. [68]	ADHD	83 (29, 28/26)	9.3	75.0	Omega-3 FA-enriched phospholipids (Enzymotec Ltd, Israel) *OR*, Fish oil (Ocean Nutrition, Canada)	See Table 2 (monotherapy)	Rapeseed oil	90	Conners[e]	Parent	7	No
Kairaluoma et al. [69]	Dyslexia	61 (30/31)	11.1	57.4	Ethyl-EPA (Oy Bio-Vita AB, Finland)	0.500 g EPA+0.400 g Carnosine (monotherapy)	Triglycerides +cellulose	90	CBCL	Teacher	7	No
Raz et al. [46]	ADHD	78 (39/39)	10.5	60.3	Essential FAs (TransCulture, Japan)	0.480 g LA+0.120 g ALA (monotherapy)	Vitamin C	49	AHDH-RS Conners[e]	Parent Parent Teacher	6	No
Bélanger et al. [47]	ADHD	26 (13/13)[a]	9.2	69.2	ABC2 (NutriSanté, Canada)	20–25 mg/kg EPA +8.5–10.5 mg/kg DHA (monotherapy)	Sunflower oil	56	Conners[d,g]	Parent (Teacher)	5	No
Gustaffson et al. [70]	ADHD	109 (57/52)	7–12	80.4	PlusEPA (Minami Nutrition, Belgium)	0.500 g EPA+0.0027 g DHA (monotherapy)	Rapeseed oil+medium-chain triglycerides	105	Conners[i]	Parent Teacher	9	No
Manor et al. [71]	ADHD	200 (137/63)	9.2	70.7	Vayarin (Enzymotec Ltd., Israel)	0.086 g EPA+0.034 g DHA+0.300 g Phosphatidylserine (monotherapy)	Cellulose (fish odorized)	105	Conners[h]	Parent Teacher	9	Yes NCT00418184
Milte et al. [72]	ADHD	87 (30, 28/29)	8.9	79.3	EPA-rich fish oil *OR*, DHA-rich fish oil (Novasel Australia Pty Ltd.)	1.109 g EPA+0.108 g DHA *OR*, 0.254 g EPA+1.032 g DHA (monotherapy)	LA-rich safflower oil	120	Conners[h]	Parent Teacher	10	Yes ACTRN12607000332426

Table 1 (*continued*)

Study [reference]	Clinical disorder	Number, total (FA/ placebo)	Mean age (y)	% Male	Fatty acid preparation (manufacturer)	Reported daily fatty acid regimen(s) (use as adjunctive, monotherapy or mixed)	Placebo content	Duration (days)	Outcome measure	Rater (missing)	Quality score	Trial registration
Perera et al. [48]	ADHD	98 (49/49)	9.3	73.4	Vegepa (Igennus Ltd., UK)	0.593 g ω3 FAs + 0.362 g ω6 FAs (adjunctive)	Sunflower oil	180	Local language questionnaire [49]	Parent	9	No
Richardson et al. [73]	Reading impairment	362 (180/ 182)	8.7	53.0	DHASCO (Martek Biosciences Inc., USA)	0.6 g DHA (monotherapy)	corn/soybean oil (taste matched)	112	Conners[j]	Parent Teacher	11	Yes NCT01066182

ACTeRS = ADD-H Comprehensive Teacher Rating Scale [81]; ADHD-RS = ADHD rating scale [82]; CBCL = Child Behavior Checklist [83]; DCD = developmental coordination disorder; DBD = Disruptive Behavior Disorders rating scale [84]; RBPC = Revised Behavior Problem Checklist [85].

[a] Cross-over design.
[b] Conners' (1969) Teachers Questionnaire [74].
[c] Revised Conners' parent and teacher rating scales [75].
[d] Conners' Parent Rating Scale, Long Version (CPRS-L) [76].
[e] Conners' Abbreviated Symptom Questionnaire [77].
[f] Scores counted only if both parent and teacher gave the same assessment.
[g] Conners' Teacher Rating Scales, Long Version (CTRS-L) [76].
[h] Conners Rating Scales–Revised [78].
[i] Conners' Rating Scales for Parents (CPRS, short form) and for Teachers (CTRS, short form) [79].
[j] Conners' Rating Scales for Parents (CPRS, long form) and for Teachers (CTRS, long form) [80].

pooling of data across studies. Inattention and hyperactive-impulsive subscales of ADHD rating scales could be reliably obtained from most studies, rated either by both parents and teachers or by either parents or teachers (in some studies a clinician rated symptoms instead of a teacher). A list of outcome measures employed is shown in Table 1.

Individual corresponding authors were contacted to provide as much missing data as possible; means and standard deviations were obtained for the Hirayama et al. study that quoted median values [45]; parent ratings for the Conners' Abbreviated Parent-Teacher questionnaire were obtained for the Raz et al. study [46]; means and standard deviations were obtained for the Bélanger et al. study that used mean percent change from baseline without a measure of variation [47]; raw data were provided for re-analysis from the Perera et al. study whose published effect size confidence interval values contained errors [48]. The authors of this last study also provided the English translation of the ADHD questionnaire used in the study [49], enabling scales for inattention and hyperactive-impulsive symptoms to be constructed. In a recent Cochrane review examining PUFA supplementation in ADHD [28], the study by Aman et al. [30] was excluded because the outcome variable contained no variation; however, we were able to compute an effect size from the published *F* statistic.

2.3. Moderator variables

Baseline symptoms, study duration, study sample size, study quality, and individual fatty acid doses were employed as potential moderating variables.

Baseline symptoms scores were constructed by calculating *t*-scores for all rating scales across studies using published normative values and prorated according to the age and sex distribution of each individual study. One study used raw DSM-IV symptom counts as a measure of ADHD symptoms [45]; in the absence of normative data to obtain a *t*-score, the baseline value for this study was imputed as the mean of all other values. One study quoted SNAP-IV baseline mean values for combined ADHD symptoms as 2.62 (range 1.89–4.00) when the maximum score for this outcome measure is 3 [50]. The authors of this latter study were contacted and provided the raw baseline data, which showed that the 4-point Likert scale had been scored from 1–4 instead of 0–3. The mean baseline value was recalculated using the conventional 0–3 scoring system.

Methodological study quality was assessed using the Jadad score [51] plus 7 additional components: (i) whether similarities in baseline characteristics were adequately described; (ii) whether attempts were made to conceal the fish taste of the active intervention; (iii) whether the outcome assessors were adequately blinded; (iv) whether all available data were reported; (v) whether data were analyzed according to intention-to-treat (ITT) methods; (vi) whether compliance was assessed through measurement of erythrocyte or plasma fatty acids; and (vii) whether blinding success was evaluated. This gave a maximum possible quality score of 12.

Individual PUFA doses were calculated for all precursor fatty acids from linoleic acid (LA) up to and including arachidonic acid (AA) constituting the omega-6 pathway, and all precursor fatty acids from α-linolenic acid (ALA) up to and including EPA and DHA constituting the omega-3 pathway, by conducting independent FAME analyses of all PUFA regimens, except where the detailed fatty acid content of the PUFA regimen was already published. FAME analyses were conducted by Eclipse ALS, Cambridge, UK. This approach conferred two major advantages. First, it gave a more reliable assessment of the precise PUFA content of the regimens; for example, some studies reported just one or two PUFAs that were considered relevant by the investigators and others gave a full PUFA profile. Second, it enabled us to conduct meta-regression analyses with no prior assumption as to which PUFA might be active or

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inactive. PUFA profiles of all regimens used across the 18 studies are shown in Supplementary eTable 1. For a summary of the omega-3 and omega-6 biosynthetic pathways, see Supplementary eFig. 2.

2.4. Statistical methods

Standardized mean differences (SMDs) in inattention, hyperactive-impulsive, and combined ADHD symptoms scores were computed using the program Comprehensive Meta-Analysis (http://www.meta-analysis.com/), identified as one of the best software tools for this purpose in a recent systematic review [52]. The program allows mean effect sizes to be computed in studies that use multiple outcome measures; for example, two different questionnaire measures of ADHD symptoms plus a categorical measure of clinical improvement, allowing all available data relating to ADHD symptoms to be included in this analysis. We have previously shown that this strategy is more

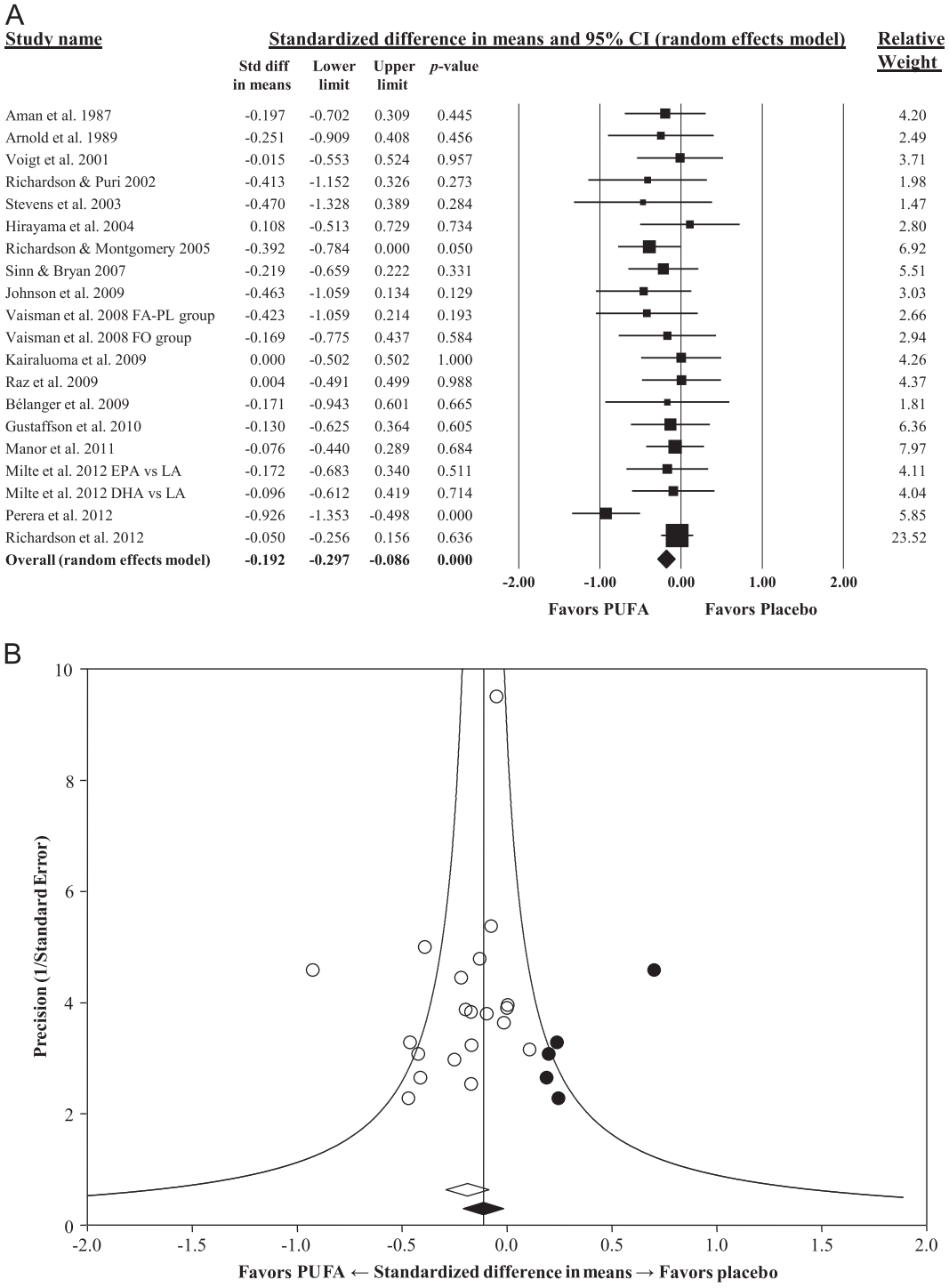

Fig. 1. (A) Forest plot for all 18 studies of standardized difference in mean of combined ADHD symptom scores (inattention and hyperactive-impulsive) rated by all raters. (B) Funnel plot for all 18 studies of precision (1/standard error) by standardized difference in mean of combined ADHD symptom scores (inattention and hyperactive-impulsive) rated by all raters. Observed studies are shown in open circles with the associated estimate in an open diamond (SMD −0.192; 95% CI: −0.297, −0.086). Imputed studies are shown in solid circles with the adjusted estimate in a solid diamond (SMD −0.118; 95% CI: −0.250, 0.014). DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA-PL, fatty acid enriched phospholipids; FO, fish oil; LA, linoleic acid.

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conservative and less likely to introduce bias than using an investigator-determined hierarchical scheme to select which outcome measure to enter into the meta-analysis [53].

In studies that measured outcomes rated by both parents and teachers, five of these failed to report negative outcomes from one or other rater [46,47,54–56]. In four of these studies [47,54–56], we were unable to obtain the missing data from authors; therefore, SMDs of zero with a standard error equal to that of the reported outcome were used to impute these missing data in order to reduce the risk of overestimation of treatment effects consequent to reporting bias. The Hirayama et al. [45] study rated ADHD symptoms by both parents and teachers but scores were counted only when both raters gave the same assessment. Whilst this strategy was consistent with diagnostic requirements that ADHD symptoms be present in more than one context, it is potentially open to bias as 'same assessment' was not defined. We contacted the author but individual parent and teacher ratings were not available and, given the composite nature of the outcome used in this study, we were unable to impute the missing data.

The meta-analytic strategy employed was as follows: (i) to compute overall effect sizes using a random effects model for combined ADHD symptoms, and inattention and hyperactive-impulsive symptoms separately, rated by both parents and teachers combined, and by parents and teachers separately; (ii) to examine for possible publication bias using funnel plots, Egger's test, and Duval and Tweedie's trim and fill method; (iii) to assess heterogeneity using Cohen's *Q*; and (iv) to explore heterogeneity with univariable and multivariable random effects meta-regression analyses using relevant moderator variables (baseline symptom scores, study duration, study sample size, study quality, mean age of children in each study, percentage of male children in each study, and individual PUFA doses). Meta-regression analyses were conducted with the metafor package in R, available via the Comprehensive R Archive Network at http://CRAN.R-project.org/package=metafor, using the restricted maximum likelihood estimator and Knapp and Hartung adjustment. The latter adjustment generates more conservative *P*-values for model parameters and an overall *F*-test of the significance of moderators in the model.

In order to reduce the number of variables simultaneously entered into the multivariable meta-regression analyses, fatty acid doses were summed into AA+precursors (18:2*n*−6 LA, 18:3*n*−6 γ-linolenic acid [GLA], 20:2*n*−6 eicosadienoic acid [EDA], 20:3*n*−6 dihomo-γ-linolenic acid [DGLA]), EPA+precursors (18:3*n*−3 ALA, 18:4*n*−3 stearidonic acid [SDA], 20:3*n*−3 eicosatrienoic acid [ETA], 20:4*n*−3 eicosatetraenoic acid [ETTA]) and DHA+precursor (22:5*n*−3 docosapentaenoic acid [DPA]). If any one of these groups were significant, between-group interactions and individual within-group fatty acids were tested to obtain the best fitting model on the basis of the *F*-test for moderators.

Statistical significance was established using $\alpha < 0.05$ without adjustment for multiple comparisons as this investigation was considered to be an exploratory analysis.

3. Results

The overall effect using a random effects model showed a small but significant decrease in combined ADHD symptoms rated by all raters with PUFA supplementation in the 18 studies (Fig. 1A); SMD −0.192 (95% CI: −0.297, −0.086; $P < 0.001$). The effect remained significant for both inattention and hyperactive-impulsive symptoms when examined separately and rated by all raters (Table 2). However, these significant effects appeared to be mediated by parent ratings as SMD estimates using parent ratings were consistently higher than those using all raters and SMD estimates using teacher ratings were consistently insignificant (Table 2).

Egger's test was not significant (intercept −0.717; 95% CI: −2.048, 0.614; $df=18$; $P=0.272$); however, there was evidence of publication bias as shown by the asymmetrical funnel plot (Fig. 1B). Using Duval and Tweedie's trim and fill, five additional imputed studies (solid circles) were needed to correct the asymmetry of the observed studies (open circles), which reduced the SMD estimate to a non-significant level of −0.118 (95% CI: −0.250, 0.014).

Although there was little evidence of statistically significant heterogeneity between studies (Table 2), a wide range of PUFA regimens were employed and thus, the studies were heterogeneous with respect to the clinical interventions employed. Univariable and multivariable meta-regression analyses were conducted to explore the possible influence of these heterogeneous PUFA regimens on outcome.

On univariable meta-regression analysis, study duration (SMD −0.098; 95% CI: −0.193, −0.003; $P=0.043$), EDA dose (SMD −49.406; 95% CI: −95.634, −3.179; $P=0.038$), and DGLA dose (SMD −25.956; (5% CI: −50.000, −1.911; $P=0.036$)) were significantly associated with decreases in combined ADHD symptoms (Supplementary eTable 2). EPA dose was associated with a decrease in combined ADHD symptoms, but this decrease was not statistically significant (SMD −0.328; 95% CI: −0.674, 0.018; $P=0.062$). DHA dose was associated with an increase in combined ADHD symptoms, but this increase was not statistically significant (SMD 0.197; 95% CI: −0.167, 0.560; $P=0.271$).

On multivariable meta-regression analysis, the following findings were identified. For all ADHD symptoms combined, precursors up to

Table 2
Effect by ADHD symptom category and rater.

Model	Number of studies	SMD estimate (95% CI)	*Z*	*P* of *Z*	*Q*	*P* of *Q*
All ADHD symptoms combined						
All raters	18	−0.192 (−0.297 to −0.086)	−3.566	<0.001	19.300	0.438
Parent	14	−0.275 (−0.416 to −0.134)	−3.823	<0.001	20.350	0.159
Teacher or Clinician	12	−0.074 (−0.197 to 0.049)	−1.176	0.240	8.892	0.632
Inattention symptoms						
All raters	16	−0.162 (−0.276 to −0.047)	−2.764	0.006	17.332	0.364
Parent	12	−0.282 (−0.464 to −0.100)	−3.037	0.002	23.688	0.022
Teacher or Clinician	10	−0.069 (−0.196 to 0.059)	1.053	0.292	7.143	0.622
Hyperactive−impulsive symptoms						
All raters	16	−0.209 (−0.358 to −0.059)	−2.740	0.006	26.136	0.052
Parent	13	−0.263 (−0.437 to −0.089)	−2.966	0.003	24.333	0.028
Teacher or Clinician	10	−0.034 (−0.163 to 0.096)	−0.510	0.610	8.867	0.450

SMD, standardized mean difference.

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and including AA plus the interaction between precursors up to and including AA and precursors up to and including EPA (but not precursors up to and including DHA) were significantly associated with a decrease in symptoms after controlling for background factors (baseline symptoms, study duration, sample size, study quality, mean age and percentage of male children). For inattention symptoms, similar findings of an interaction between precursors up to and including AA and precursors up to and including EPA were evident, but specifically, the best fitting model (highly significant *F*-test of moderators and very low residual heterogeneity) identified that GLA and the interaction between GLA and EPA were the key PUFAs significantly associated with a decrease in inattention symptoms after controlling for background factors (See Model 8 in Table 3). For hyperactive symptoms, the background factors of baseline hyperactive symptoms, study duration, and study sample size were significantly associated with changes in hyperactive symptoms; however, PUFA supplementation was not (Table 3).

A subgroup analysis dividing the studies on the basis of whether GLA and EPA were present in combination (threshold values ≥ 1 mg for both GLA and EPA) showed that the pooled SMD in inattention symptoms (rated by all raters) was significantly lower for the GLA+EPA present group (−0.309; 95% CI: −0.462, −0.155;

Table 3
Multivariable meta-regression models to explore the influence of moderator variables on residual heterogeneity in combined ADHD, inattention, and hyperactive-impulsive symptoms (rated by all raters).

Model	Moderator variable	SMD estimate (95% CI)	*t*-Value	*P*-value	Overall test of moderators		Test of residual heterogeneity	
					F	*P*-value	*Q*	*P*-value
All ADHD symptoms combined								
1.	Baseline symptoms (all)	0.010 (−0.005, 0.025)	1.385	0.189	2.617	0.069	8.742	0.792
	Study duration (months)	−0.175 (−0.295, −0.054)	−3.128	**0.008**				
	Sample size	0.0004 (−0.001, 0.002)	0.539	0.599				
	Study quality score	0.027 (−0.048, 0.103)	0.778	0.451				
	Mean age (years)	−0.001 (−0.148, 0.147)	−0.011	0.992				
	Percent male	−0.007 (−0.021, 0.007)	−1.138	0.276				
2.	Study duration (months)	−0.179 (−0.273, −0.086)	−4.077	**0.001**	6.698	**0.003**	6.927	0.960
	AA+precursors	−0.209 (−0.346, −0.072)	−3.255	**0.005**				
	EPA+precursors	−0.161 (−0.399, 0.076)	−1.446	0.169				
	DHA+precursors	0.189 (−0.071, 0.448)	1.549	0.142				
3.	Study duration (months)	−0.169 (−0.264, −0.073)	−3.768	**0.002**	6.129	**0.004**	7.326	0.948
	AA+precursors	−0.190 (−0.336, −0.044)	−2.771	**0.014**				
	AA+precursors-by-EPA+precursors	−0.686 (−1.358, −0.015)	−2.178	**0.046**				
	AA+precursors-by-DHA+precursors	0.152 (−0.445, 0.748)	0.541	0.596				
4.	Study duration (months)	−0.158 (−0.251, −0.065)	−3.593	**0.002**	7.495	**0.002**	8.024	0.948
	GLA	−1.242 (−2.192, −0.291)	−2.769	**0.014**				
	GLA-by-EPA	−4.39 (−9.303, 0.523)	−1.894	0.076				
Inattention symptoms								
5.	Baseline symptoms (Inat)	−0.06 (−0.031, 0.020)	−0.493	0.633	2.345	0.114	9.729	0.640
	Study duration (months)	−0.140 (−0.282, 0.003)	−2.184	0.054				
	Sample size	−0.0004 (−0.003, 0.002)	−0.447	0.664				
	Study quality score	0.028 (−0.066, 0.122)	0.660	0.524				
	Mean age (years)	−0.006 (−0.162, 0.149)	−0.092	0.929				
	Percent male	−0.008 (−0.029, 0.013)	−0.849	0.416				
6.	Study duration (months)	−0.180 (−0.263, −0.097)	−4.729	**0.001**	9.536	**0.001**	4.148	0.981
	AA+precursors	−0.320 (−0.477, −0.163)	−4.446	**0.001**				
	EPA+precursors	−0.193 (−0.403, 0.018)	−1.990	0.070				
	DHA+precursors	0.043 (−0.192, 0.278)	0.398	0.697				
7.	Study duration (months)	−0.176 (−0.255, −0.098)	−4.886	**<0.001**	10.920	**0.001**	3.735	0.988
	AA+precursors	−0.268 (−0.427, −0.108)	−3.648	**0.003**				
	AA+precursors-by-EPA+precursors	−0.545 (−1.080, −0.010)	−2.219	**0.047**				
	AA+precursors-by-DHA+precursors	−0.092 (−0.592, 0.407)	−0.403	0.694				
8.	Study duration (months)	−0.171 (−0.236, −0.107)	−5.740	**<0.001**	20.658	**<0.001**	3.005	0.998
	GLA	−1.952 (−2.818, −1.085)	−4.867	**<0.001**				
	GLA-by-EPA	−4.210 (−7.636, −0.785)	−2.655	**0.020**				
Hyperactive–impulsive symptoms								
9.	Baseline symptoms (HI)	0.019 (0.001, 0.036)	2.410	**0.037**	4.277	**0.021**	7.329	0.694
	Study duration (months)	−0.240 (−0.373, −0.107)	−4.014	**0.003**				
	Sample size	0.002 (−0.001, 0.004)	1.662	0.128				
	Study quality score	0.034 (−0.047, 0.115)	0.929	0.375				
	Mean age (years)	0.006 (−0.144, 0.156)	0.088	0.932				
	Percent male	−0.003 (−0.021, 0.015)	−0.361	0.725				
10.	Baseline symptoms (HI)	0.015 (0.002, 0.029)	2.500	**0.031**	7.599	**0.003**	4.701	0.910
	Study duration (months)	−0.248 (−0.353, −0.142)	−5.223	**<0.001**				
	Sample size	0.001 (00.0003, 0.003)	2.858	**0.017**				
	AA+precursors	−0.152 (−0.316, 0.011)	−2.075	0.065				
	EPA+precursors	−0.106 (−0.442, 0.230)	−0.705	0.497				
	DHA+precursors	0.174 (−0.126, 0.474)	1.293	0.225				

GLA=18:3-n6 γ-linolenic acid; AA=20:4-n6 arachidonic acid; EPA=20:5-n3 eicosapentaenoic acid; DHA=22:6-n3 docosahexaenoic acid; HI=hyperactive-impulsive; Inat=Inattention.; SMD=standardized mean difference. Significant *p*-values ($p < 0.05$) are shown in bold.

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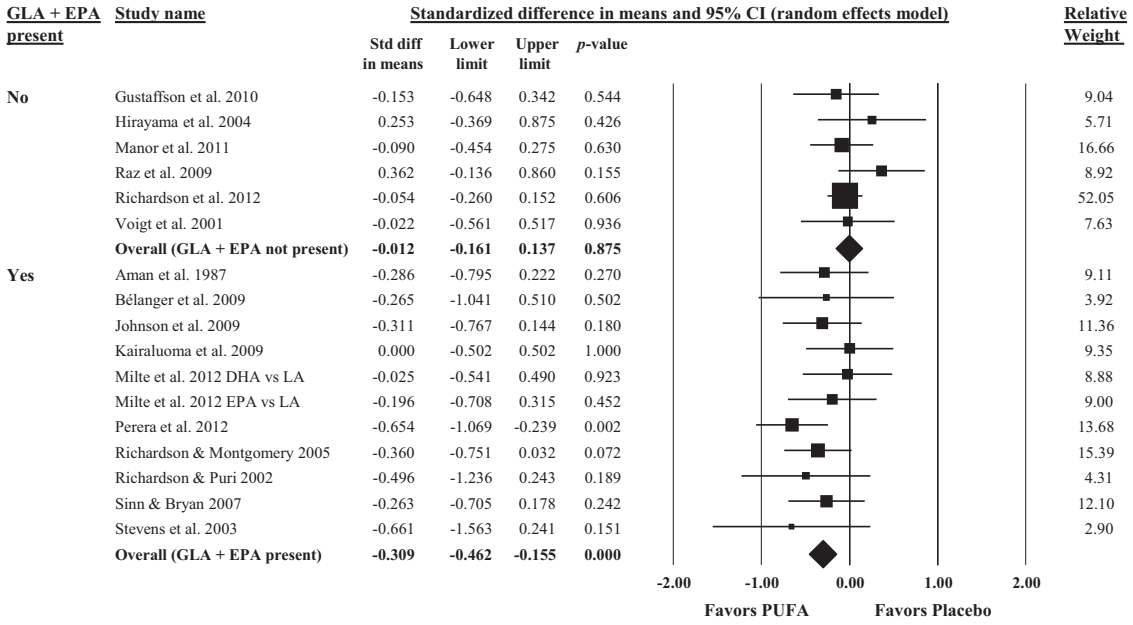

Fig. 2. Forest plot of standardized difference in mean of inattention symptom scores rated by all raters for the 16 studies with available ratings of inattention and grouped by whether GLA and EPA were present in the PUFA regimen. Threshold values of ≥ 1 mg were used to determine the presence of both GLA and EPA. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, γ-linolenic acid; LA, linoleic acid.

$P < 0.0001$) but not significantly different for the GLA+EPA not present group (-0.012; 95% CI: -0.161, 0.137; $P=0.875$). See Fig. 2 for a forest plot of this subgroup analysis.

4. Discussion and conclusions

We found that PUFA supplementation was associated with a small decrease in combined ADHD symptoms and that GLA plus the interaction between GLA and EPA was effective for inattention symptoms.

Significant pooled effects were found for parent ratings but not for teacher or clinician ratings. This might have resulted from a failure of blinding to group status during the trials as only a few studies assessed blinding success. A recent meta-analysis examining both dietary and psychological interventions for ADHD also found a greater likelihood of significant results if symptoms were rated by those closest to the therapeutic setting [29]. An alternative explanation is that parents may be better at discerning subtle behavioral changes in their children than are teachers.

Regarding the univariable meta-regression, longer study duration, EDA and DGLA dose were found to be significantly associated with a decrease in combined ADHD symptoms. We did not find a univariable relationship with EPA dose as in an earlier meta-analysis by Bloch and Qawasmi [27]. However, we included more studies, we employed a combined outcome measure strategy that we have previously shown is less subject to bias and generates more conservative SMD estimates [53], and we imputed missing data for studies failing to report negative outcomes, again generating more conservative SMD estimates. Although the univariable estimate for EPA dose in the current meta-analysis (-0.328; 95% CI: -0.674, 0.018; $p=0.062$) was of a similar magnitude to that found by Bloch and Qawasmi (0.36; 95% CI: 0.01, 0.72; $p=0.04$) [27], the methodological differences in the current meta-analysis, in which reporting bias was accounted for and which included a larger number studies, explain why the univariable estimate for EPA dose did not reach statistical significance.

Regarding the multivariable meta-regression findings, first, there was no effect of PUFAs on hyperactive symptoms; however, high baseline hyperactive symptoms were associated with persistent symptoms and longer study duration with a decrease in symptoms. This might represent a developmental maturation phenomenon independent of PUFA supplementation. Second, there was strong evidence that longer study duration, GLA, and the interaction between GLA and EPA were associated with reduced inattention symptoms. These meta-regression findings were further confirmed by a subgroup analysis showing a reduction in inattention symptoms using a regimen containing EPA and GLA, but no reduction in inattention symptoms in studies that did not include these PUFAs in combination.

EPA has long been recognized as being an omega-3 anti-inflammatory PUFA with potential benefits in cardiovascular disorders and depression [57]. However, the potential anti-inflammatory benefit of GLA has tended to be overshadowed; interestingly, in animal models of cognitive function, GLA and EPA block lipopolysaccharide-induced inhibition of long-term potentiation [58]. The first step for omega-6 and omega-3 PUFA biosynthesis from the essential fatty acids LA and ALA, respectively, involves the enzyme delta-6-desaturase, which may be vulnerable to inhibition by factors such as micronutrient deficiencies, viral infections, and the stress hormone cortisol [59]. Given that plasma AA and DHA are low in children with ADHD [24,60,61], supplementation with GLA and EPA would bypass this step for both AA and DHA biosynthesis, respectively. There was no evidence for DHA effectiveness. We have previously argued that because DHA is at the end of the biosynthetic pathway, and supplementation with exogenous DHA risks accumulation of pro-inflammatory reactive derivatives, EPA supplementation may be safer way to increase membrane DHA, notwithstanding the potential influence of the anti-inflammatory effects of EPA itself [62].

This study has several strengths: a combined outcome measure strategy reduced investigator bias [53]; the influence of reporting bias was reduced by imputing data for studies that failed to report negative outcomes; an independent FAME analysis of fatty acid content was conducted enabling assessment of all PUFAs of potential relevance; and, a multivariable meta-regression controlled for background study-related factors, which allowed for limited hypothesis-generating testing of PUFA interactions.

Weaknesses of this study include the following: although the pooled effect was statistically significant, only two studies showed a

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significant effect by themselves [48,63]; the funnel plot showed evidence of publication bias; there was evidence of reporting bias; few studies were formally registered; study methodological quality was variable; and the placebo used across studies varied. Regarding this latter issue, some of the placebo preparations may have been psychoactive and thereby reduced the apparent effectiveness of PUFAs. Some studies employed placebo preparations containing omega-6 PUFAs, which could, on this analysis, have been psychoactive. Others used olive oil, which contains oleic acid, which is also psychoactive [64]. Indeed, the oleic acid content of regimens was associated in the present analysis with a decrease in symptoms, but this decrease was not significant (Supplementary eTable 2). However, even a non-significant decrease in symptoms might mask genuine differences between regimens if these were present. A further weakness of all included studies is that none attempted to control for the PUFA content of the background diets consumed, which could have varied widely.

In conclusion, while this meta-analysis shows evidence of PUFA efficacy in ADHD, and especially GLA plus GLA-EPA interaction for inattention, it has highlighted the need for better designed trials. Not only should such trials be properly registered, adequately powered, and methodologically rigorous with the use of non-psychoactive placebos and controlled diets, but also, given the identified importance of study duration, they should last for at least six months in order reliably to identify an effect.

Acknowledgments

JGM conducted the literature search, data extraction and statistical analysis. BKP and JGM jointly wrote this report and had full access to the data in the meta-analysis and take responsibility for the integrity of the data and the accuracy of the data analysis.

BKP is the author of a patent for a product comprising botanical triterpenes, ethyl-eicosapentaenoate and gamma-linolenic acid and received partial salary support as principal investigator of a phase III trial of ethyl-eicosapentaenoate in Huntington's chorea (Huntington disease) from Amarin Neuroscience Ltd. (formerly by Laxdale Ltd.) published as Puri B K et al., *Neurology* 2005;65:286–292. JGM provides research consultancy to the Academy of Nutritional Medicine, which oversees a clinic providing nutritional interventions for a variety of disorders, including ADHD. JGM has not participated in this clinic and has never prescribed nutritional interventions to patients.

Fatty acid methyl ester (FAME) analysis of study regimens was funded by the Academy of Nutritional Medicine, Cambridge, UK.

Appendix A. Supplementary information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.plefa.2014.01.004.

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Please cite this article as: B.K. Puri, J.G. Martins, Which polyunsaturated fatty acids are active in children with attention-deficit hyperactivity disorder..., Prostaglandins Leukotrienes Essent. Fatty Acids (2014), http://dx.doi.org/10.1016/j.plefa.2014.01.004

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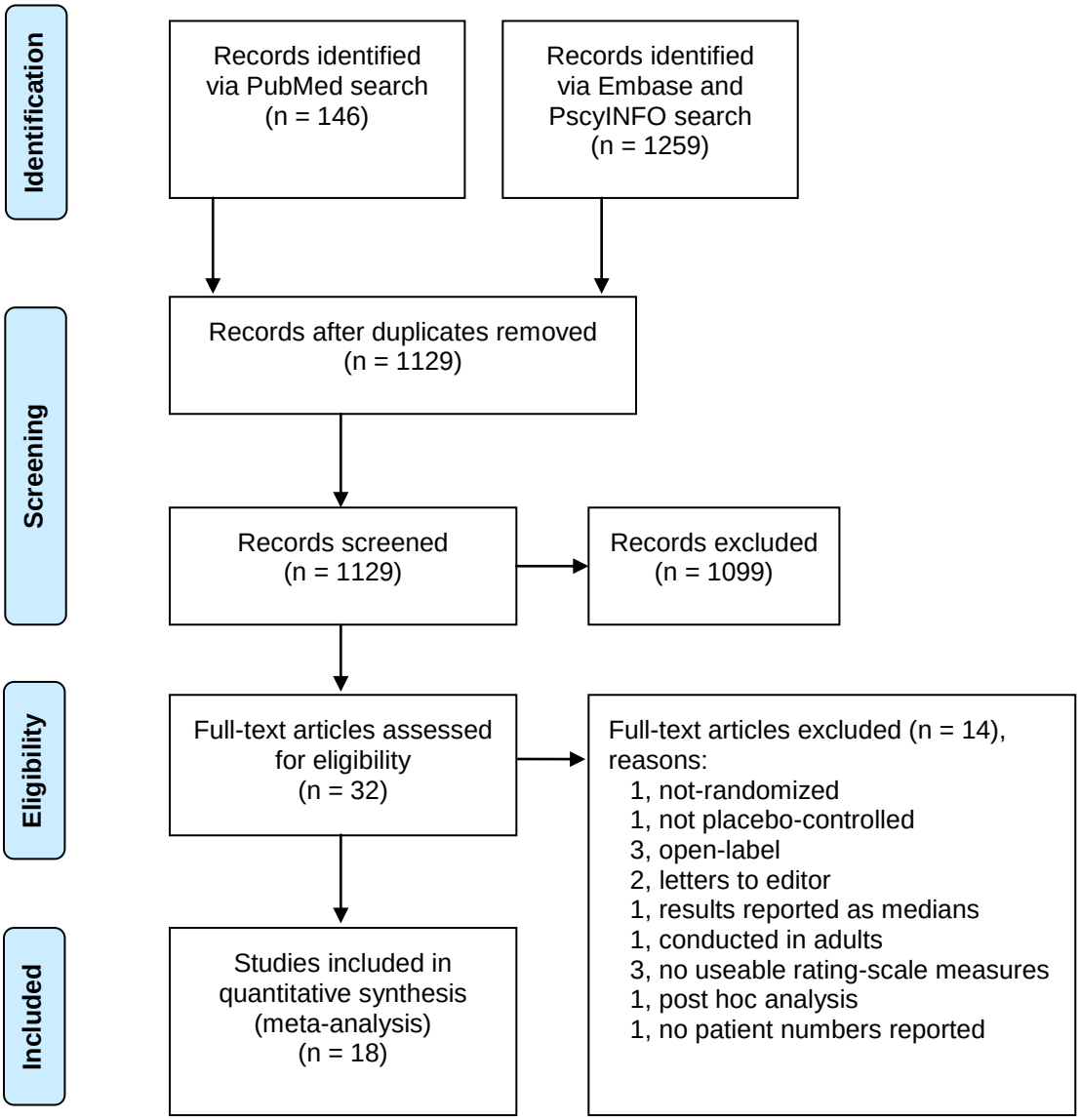
Electronic Supplementary Material

eFigure 1. PRISMA flow diagram



eTable 1. Daily polyunsaturated fatty acid doses across the 18 studies

		Omega-6 content, mg/day						Omega-3 content, mg/day					
Study [reference]	**Preparation**	**LA**	**GLA**	**EDA**	**DGLA**	**AA**	**ALA**	**SDA**	**ETA**	**ETTA**	**EPA**	**DPA**	**DHA**
Aman *et al.*1987 [1]	Efamol[a]	2141.11	364.96	1.57	0.63	0.00	6.59	3.14	0.00	0.00	2.51	0.00	0.00
Arnold *et al.* 1989 [2]	Efamol[a]	2854.81	486.61	2.09	0.84	0.00	8.79	4.18	0.00	0.00	3.35	0.00	0.00
Voigt *et al.* 2001 [3]	DHASCO[b]	37.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	345.00
Richardson & Puri 2002 [4]	Efalex[a]	853.56	157.74	8.79	9.62	56.07	27.62	29.29	5.44	13.81	196.23	37.66	722.18
Stevens *et al.* 2003 [5]	Efalex[a]	853.56	157.74	8.79	9.62	56.07	27.62	29.29	5.44	13.81	196.23	37.66	722.18
Hirayama *et al.* 2004 [6]	Enriched food[c]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	514.00
Richardson & Montgomery 2005 [7]	eye q[a]	450.31	84.10	4.39	8.79	25.10	21.34	67.78	4.08	22.28	532.22	55.23	169.14
Sinn & Bryan 2007 [8]	eye q[a]	450.31	84.10	4.39	8.79	25.10	21.34	67.78	4.08	22.28	532.22	55.23	169.14
Johnson *et al.* 2009 [9]	eye q[a]	450.31	84.10	4.39	8.79	25.10	21.34	67.78	4.08	22.28	532.22	55.23	169.14
Vaisman *et al.* 2008 [10]	PL-Omega3[cd]	11.00	1.00	0.00	0.00	4.00	7.00	0.00	0.00	0.00	156.00	4.00	95.00
	Fish Oil[cd]	18.00	2.00	0.00	0.00	7.00	25.00	0.00	0.00	0.00	153.00	0.00	96.00
Kairaluoma *et al.* 2009 [11]	Ethyl-EPA[a]	3.52	5.83	2.62	6.36	24.68	4.26	6.73	2.69	20.49	492.27	0.00	0.00
Raz *et al.* 2009 [12]	EFAs[c]	480.00	0.00	0.00	0.00	0.00	120.00	0.00	0.00	0.00	0.00	0.00	0.00
Bélanger *et al.* 2009 [13]	ABC2[ae]	15.25	14.02	2.93	7.86	42.99	9.71	35.13	3.39	29.43	708.14	77.04	312.01
Gustaffson *et al.* 2010 [14]	PlusEPA[a]	2.44	0.64	0.52	3.13	23.34	0.75	5.22	0.93	13.35	484.52	0.70	1.57
Manor *et al.* 2011 [15]	Vayarin[c]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	86.00	0.00	34.00
Milte *et al.* 2012 [16]	EPA-rich oil[a]	44.77	26.57	2.93	12.55	62.34	30.54	111.09	3.35	42.26	1187.03	40.79	231.17
	DHA-rich oil[a]	37.66	13.60	4.60	8.58	82.22	15.69	25.10	6.28	19.25	310.04	59.41	1200.84
Perera *et al.* 2012 [17]	Vegepa[a]	153.97	25.84	2.30	6.28	31.28	6.28	9.73	1.78	17.57	548.54	0.00	0.00
Richardson *et al.* 2012 [18]	DHASCO[b]	75.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	600.00

[a]Full PUFA content obtained from Fatty Acid Methyl Esters (FAME) analysis, Eclipse ALS, Cambridge, UK. [b]Full PUFA content obtained from Food Standards Australia New Zealand.[19] [c]PUFA content obtained from published reference. [d]Data for EDA, DGLA, SDA, ETA and ETTA were not present in the published reference and were, therefore, assumed to be negligible and assigned a value of zero (the authors and manufacturers of these regimens were contacted on several occasions but no further clarification was obtained). [e]In this study, the number of capsules administered was according weight bands (participants between 16–25 kg received 2 capsules/day, between 26–35 kg, 3 capsules/day, and between 36–45 kg, 4 capsules/day). The authors were contacted to confirm that 12 children received 2 capsules/day, 15, 3 capsules/day and 10, 4 capsules/day, giving an average capsule consumption of 2.95 capsule/day.

LA = 18:2-n6 linoleic acid; GLA = 18:3-n6 γ-linolenic acid; EDA = 20:2-n6 eicosadienoic acid; DGLA = 20:3-n6 dihomo-γ-linolenic acid; AA = 20:4-n6 arachidonic acid; ALA = 18:3-n3 α-linolenic acid; SDA = 18:4-n3 stearidonic acid; ETA = 20:3-n3 eicosatrienoic acid; ETTA = 20:4-n3 eicosatetraenoic acid; EPA = 20:5-n3 eicosapentaenoic acid; DPA = 22:5-n3 docosapentaenoic acid; DHA = 22:6-n3 docosahexaenoic acid.

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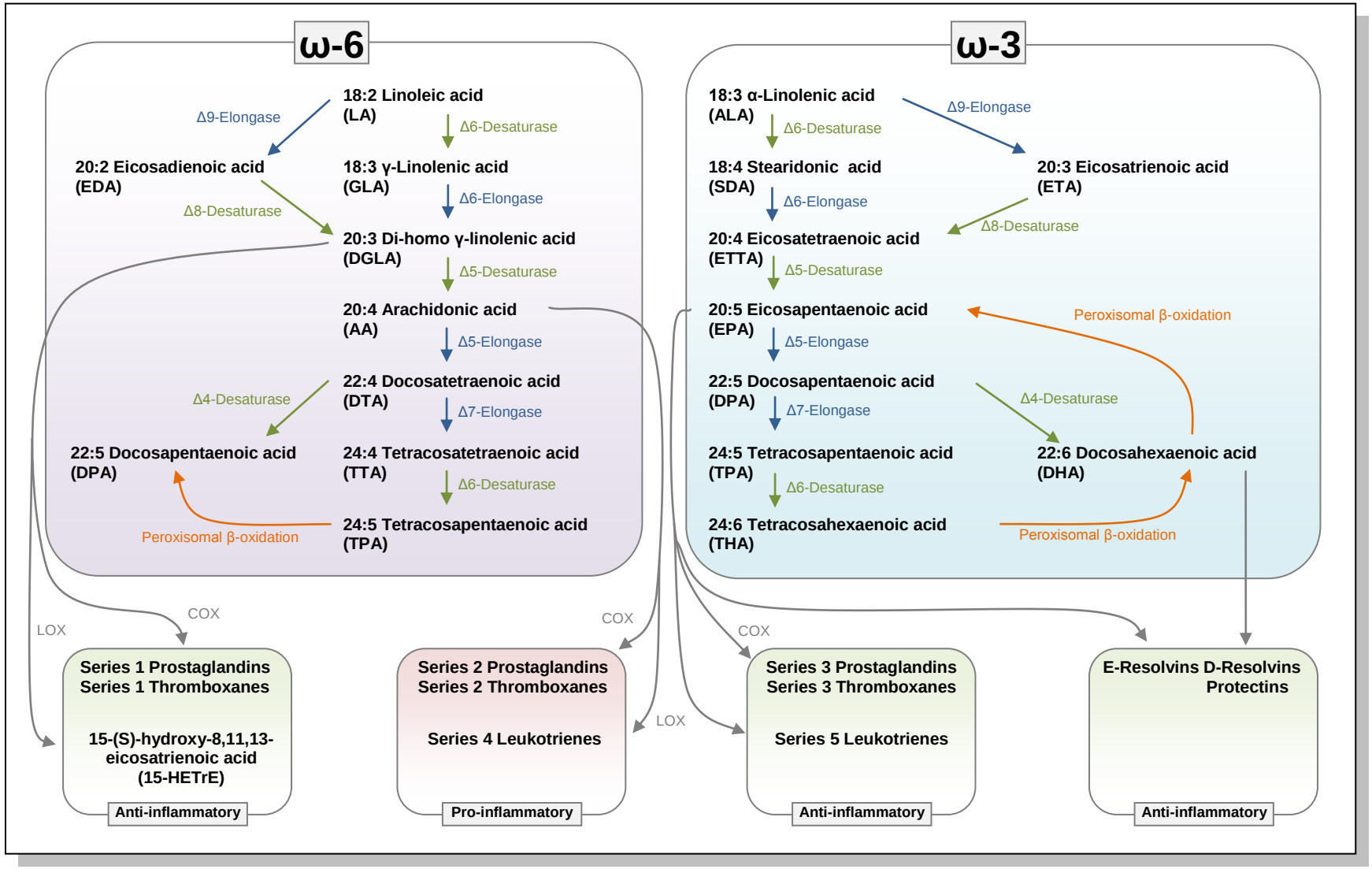
eFigure 2. Overview of omega-6 and -3 fatty acid biosynthesis. COX = cyclooxygenase. LOX = lipoxygenase.



eTable 2. Univariable meta-regression models to explore the influence of moderator variables on residual heterogeneity in combined ADHD symptoms (rated by all raters)

				Test of moderators		Test of residual heterogeneity	
Variable	**Estimate (95% CI)**	***t*-value**	***P*-value**	***F***	***P*-value**	***Q***	***P*-value**
Baseline	−0.002 (−0.016, 0.013)	−0.230	0.820	0.053	0.820	19.018	0.391
Duration (months)	−0.098 (−0.193, −0.003)	−2.177	**0.043**	4.740	0.043	15.697	0.614
Sample size	0.001 (0.0004, 0.002)	1.180	0.253	1.392	0.253	17.173	0.511
Quality	−0.001 (−0.053, 0.051)	−0.045	0.965	0.002	0.965	19.130	0.384
Mean age	−0.025 (−0.174, 0.123)	−0.358	0.724	0.128	0.724	18.992	0.724
% Male	−0.006 (−0.016, 0.003)	−1.405	0.177	1.974	0.177	16.870	0.532
LA	−0.051 (−0.231, 0.129)	−0.598	0.558	0.357	0.558	18.800	0.404
GLA	−0.401 (−1.433, 0.631)	−0.817	0.425	0.667	0.425	18.421	0.428
EDA	−49.406 (−95.634, −3.179)	−2.245	**0.038**	5.042	0.038	15.030	0.660
DGLA	−25.956 (−50.000, −1.911)	−2.268	**0.036**	5.144	0.036	15.011	0.661
AA	−3.322 (−8.166, 1.522)	−1.441	0.167	2.076	0.167	16.929	0.528
ALA	0.552 (−3.970, 5.074)	0.257	0.800	0.066	0.800	19.297	0.374
SDA	−1.927 (−5.531, 1.678)	−1.123	0.276	1.261	0.276	17.711	0.475
ETA	−38.958 (−92.836, 14.920)	−1.519	0.146	2.308	0.146	16.752	0.540
ETTA	−7.419 (−16.393, 1.555)	−1.737	0.100	3.017	0.100	16.250	0.575
EPA	−0.328 (−0.674, 0.018)	−1.992	0.062	3.967	0.062	15.770	0.609
DPA	−1.977 (−6.520, 2.567)	−0.914	0.373	0.836	0.373	18.154	0.446
DHA	0.197 (−0.167, 0.56)	1.137	0.271	1.292	0.271	17.506	0.489
OA	−0.399 (−1.155, 0.358)	−1.107	0.283	1.225	0.283	18.802	0.404

LA = 18:2-n6 linoleic acid; GLA = 18:3-n6 γ-linolenic acid; EDA = 20:2-n6 eicosadienoic acid; DGLA = 20:3-n6 dihomo-γ-linolenic acid; AA = 20:4-n6 arachidonic acid; ALA = 18:3-n3 α-linolenic acid; SDA = 18:4-n3 stearidonic acid; ETA = 20:3-n3 eicosatrienoic acid; ETTA = 20:4-n3 eicosatetraenoic acid; EPA = 20:5-n3 eicosapentaenoic acid; DPA = 22:5-n3 docosapentaenoic acid; DHA = 22:6-n3 docosahexaenoic acid; OA = 18:1 oleic acid.