Effect of Supplementation with Polyunsaturated Fatty Acids and Micronutrients on Learning and Behavior Problems Associated with Child ADHD

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ABSTRACT: ***Methods:*** **Various developmental problems including attention-deficit/hyperactivity disorder (ADHD) have been linked to biological deficiencies in polyunsaturated fatty acids (PUFAs). Additionally, there is evidence that symptoms may be reduced with PUFA supplementation. This study investigated effects of supplementation with PUFAs on symptoms typically associated with ADHD. Because nutrients work synergistically, additional effects of micronutrient supplementation were also investigated. A total of 132 Australian children aged 7 to 12 years with scores ≥2 SD above the population average on the Conners ADHD Index participated in a randomized, placebo-controlled, double-blind intervention over 15 weeks, taking PUFAs alone, PUFAs + micronutrients, or placebo. Due to unreturned questionnaires, data were only available for 104 children.** ***Results:*** **Significant medium to strong positive treatment effects were found on parent ratings of core ADHD symptoms, inattention, hyperactivity/impulsivity, on the Conners Parent Rating Scale (CPRS) in both PUFA treatment groups compared with the placebo group; no additional effects were found with the micronutrients. After a one-way crossover to active supplements in all groups for a further 15 weeks, these results were replicated in the placebo group, and the treatment groups continued to show significant improvements on CPRS core symptoms. No significant effects were found on Conners Teacher Rating Scales.** ***Conclusion:*** **These results add to preliminary findings that ADHD-related problems with inattention, hyperactivity, and impulsivity might respond to treatment with PUFAs and that improvements may continue with supplementation extending to 30 weeks.**

*(J Dev Behav Pediatr 28:*82–91, 2007) **Index terms:** attention-deficit/hyperactivity disorder, attention, behavior, polyunsaturated fatty acids, micronutrients.

The aim of this study was to investigate effects of polyunsaturated fatty acids (PUFAs) and micronutrients on cognitive and behavioral problems associated with attention-deficit/hyperactivity disorder (ADHD). ADHD is one of the most prevalent developmental disorders in childhood, and finding safe and effective treatments presents a challenge to both practitioners and parents. More commonly diagnosed in boys, major symptoms include poor impulse control, hyperactivity, and/or difficulty in sustaining attention. Prevalence rates vary, possibly due to diagnostic inconsistencies, and are estimated at 5% to 10% in Europe,[1] 3% to 7% in the United States,[2] and 11% in Australia.[3]

Problems associated with ADHD can adversely affect school performance, families, relationships, and social interactions. ADHD is also associated with cognitive deficits and specific learning disabilities in math, reading, or spelling. These children may have poor self-discipline and low self-esteem, and at least half of children with ADHD experience comorbidities with psychiatric problems including anxiety, mood disorders, and antisocial problems such as conduct disorder and oppositional defiant disorder,[4–6] which can later lead to antisocial behavior and substance abuse. It is believed that two thirds of children will carry problems associated with ADHD into adulthood.[2]

There is emerging evidence that ADHD and other neurodevelopmental disorders such as dyspraxia, dyslexia, and autism, as well as mood disorders, are associated with deficiencies in omega-3 fatty acids.[7–9] Omega-3 (n-3) and omega-6 (n-6) fatty acids constitute the group of polyunsaturated fatty acids. PUFAs are essential fatty acids because they cannot be synthesized by humans and must be provided via dietary sources. They are key constituents of all cellular and intracellular membranes or phospholipids, where they perform vital structural and chemical functions. PUFAs, available in various vegetables, nuts, and seeds, can be converted to some degree by humans into long-chain (LC) PUFAs, which can also be derived directly from the diet via fish oil. However, research indicates that dietary intake of n-3 fatty acids has been declining in Western societies,[10,11] as well as other micronutrients that might be required for the metabolism of PUFAs.[12]

See related Commentary on page 139 of this issue.

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Furthermore, in clinical populations, there is evidence that these people may have genetic difficulties with metabolizing PUFAs[13,14] and therefore have higher than normal PUFA requirements.

LC-PUFAs are highly active and are concentrated in the brain and nervous system. The most abundant LC-PUFA in the brain is docosahexaenoic acid (DHA), from the n-3 group, which is particularly concentrated at nerve cell synapses where it appears to be involved in neural cell signaling and neurotransmitter processes.[15–19] Eicosapentaenoic acid (EPA), a DHA precursor, is also believed to play important roles in the brain, along with n-6 PUFA, arachidonic acid (AA), and gamma-linolenic acid (GLA). Accordingly, deficiencies in essential fatty acids have been associated with a range of psychiatric problems including developmental disorders.[15] Importantly, there is evidence that supplementation of these essential fatty acids can alleviate symptoms associated with these conditions.[7,20–23]

The link between hyperactivity and PUFA deficiency was first proposed by Colquhoun and Bunday.[24] Since then, a number of researchers have reported lower PUFA levels in blood indices of hyperactive children compared with matched controls.[25–31] Five randomized, placebo-controlled supplementation studies among children displaying ADHD-related symptoms[16,32–35] have produced inconsistent results. This could be attributable to variations in sample sizes, exclusion criteria, ratios, and doses of n-3 and n-6 fatty acids, length of supplementation, and baseline fatty acid status. A review of these studies is provided by Richardson.[7]

Two studies have found significant improvements with PUFA supplementation in children with ADHD-related symptoms on Conners ADHD Rating Scales[36]; a pilot study,[33] and a placebo-controlled, double-blind trial recently completed in Durham, UK.[21] The latter study was conducted with 117 children with developmental coordination disorder. One third of this sample had scores ≥2 SD above the population mean on the DSM-IV ADHD symptoms subscale of Conners Teacher Rating Scale (CTRS). Across the whole sample, significant treatment effects were observed for teacher ratings of inattention, hyperactivity, restlessness/impulsivity, anxiety/shyness, and oppositional behavior in the PUFA treatment group compared with a placebo group over 3 months. There were also significant improvements in reading and spelling. Following a one-way crossover to active treatment, the placebo group demonstrated similar improvements, while the original treatment group's mean scores continued to improve.

Both of these studies used fish oil supplements containing n-3 fatty acids EPA and DHA along with n-6 fatty acids AA and GLA. This combination has so far had the most effective outcomes in PUFA research with ADHD symptoms. The present study aimed to extend this research by investigating the effect of supplementation with these PUFAs on children with ADHD-related symptoms as identified on Conners ADHD Index, which is recommended for screening children who may qualify for a clinical diagnosis of ADHD.[36] This study also aimed to investigate any additional effects derived from supplementation with micronutrients. All nutrients required by the body interact with each other in their metabolism and functions,[37,38] so supplementation with PUFAs might not yield maximum benefits if other nutrients are lacking. Effective PUFA metabolism relies on other nutrients such as vitamins C, B_3, and B_6 and the minerals zinc and magnesium[39]; and zinc, B_3, and vitamin C are involved in the PUFA role of synthesizing prostaglandins, chemicals with important biological roles in brain function. Tacconi et al[37] add B_1, folates, and B_{12} to this list of vitamins involved in lipid synthesis. Given that many children have nutritional deficiencies,[12,40] and specifically many children with ADHD, for instance, are deficient in zinc[41] and iron,[42] this might have an important bearing on the efficacy of nutritional supplementation.

Therefore, this study compared the effect of 15 weeks of supplementation with PUFAs alone, PUFAs with a commercially available multivitamin/mineral (MVM) supplement that contained the nutrients outlined above, or placebo on problems with attention and behavior that are typically associated with (but not necessarily diagnosed as) ADHD. Furthermore, the additional effects of a further 15 weeks of supplementation with PUFAs and micronutrients in all groups were investigated. It was hypothesized that (1) PUFA supplementation (with or without MVM) would result in improvements in parent and teacher ratings of attention and behavior on Conners Parent and Teacher Rating Scales–Long Versions compared with placebo, (2) PUFA + MVM supplementation would show additional improvements over and above PUFAs alone, and (3) the placebo group would show significant improvements during phase 2 similar to those seen in the two active groups in phase 1, and that after an additional 15 weeks of supplementation, both PUFA groups would continue to improve.

METHODS AND MATERIALS

Participants

A total of 201 children in South Australia aged 7 to 12 years were registered by their parents for the study, of whom 182 attended their first appointment. Of those, 167 children (128 boys, 39 girls) had scores ≥2 SD above the general population average (derived from a normative sample of 8000 children in the United States and Canada) on Conners ADHD Index.[36] Thirty-five of this group dropped out during the first 15 weeks, and subsequently a further 23 dropped out. Therefore, 132 children completed the first 15-week phase of the study, and a total of 109 completed the 30 weeks, although data were only available for 104 and 87 of these children, respectively, due to unreturned parent questionnaires as detailed under Results.

Participants were told they could withdraw at any time without giving a reason. From information volunteered by parents, however, attrition was mainly due to noncompliance, and some children were prescribed stimulant medication, which was an exclusion criterion. A χ^2 analysis on study compliance revealed that there were no significant differences in dropout rates between the groups, $\chi^2_4 = 1.91$, $p = .75$ during the first or second

phase of the study (N = 167). There was also no difference in the age of children who pulled out before or during the study, F(2,179) = 0.99; p = .37. However, comparison of baseline scores on Conners Index, completed by parents upon registration for the study, found that children who withdrew either before starting (mean = 28.97) or before the end of phase 1 (mean = 28.74) had significantly higher scores than children who completed phase 1 (mean = 26.27) or the whole study (mean = 25.65), F(3,195) = 3.37, p = .02.

Participants scored on average above the 90th percentile for social problems on Conners parent indices and between the 74th and 90th percentiles on emotional lability, anxious/shyness, and perfectionism. Table 1 shows participant demographics for each group. There were no significant differences between the groups on background variables at baseline except for parent ratings of health, for which the placebo group had higher scores than the polyunsaturated fatty acid (PUFA) group.

Inclusion/Exclusion Criteria

Children were included in the study if they were between the ages of 7 and 12 years and had scores ≥2 SD above the general population average (above the 90th percentile) on Conners abbreviated ADHD Index,[36] which assesses problems with hyperactivity, impulsivity, and attentional/cognitive problems. They were excluded if they were taking any form of stimulant medication and if they had taken any form of omega-3 supplementation in the previous 3 months.

Procedure

Children were recruited via media releases, newspaper advertisements, and school newsletters advertising for children aged 7 to 12 years with attention-deficit/hyperactivity disorder (ADHD)–related learning and behavioral difficulties (but not necessarily diagnosed). Parents were given the 12-item Conners ADHD Index[36] upon registration to determine their child's eligibility for the study. As children were registered for the study, they were categorized according to their age and gender and then within each age/gender category randomly allocated in sequential order to one of three experimental conditions. Upon commencement of the study, parents were required to complete a background questionnaire and Conners Parent Rating Scale–Long Version (CPRS-L) at baseline (week 0) and the CPRS-L at weeks 15 and 30. School principals and teachers were contacted about those children taking part to seek permission for the teachers to complete the teacher questionnaires. Teachers were given the Conners Teachers Rating Scale–Long Version (CTRS-L) to complete at weeks 0, 15, and 30. Children's height and weight were taken at weeks 0, 15, and 30 to calculate their body mass index, which was converted into age- and gender-appropriate percentiles.[43] They were also given a range of individual cognitive assessments at 0, 15, and 30 weeks (to be reported in a separate publication) at the Commonwealth Scientific and Industrial Research Organisation (CSIRO) Human Nutrition, which included tests that were used as an IQ estimate in the present study. At baseline, parents were given supplements or placebo, depending on the group to which children were allocated, with appropriate instructions. It was not possible to obtain a placebo tablet for the multivitamins/minerals, so boxes were independently packed and sealed to maintain the double-blind status for the first phase of the study. At week 15, all participants were given long-chain (LC)–PUFA and micronutrient supplements. To monitor compliance, parents were asked to return all unused capsules, and children were given calendars along with stickers to record each time they took the capsules. The study was approved by the Human Research Ethics Committees of the CSIRO and University of South Australia, and the South Australian Department of Education and Children's Services and Catholic Education Centre.

Materials

Supplements

The LC-PUFA capsules used for the study were eye q™, each containing 400 mg fish oil and 100 mg evening primrose oil with active ingredients eicosapentaenoic acid (EPA) (93 mg), docosahexaenoic acid (DHA) (29 mg), gamma-

Table 1. Means, standard deviations, and differences between groups on demographic variables at baseline for phase 1 data (weeks 1–15), N = 104

	PUFAs + MVM (n = 41)		PUFAs (n = 36)		Placebo (n = 27)		One-way ANOVA
	Mean	SD	Mean	SD	Mean	SD	$F_{2,101}$
Age, yr	9.20	1.72	9.44	1.90	9.67	1.90	0.55
BMI percentile	49.6	29.5	64.3	30.1	59.4	30.7	2.39
Health	4.12	0.84	3.81	0.99	4.37	0.56	3.57[a]
IQ estimate	96.4	20.6	92.1	18.2	93.3	17.1	0.51
PC[a] age	40.3	6.51	41.3	6.13	38.5	10.1	1.10
PC years education	14.0	2.54	13.5	2.25	14.2	6.16	0.34
PC education level	3.76	1.18	3.61	1.05	3.44	1.16	0.62
PC occupation[b]	49.9	14.1	51.5	14.3	51.7	14.3	0.18
Participant gender	29 M, 12 F		29 M, 7 F		19 M, 8 F		χ^2_2 = 1.22

PUFAs, polyunsaturated fatty acids; MVM, multivitamin/mineral; BMI, body mass index; PC, primary caregiver. [a] $p < .05$. IQ estimate taken from Wechsler Intelligence Scale for Children dyad: Vocabulary and Block Design. [b]Occupation rated on Daniel's[44] prestige scale (12 = high, 69 = low).

linolenic acid (GLA) (10 mg), and vitamin E (1.8 mg). Placebo capsules contained palm oil. Children were required to take six active or six placebo capsules per day. The multivitamin/mineral (MVM) supplement were fruit-flavored chewable tablets. The tablets contained active ingredients: vitamin A 175 IU, thiamine nitrate 700 μg, vitamin B_2 1.1 mg; vitamin B_6 1.3 mg, nicotinamide 12 mg, vitamin C 60 mg, vitamin D_3 100 IU, vitamin B_{12} 1.5 μg, vitamin E 6 IU, biotin 50 μg, vitamin B_5 2.7 mg, folic acid 100 μg, calcium hydrogen phosphate anhydrous 33.9 mg, ferrous fumarate 7.5 mg, magnesium oxide 8.32 mg, manganese sulfate 77 μg, zinc oxide 1.25 mg, copper gluconate 178.6 μg, and potassium iodide 118 μg. Those in the LC-PUFAs + MVM group and all children from 15 weeks onward were required to take one tablet per day.

Conners Rating Scales

The Conners Rating Scales–Revised (CRSs-R)[36] are designed separately for parents (CPRS) and teachers (CTRS). They assess parent and teacher ratings of ADHD symptoms, including an index that is aligned with the DSM-IV criteria for ADHD, as well as subscales for co-occurring problems. Each item is measured on a 0 to 4 scale (0 = not true at all; 4 = very much true). Subscales measuring core ADHD factors are Cognitive Problems/Inattention, Hyperactivity, ADHD Index, Conners Global Restless/Impulsive Index, and DSM-IV symptoms inattentive, hyperactive-impulsive. The remaining subscales assess the following problems: oppositional behavior, anxious/shy, perfectionism, social problems, psychosomatic, and Conners Global Emotional Lability Index. Internal reliability coefficients reported in Conners manual[36] range from .73 to .94 for CPRS and .77 to .96 for CTRS subscales. In the current study, internal reliability coefficients for all questionnaires returned at baseline ranged from .76 to .92 on the CPRS and from .72 to .94 on the CTRS.

Background questionnaires

These included questions about the child's age, gender, and health (from 1, poor, to 5, excellent). Questions about children's primary caregivers included age, number of years of formal education, highest level of education attained (from 1, primary school, to 6, postgraduate degree) and occupation (coded according to Daniel's[44] prestige ratings: 12 = high, 69 = low).

IQ estimate

An IQ estimate was included as a potential covariate because parent- and teacher-reported problems with cognition/inattention was an outcome measure and IQ is typically lower in children with attention problems. IQ was estimated with the Block Design and Vocabulary subtests of the Wechsler Intelligence Scale for Children, version 3 (WISC-III), which were included in the cognitive assessments. This dyad is recommended by Sattler[45] as a valid estimate of Full Scale IQ.

Design

The study employed a randomized, placebo-controlled design providing within- and between-group comparisons, constituting 30 weeks' participation for each child with a one-way crossover at 15 weeks. During weeks 0 to 15 (phase 1), participants were given PUFA capsules with an MVM tablet, PUFA capsules alone, or placebo oil capsules. At 15 weeks, all children were given PUFAs + MVM for weeks 16 to 30 (phase 2). The first phase of the study was double blind; phase 2 was single blind in that the researchers knew that all children were receiving active treatment after 15 weeks. Dependent variables included parent and teacher ratings of ADHD-related problems with attention and behavior. Background measures including an IQ estimate were examined as potential covariates. Parent ratings of children's health were used as a covariate in CPRS analyses involving the placebo group because this group differed significantly from the PUFA group on this variable (Table 1). Mixed design 2 × 2 analyses of covariance were performed to test hypotheses 1 and 2, testing for treatment x condition interactions from baseline to week 15, first between both PUFA groups (combined) and the placebo group and then between the PUFA + MVM and PUFA groups. Within-group analyses of variance were used to test both parts of hypothesis 3, that the placebo group would show significant improvements following their switch to active treatment from weeks 16 to 30 and that the PUFA groups would continue to improve with extended supplementation from weeks 16 to 30.

Data Preparation and Analysis

Data were analyzed using SPSS 11.5.0. Missing data were replaced with that variable's mean[46]; on Conners scales, cases with three or more missing responses on any one subscale were deleted from the data set. Parents returned 131 questionnaires at both baseline and week 15. Of these, two cases were deleted due to low compliance (fewer than 200 capsules during phase 1), and a further 27 deleted due to missing data. Therefore, there were 104 cases available for phase 1 analysis (0–15 weeks). For those who completed the whole trial, 111 questionnaires were returned for all three time points. Of those, 24 were deleted due to missing data, leaving 87 cases available for all three times of measurement. Outliers falling ≥3.29 SD from the mean were brought alongside the next closest score, and then the distributions for all measures showed no significant departures from normality. Bonferroni adjustments were not applied to analyses because many of the CRS-R items overlap in multiple subscales.[21,36] Furthermore, although multiple analyses were performed, predicted outcomes based on previous research have practical significance.[47] For these reasons, an alpha level of $p < .01$ was applied to all analyses.

Of the cases with available data, 88% to 95% had data on compliance, and the average number of capsules taken per day overall was 5.33 of the stipulated daily dose of six. There were no significant differences between the groups on number of capsules taken for phase 1 ($F[2,94] = 2.90$, $p = .06$) or the whole study ($F[2,84] = 0.06$, $p = .94$).

RESULTS

Conners Parent Rating Scales

Phase 1: weeks 0 to 15

Repeated-measures analyses of covariance (ANCOVAs), with health as a covariate, were used to test the hypothesis

that the two polyunsaturated fatty acid (PUFA) groups combined would show significant improvements in parent ratings of outcome measures compared with placebo after 15 weeks of supplementation (N = 104). Means and SDs for health and Conners Parent Rating Scales (CPRSs) at weeks 0 and 15 are given in Table 2, along with ANCOVA results that report treatment × condition interactions. There were significant improvements in the PUFA treatment groups (combined) compared with placebo after the first 15 weeks on the following CPRS scores: Cognitive Problems/Inattention, Conners ADHD Index, Conners Global Index: Restless-Impulsive, both DSM-IV symptoms subscales Inattentive and Hyperactive-Impulsive, and Oppositional Behavior. Effect sizes are reported as the standardized mean difference (Cohen's *d*). Significant treatment effects range in magnitude from medium to large.

To test the hypothesis that there would be additional improvements with the PUFAs + MVM treatment over and above the PUFA treatment alone, 2 x 2 analyses of variance (ANOVAs) were performed to investigate treatment x condition interactions from baseline to week 15 in the PUFA and PUFA + MVM groups. There were no additional treatment effects in the PUFA + MVM group compared with the PUFAs alone group.

Phase 2: Treatment Crossover, Weeks 16 to 30

Table 3 shows means and SDs at weeks 0, 15, and 30 on the Conners parent questionnaires returned for participants who completed the full 30-week trial (n = 87).

Repeated-measures one-way ANOVAs were conducted on the placebo group, comparing their scores at weeks 15 and 30 to test whether there were significant improvements in scores following their switch to active PUFA capsules (Table 3). After switching to active PUFAs, this group showed significant improvements on Cognitive Problems/Inattention, Hyperactivity, ADHD Index, Conners Global Index: Restless-Impulsive, and both DSM-IV

Table 2. Adjusted Means, Standard Deviations, and Mixed Design ANCOVA Results Showing Treatment × Condition Interactions Between PUFAS and Placebo Groups at Baseline and 15 Weeks (N = 104) on the Conners Parent Rating Scales

		Baseline		15 Weeks		2 × 2 ANCOVAs	
Variable/Subscale	**Group**	**Mean**	**SD**	**Mean**	**SD**	**F(1,102)[a]**	**Effect Size[b]**
Cognitive Problems/Inattention	PUFAs	24.91	6.42	20.89	7.30		
	Placebo	25.30	7.05	24.51	6.68	10.06**	.52
Hyperactivity	PUFAs	13.82	6.69	10.67	6.42		
	Placebo	13.19	6.21	11.74	5.93	4.21*	.17
ADHD Index	PUFAs	26.43	5.98	21.53	7.22		
	Placebo	26.99	5.78	25.29	5.27	9.09**	.59
Global: Restless/Impulsive	PUFAs	13.54	4.64	10.81	4.66		
	Placebo	13.33	3.11	12.63	3.31	7.88**	.45
Global: Emotional Lability	PUFAs	3.97	2.54	3.09	2.42		
	Placebo	3.63	2.68	3.44	2.42	2.70	.14
Global: Total	PUFAs	17.50	6.45	13.92	6.06		
	Placebo	16.96	4.65	16.07	4.86	8.37**	.39
DSM-IV Inattentive	PUFAs	20.05	4.82	16.10	5.97		
	Placebo	19.85	5.29	19.26	4.25	11.24**	.61
DSM-IV Hyperactive/Impulsive	PUFAs	15.37	6.50	12.19	6.44		
	Placebo	14.33	5.16	13.40	5.49	7.68**	.20
DSM-IV Total	PUFAs	35.41	9.56	28.31	10.77		
	Placebo	34.23	7.75	32.68	6.67	12.91**	.49
Oppositional	PUFAs	15.74	7.38	12.45	6.94		
	Placebo	15.92	7.40	15.66	8.10	8.06**	.43
Anxious/Shy	PUFAs	6.50	4.71	4.96	4.12		
	Placebo	6.29	4.59	5.09	4.32	0.89	.03
Perfectionism	PUFAs	5.36	4.55	4.35	4.34		
	Placebo	4.89	4.26	4.64	3.61	1.76	.07
Social Problems	PUFAs	5.09	3.99	4.43	3.81		
	Placebo	5.11	4.04	5.33	4.13	2.12	.23
Psychosomatic	PUFAs	4.21	3.64	3.20	3.04		
	Placebo	4.26	3.70	4.33	3.26	3.68	.36

ANCOVA, analysis of covariance; PUFAs, polyunsaturated fatty acids. Groups: PUFA and PUFA + multivitamin/mineral, n = 77; placebo, n= 27. [a]F values represent interaction effects between group condition and time. Health was a covariate (the placebo group differed significantly from the PUFA group on baseline health ratings). There were no significant interaction effects between group condition and time for the covariate. [b]Effect size calculated as Cohen's *d*. *$p < .05$; **$p < .01$.

Table 3. Conners Parent Rating Scale Means and Standard Deviations at 0, 15, and 30 Weeks (n = 87) plus One-Way RM ANOVA Results for PUFAs Groups from Weeks 16 to 30 Following 15 Weeks of Continued PUFAs (n = 65) and Placebo Group from Weeks 16 to 30 Following Switch to Active PUFAs (n = 22)

		Baseline		15 Weeks		30 Weeks		2 × 2 RM ANOVA 16–30 Weeks	
Subscale	**Group**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F(1,26)[a]**	**Effect Size[b]**
Cognitive Problems/Inattention	PUFAs	25.26	6.41	21.04	7.62	18.50	8.74	17.78**	.31
	Placebo	24.86	7.08	24.49	6.78	18.64	7.52	26.95**	.82
Hyperactivity	PUFAs	14.28	6.45	11.07	6.18	9.71	6.04	9.45**	.22
	Placebo	13.32	5.93	12.45	5.29	9.80	5.82	9.48**	.48
ADHD Index	PUFAs	26.68	6.19	21.90	7.44	18.88	8.37	19.74**	.38
	Placebo	26.67	6.26	25.76	5.17	19.53	6.77	35.47**	1.03
Global: Restless/Impulsive	PUFAs	13.82	4.61	11.22	4.49	9.84	4.69	15.40**	.30
	Placebo	13.18	3.07	12.95	2.77	10.50	4.11	14.54**	.70
Global: Emotional Lability	PUFAs	4.13	2.48	3.22	2.44	2.89	2.17	2.38	.14
	Placebo	3.18	2.54	3.09	2.41	2.77	2.25	1.15	.14
Global: Total	PUFAs	17.95	6.38	14.45	5.84	12.72	6.10	13.73**	.29
	Placebo	16.36	4.42	16.05	4.50	13.27	5.59	11.54**	.55
DSM Inattentive	PUFAs	20.34	4.94	16.28	6.22	14.38	7.13	13.13**	.28
	Placebo	19.50	5.60	19.41	4.53	14.41	5.37	40.67**	1.00
DSM Hyperactive/Impulsive	PUFAs	15.87	6.26	12.71	6.13	11.15	6.24	10.86**	.25
	Placebo	14.77	5.15	14.54	4.71	11.93	5.76	9.60**	.50
DSM Total	PUFAs	36.19	9.71	29.01	10.86	25.54	11.87	14.65**	.31
	Placebo	34.33	8.55	33.97	6.12	26.37	9.69	33.89**	.94
Oppositional	PUFAs	15.99	7.40	12.79	7.08	11.70	6.73	3.78	.16
	Placebo	14.81	7.42	15.05	8.32	12.81	7.17	6.78*	.29
Anxious/Shy	PUFAs	6.84	4.77	5.26	4.24	4.76	4.16	1.98	.12
	Placebo	5.49	4.27	4.66	4.52	3.45	3.94	7.23*	.29
Perfectionism	PUFAs	5.74	4.61	4.78	4.44	4.13	4.09	5.88*	.15
	Placebo	4.64	4.50	4.47	3.59	2.95	3.43	9.04**	.43
Social Problems	PUFAs	5.38	4.14	4.65	3.98	4.52	3.93	0.15	.03
	Placebo	5.27	4.37	5.95	4.34	4.19	3.90	17.41**	.43
Psychosomatic	PUFAs	4.58	3.74	3.48	3.18	3.08	3.23	1.88	.12
	Placebo	3.64	3.46	3.77	2.89	2.59	3.11	5.24*	.39

PUFAs, polyunsaturated fatty acids; RM ANOVA, repeated-measures analysis of variance. Groups: PUFAs + MVM (multivitamin/mineral), $n = 36$; PUFAs, $n = 29$; placebo, $n = 22$. PUFAs + MVM group continued on PUFAs + MVM from weeks 16 to 30; PUFAs and placebo groups had treatment crossover to PUFAs + MVM from weeks 16 to 30. [a]F values represent within group changes from weeks 16 to 30. [b]Effect size calculated as Cohen's *d*. *$p < .05$; **$p < .01$.

symptoms subscales Inattentive and Hyperactive-Impulsive, as well as on the Perfectionism and Social Problems subscales.

The same analyses were performed on the active PUFA groups to assess whether their scores continued to improve significantly following an additional 15 weeks of supplementation. Both PUFA groups showed continued improvement on Cognitive Problems/Inattention, ADHD Index, Conners Global Index: Restless-Impulsive, both DSM-IV symptoms subscales Inattentive and Hyperactive-Impulsive and on the Hyperactivity subscale.

Conners Teacher Rating Scales

As with parent ratings, repeated-measures ANOVAs were performed with the Conners Teacher Rating Scales data to test the hypotheses that the PUFA groups would show significant improvements in teacher ratings of outcome measures compared with placebo after 15 weeks of supplementation. No significant results were found. Similarly, repeated-measures ANOVAs revealed no significant effects of teacher ratings in the placebo group following their switch to active treatment after 15 weeks.

DISCUSSION

This study tested the effect of polyunsaturated fatty acid (PUFA) supplementation on parent and teacher ratings of attention and behavior in a sample of South Australian children with problems with hyperactivity, impulsivity, and inattention as rated by parents on Conners abbreviated ADHD Index. Supplementation with PUFAs

over 15 weeks resulted in significant improvements compared with placebo in parent ratings of core attention-deficit/hyperactivity disorder (ADHD)–related behavioral and cognitive difficulties, namely inattention, hyperactivity, and impulsivity, with medium to large effect sizes, and also in ratings of oppositional behavior. Following a one-way crossover to active treatment for a further 15 weeks, the placebo group showed significant improvements comparable with the active groups during the first 15 weeks, with the exception of oppositional behavior but with significant improvements also shown on subscales measuring coexisting problems of social problems and perfectionism. The PUFA groups continued to demonstrate significant improvements in attention, impulsivity, and hyperactivity following an additional 15 weeks of supplementation. Overall, 30% to 40% of children over 15 weeks and 40% to 50% of children over 30 weeks had improvements of >1 SD in scores.

However, there were no significant treatment effects on the Conners Teacher Rating Scales. This may mean that the teacher rating scales were unable to detect treatment effects in this study. Research on parent ratings of developmental problems, including cognitive ability, has found a high degree of accuracy in identifying children with ADHD. In some cases, parent ratings were more accurate in identifying cognitive problems than were psychometric assessments, with 81% accuracy.[49] It has also been reported that parent and teacher rating scales are the most efficient method for assessing ADHD compared with other diagnostic methods. Indeed, both are preferred for clinical purposes.[50] However, how well these correlate with each other is unclear. A comparison of parent and teacher ratings of behavior in a normal population of children found no significant differences between them except on externalizing behavior/social skills, possibly because teachers have more opportunity to observe children in a social setting.[51] In a clinical population, however, it was found that teachers showed significantly less agreement with parent and youth ratings than expected.[52] These researchers reported that the significant variability that is often found in responses by different raters can be accounted for by various demographic and psychological factors. All in all, variability in responses may be attributed to a number of rater characteristics and environmental factors and are also likely to be influenced by the context of the research involved. The parent ratings in the present trial are similar to those obtained recently using the same PUFA supplement on teacher ratings of children in Durham.[21] In the latter study, the local education authority and teachers were actively involved in the project and in administering the supplements to the children each day at school. Conversely, in the current study, the parents were actively involved in bringing their children in for assessments and administering the supplements. In the present study, there were also multiple incidences of teacher sharing (i.e., two teachers taking the same class on different days), long-service leave/holidays, and children moving schools or changing teachers. Validity of ratings might also have been affected by large class sizes of 30 children per class. Therefore, all things considered, and although this discrepancy should be considered when interpreting these results, it is likely that the parent ratings have greater validity in the current study.

Contrary to hypotheses, there was no benefit derived from a multivitamin/mineral supplement over and above the PUFAs. Although they were set at recommended daily doses for children, it is possible that greater quantities are required in clinical populations.[53] For instance, in a recently published randomized, double-blind, placebo-controlled study,[54] supplementation with 150 mg zinc per day reduced symptoms of hyperactivity, impulsivity, and poor social skills in a group of children with ADHD. In contrast, the supplement used in the current study provided a daily dose of less than 2 mg zinc. It must be noted that high doses of zinc can be toxic or cause gastrointestinal side effects, and caution has been advised as the above trial experienced a 60% dropout rate[55] (although there was no notable difference in dropout rates between placebo and active zinc treatment). It is possible that the safe or optimal dose level is dependent on individual requirements and/or level of deficiency.[52] This possibility remains to be explored in an ADHD population.

Correlations have previously been observed between PUFA deficiency in red blood cells and learning and behavioral problems, not only in boys with ADHD, but also in controls. Furthermore, although the children recruited for this study met the criteria for a possible clinical diagnosis according to Conners Parent Rating Scales,[36] they did not necessarily all have a formal diagnosis. Other studies reviewed in this paper also found biochemical PUFA deficiencies in children with hyperactivity and learning problems that had not necessarily been diagnosed as ADHD and linear relationships have been found between the degree of PUFA deficiency and the severity of mental health outcomes.[56,57] It is possible therefore that symptoms associated with ADHD may fall on a continuum rather than into a fixed diagnostic category. The biochemical approach to treating behavioral problems as applied in this study could have an advantage of treating symptoms without some of the issues and limitations inherent in diagnosis.[58] This possibility is important to consider because children with these developmental problems do not all necessarily have PUFA deficiencies and those who do might benefit from supplementation without necessarily reaching the cutoff for a formal diagnosis. Therefore, further exploration is warranted via correlational analyses between PUFA status, degree of attention and behavioral problems, and degree of improvement through supplementation.

It should be noted that this study did not employ an intent-to-treat analysis because the study was concerned with treatment efficacy and not with adherence to the treatment. Therefore, the results focus only on those who completed the trial. It was found, however, that those who did not turn up for the first appointment and who dropped out before completing phase 1 had significantly higher scores on Conners Index as completed by parents upon registration for the study than those who completed phase 1 or the whole study. There are two most probable

explanations for this, according to parent feedback that was received. First, parents are likely to have put their children on stimulant medication (an exclusion criterion) because their behavior became too hard for them to manage, and second, some of these children were not compliant. This poses a couple of limitations on the use of PUFAs as a possible treatment for problems that are symptomatic of ADHD because in contrast to stimulant medication, it can take 8 to 12 weeks of supplementation to notice an improvement in symptoms,[59,60] and it might be more difficult in children with problematic behavior to elicit compliance in taking up to six capsules per day. Another implication of children with higher scores dropping out is that the results may be a more conservative reflection of treatment effects as the children who completed the study had lower mean scores on the Conners ADHD Index.

A further limitation to the study was that it was not possible to take biochemical analyses of nutritional status, so it is not known whether the children had nutritional deficiencies. The possibility that supplementation of nutrients in combination with each other might provide greater benefits than isolated nutrients, e.g., zinc and PUFAs, requires further investigation. Future inspection of both PUFA and nutrient status at baseline and correlations of supplementation with magnitude of improvement could confirm relationships between nutrients and PUFAs and deficiency and response. Furthermore, although the study included indirect measures of compliance via returned bottles and calendars, biochemical analyses of PUFA status or independent administration of supplements (e.g., by teachers as in the Durham trial) would have provided a more direct and reliable measure of compliance.

Where treatment effects have been found in research to date, core ADHD-related symptoms of inattention, hyperactivity, and impulsivity seem to respond most consistently to PUFA supplementation. Behavioral problems associated with ADHD and measured by Conners Rating Scales such as social problems, anxiety, and perfectionism, are less consistent in their response to PUFA treatment. This may be because the children in this sample did not have significant enough problems in these areas at baseline, and indeed oppositional behavior, which was higher in this group at baseline, was more responsive to PUFA supplementation. Alternatively, it may be that these types of behaviors are learned as a result of the biological symptoms. For instance, a child might become anxious about his/her behavior and the impact that it has on others or defiant as a result of behavioral consequences or to cover up difficulties with paying attention in class or develop social problems as a result of disruptive behavior. Over time, some of these problems might be naturally alleviated as other symptoms are reduced; however, behavioral interventions might address these comorbid issues more effectively. In any event, ADHD-related problems have complex etiological influences, and future researchers should therefore explore the possibility that some children with ADHD-related problems may derive increased benefit from combined PUFA/behavioral interventions. It is also important to note that, although docosahexaenoic acid (DHA) is the most concentrated PUFA in the brain and at neural synapses, fatty acid research in mental health to date has had more positive results using a combination of omega-3 fatty acids eicosapentaenoic acid (EPA) and DHA than research using DHA alone, and it has been suggested that EPA is an important PUFA for mental health outcomes.[7] The current study and the Durham trial used a supplement with a high EPA:DHA ratio and therefore lend further support to this notion. As noted by Richardson and Montgomery,[21] however, this research does not explain the underlying biological mechanisms of PUFA; therefore, nutritional/behavioral research requires integration of research from different fields of specialization.

The present study is the largest PUFA trial to date with children falling in the clinical ADHD range on Conners Index. The results support those of other studies that have found improvements in developmental problems symptomatic of ADHD with PUFA supplementation.[21,33] These results have significant implications for children with ADHD-related symptoms, parents, and clinicians. Importantly, core symptoms of hyperactivity, impulsivity, and inattention improved on average from the upper clinical range on Conners ADHD Index to mildly clinical after 30 weeks of supplementation. It is possible that symptoms may continue to improve over time with continued supplementation and in combination with psychosocial therapies to assist children in learning more adaptive behaviors.

There has been a great deal of controversy surrounding the diagnosis and treatment of ADHD and concern regarding the increasing prescription of stimulant medication to children. As noted by Richardson and Montgomery,[33] the medium effect sizes observed in their study, as also observed in the present trial, are comparable with those calculated from a meta-analysis of medication trials.[61] However, there is no known evidence that medication provides any benefits beyond 4 weeks, whereas in the present trial, symptoms continued to improve after 15 weeks of supplementation. Importantly, there have been no reports of adverse effects in fatty acid trials with children to date. This was not directly assessed in the current study, but two parents commented that their children felt a little sick after taking the supplements, and one boy had nose bleeds (possibly due to the blood-thinning effect of PUFAs). These effects may not be as serious as the short-term effects reported from various stimulant medications, which include weight loss, reduced appetite, sleep disturbances, sedation, dulled affect, social withdrawal, irritability, abnormal thinking, stomachache, and vomiting.[62] Therefore, PUFA supplementation could provide a safe, healthy option for some children with ADHD symptoms and particularly the large subgroup with comorbid symptoms who are more likely to experience adverse side effects from medication.[63] Studies comparing the efficacy and safety of medication and fatty acid supplementation are clearly warranted and particularly over the longer term given the paucity of long-term medication trials.[64,65]

Evidence that a proportion of children with ADHD symptoms might experience reduced symptoms with nutritional supplementation is therefore important for practitioners to consider as a possible treatment adjunct. Further investigation and refinement of research in this area are required, including optimal doses of PUFAs and micronutrients, continued treatment effects with extended supplementation, and the identification of children most likely to respond to supplementation that includes investigation of comorbid symptoms and the issue of treating children with an official diagnosis versus treatment of symptoms that have not necessarily been diagnosed.

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