

1 **Effects of an open-label pilot study with high-dose EPA/DHA concentrates on plasma**  
2 **phospholipids and behavior in children with attention deficit hyperactivity disorder.**

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4 Paul J. Sorgi<sup>1</sup>, Edward M. Hallowell<sup>1</sup>, Heather L. Hutchins<sup>2</sup>, Barry Sears<sup>2\*</sup>.

5 <sup>1</sup>Hallowell Center, <sup>2</sup>Inflammation Research Foundation.

6 <sup>1</sup> Hallowell Center  
7 142 North Road, Suite F 105  
8 Sudbury, MA 01776

9 <sup>2</sup> Inflammation Research Foundation  
10 222 Rosewood Drive, Suite 500  
11 Danvers, MA 01923

12 Paul J. Sorgi, MD pjsorgi@aol.com

13 Edward M. Hallowell, MD [EHallowell@aol.com](mailto:EHallowell@aol.com)

14  
15 Heather L. Hutchins MS, RD [HHutchins@eicosresearch.org](mailto:HHutchins@eicosresearch.org)

16  
17 Barry Sears, PhD [bsears@drsears.com](mailto:bsears@drsears.com)

18  
19  
20  
21 \*Corresponding Author

22 Barry Sears, PhD  
23 Inflammation Research Foundation  
24 222 Rosewood Drive, Suite 500  
25 Danvers, MA 01923  
26 (978) 539-0100  
27 (978) 539-0088 FAX  
28 bsears@drsears.com

29  
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43

1 **Abstract:**

2 Attention deficit hyperactivity disorder (ADHD) is the most common neurological condition in  
3 children. This pilot study evaluated the effects of high-dose eicosapentaenoic acid (EPA) and  
4 docosahexaenoic acid (DHA) supplementation on the isolated plasma phospholipids and  
5 behavior in children with ADHD (primarily inattentive subtype and combined subtype). Nine  
6 children were initially supplemented with 16.2g EPA/DHA concentrates per day. The dosage  
7 was adjusted dependent on the ratio of arachidonic acid (AA) to EPA in the isolated plasma  
8 phospholipids at four weeks. At the end of the eight-week study, supplementation resulted in  
9 significant increases in EPA and DHA, as well as a reduction in the AA:EPA ratio. A psychiatrist  
10 (blind to supplement compliance or dosage modifications) reported significant improvements in  
11 behavior (inattention, hyperactivity, oppositional/defiant behavior, and conduct disorder). There  
12 was also a significant correlation between the reduction in the AA:EPA ratio and global severity  
13 of illness scores. The findings of this small pilot study suggest supplementation with high-dose  
14 EPA/DHA concentrates may improve behavior in children with ADHD.

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16 **Key Words:**

17 Omega-3 fatty acids, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), attention  
18 deficit hyperactivity disorder (ADHD), behavior

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**Background:**

Attention deficit hyperactivity disorder (ADHD) is a neurological condition characterized by the inability to concentrate in a sustained manner, to pay attention to tasks, and to control impulsive actions [1]. It is estimated that 3 to 7 percent of children have this disorder, and boys are affected to a much greater extent than girls [2]. As many as 60 to 80 percent of children with ADHD continue to have problems with this condition as they become adults [1]. The etiology appears to be multi-factorial with both genetic and environmental influences. Among these influences is an observed decrease in long-chain (LC) polyunsaturated fatty acids (PUFAs) in children with ADHD. Some proposed mechanisms for the low levels of PUFAs include insufficient dietary intake, inefficient conversion of shorter chain PUFAs to LC PUFAs and/or rapid metabolism [3]. Stevens et al found that young boys with ADHD and symptoms of essential fatty acid deficiency (EFA) (excessive thirst, dry skin and hair, brittle nails, frequent urination and and/or hyperfollicular keratoses) are characterized by low levels of LC PUFAs, including AA, EPA and DHA in the plasma phospholipids compared to control [4, 5]. This group of children with ADHD also had a high ratio of AA to EPA compared to control suggesting the depression of EPA was greater than that of AA [4, 5].

The altered levels of PUFAs in children with ADHD led to interventional studies that supplemented with these fatty acids. Stevens et al [6] supplemented children with ADHD and symptoms of essential fatty acid deficiency with 660 mg per day of both omega-3 and omega-6 PUFAs for four months. Although the plasma levels of these supplemented fatty acids increased, only two of 16 behavioral outcome measures significantly improved compared to the placebo group. Hirayama et al found that supplementation of 614 mg of LC omega-3 fatty acids per day for two months (primarily DHA in foods) had no effect when analyzing parent and teacher assessments separately in children with ADHD [7]; however, when analyzing assessments together, physical aggression significantly improved compared to the placebo

1 group [8]. Voigt et al [9] supplemented children with ADHD for four months with 345 mg of DHA  
2 per day and found no improvements in any ADHD symptoms. Richardson and Puri [10]  
3 supplemented children with ADHD related symptoms, primarily dyslexia, for three months with  
4 1668mg of omega-3 and omega-6 fatty acids plus 8 mg thyme oil and 60 IU vitamin E or olive  
5 oil placebo in a double-blind randomized fashion. Half of the scales tested (7 of 14) improved  
6 compared to placebo, including cognition, anxiety/shyness, psychosomatic subscales,  
7 restlessness/impulsivity and three global scales; however, the participants were children with  
8 ADHD-related symptoms not diagnosed with ADHD in accordance to DSM IV criteria.

9         The interventional studies in children with ADHD demonstrate that some behavior may  
10 improve with PUFA supplementation; however, the findings have not been consistent. The lack  
11 of consistent results led us to hypothesize that insufficient levels of omega-3 fatty acids, or lack  
12 of sufficient reduction of the AA:EPA ratio are two possible explanations for the inconsistent  
13 findings of previous studies. To address this hypothesis, we undertook an open-label pilot study  
14 to first determine tolerability in children taking high-dose EPA/DHA concentrates (initial dosage  
15 of 16.2g EPA and DHA per day) and secondly, what effect the high dosage would have on fatty  
16 acid levels in the isolated plasma phospholipids, particularly the AA:EPA ratio, and behavior in  
17 children with ADD and ADHD assessed by a psychiatrist specialized in this childhood disorder.

18

## 19 **Methods:**

20 *Study design and participants.* This was an eight-week, open-label, proof-of-efficacy pilot study.  
21 Nine children aged 8-16 were recruited from the patient population under treatment for ADHD-  
22 primarily inattentive subtype or ADHD-combined subtype at the Hallowell Center, Sudbury, MA.  
23 There were more boys (n=6) than girls (n=3). Two-thirds (n=6) presented with ADHD-  
24 combined subtype, and one-third (n=3) with ADHD- primarily inattentive subtype according to  
25 criteria of the Diagnostic Statistical Manual (DSM) IV [11]. Participant characteristics are  
26 outlined in Table 1. All participants had an established relationship with the psychiatrist involved

1 in the study. Three participants voluntarily discontinued stimulant medication prior to study  
2 initiation with the psychiatrist's approval. The remainder continued with their treatment regime  
3 for the duration of the study. There were no medication dosage changes during the course of  
4 the eight-week study. Children and parents/guardians provided informed and written assent  
5 and consent respectively. Integreview, Houston, TX, approved the study for the use of human  
6 subjects in research.

7 Table 1 about here.

8 *Study Intervention:* At the start of the study, all participants were instructed to consume two  
9 tablespoons (30mL) of a liquid EPA/DHA concentrate (supplied by the Inflammation Research  
10 Foundation) providing 16.2g of LC omega-3 fatty acids (10.8 g EPA and 5.4 g DHA) per day.  
11 The EPA/DHA concentrate dosage was adjusted at week four based on the AA:EPA ratio in the  
12 isolated plasma phospholipids. The participant's parent/guardian was phoned once per week to  
13 monitor tolerability and adverse effects of the EPA/DHA concentrates. The children and at least  
14 one parent/guardian met with the psychiatrist at three time points, baseline (week 0), midpoint  
15 (week four) and conclusion (week eight). At the initial (baseline) visit participants were advised  
16 to follow a "healthy diet" that encouraged fruits, vegetables and balanced intake of  
17 macronutrients at meals and snacks. At each of the three meetings, the psychiatrist conducted  
18 behavioral assessments, and a phlebotomist drew blood for fatty acid analysis. Fatty acid  
19 analysis of the isolated serum phospholipids was completed by Nutrasource Diagnostics,  
20 Guelph, ON, Canada, as described by Laidlaw and Holub [12].

21  
22 *Behavioral Assessment:* The ADHD Symptom Checklist-4 (ADHD SC-4) was used to monitor  
23 behavioral changes by the psychiatrist at each meeting. This questionnaire categorizes  
24 behavior as inattention, hyperactivity, oppositional/defiant, conduct disorder and medication side  
25 effects. Inattention and hyperactivity scores can range from 0 to 27 each. Oppositional/defiant  
26 scores range from 0 to 24 and conduct disorder from 0 to 3 [13, 14].

1           The psychiatrist also used the Clinical Global Impression Scale to rate participants'  
2 severity of illness [15]. The scores are derived from a 7-point Likert scale [15]. Severity of  
3 illness ranged from 1 as normal (not at all symptomatic), to 7 as among the most symptomatic  
4 patients. The psychiatrist was blind to dosage adjustments and compliance throughout the  
5 study.

6

7 *Statistical Analysis:* Summary statistics are reported as mean±SD and medians. Statistical  
8 analyses were performed using Stata for Mac (version 9, StataCorp LP, College Station,  
9 Texas). Fatty acids, ADHD SC-4, and severity of illness were reported for baseline (week 0),  
10 midpoint (week four) and at the conclusion of the study (week eight). The non-parametric  
11 Friedman test was used to assess changes over time. If the Friedman test was statistically  
12 significant at the 0.05 level, then the Wilcoxon signed rank test was used as a post-hoc test to  
13 compare changes from baseline to four and eight weeks. Spearman correlations were used to  
14 identify a relationship between changes in the primary fatty acid outcome variable, the AA:EPA  
15 ratio, and the primary behavioral outcome variable, severity of illness.

16

## 17 **Results:**

18 *Effect of EPA/DHA Concentrates on Isolated Plasma Phospholipid Fatty Acid Levels:* Blood  
19 was monitored throughout the study to ensure that the AA:EPA ratio was greater than 1  
20 because of the high levels of LC omega-3 fatty acids given to the participants. The goal was to  
21 maintain an AA:EPA ratio in the isolated serum phospholipids between 1.5 and 3. This AA:EPA  
22 ratio is similar to those found in epidemiological data from the Japanese [16] who have high  
23 intakes of fish (rich in EPA and DHA) and low levels of depression [17], coronary heart disease  
24 [18], and long life expectancies [19]. If the AA:EPA ratio of a participant was found to be less  
25 than 1.5 at week four, the EPA/DHA concentrate dosage was decreased. At week four, three  
26 participants had an AA:EPA ratio below 1.0; they were instructed to decrease the EPA/DHA

1 concentrate dosage to 15 ml, providing 5.4 g EPA and 2.7 g DHA per day. Two participants had  
2 AA:EPA ratios between 1.0 and 1.5 and were instructed to decrease their dosage to 20 ml of  
3 the EPA/DHA concentrate, providing 8.1 g EPA and 4 g DHA per day. The remaining four  
4 participants had an AA:EPA ratio of 1.5 or above at week four, and were instructed to continue  
5 with the initial daily dosage.

6 At the conclusion of the eight weeks of supplementation, the average EPA and DHA  
7 levels in the isolated plasma phospholipids significantly increased by a factor of 9.5 and 2.4  
8 respectively (Table 2). The AA tended to decrease at eight weeks, although the reduction was  
9 not significant ( $p=0.07$ ). As a consequence of AA and EPA changes, there was a 71% reduction  
10 in the mean AA:EPA ratio ( $20.8\pm 5.3$  to  $6.0\pm 7.4$ ,  $p<0.01$ ) from baseline to week eight. The  
11 EPA/DHA concentrate dosage adjustment at week four resulted in the average EPA and DHA  
12 levels to increase from week four to eight with a corresponding 42% relative increase ( $4.2\pm 5.5$   
13 to  $6.0\pm 7.4$ ,  $p=0.07$ ) in the AA:EPA ratio; this increase demonstrates sensitivity to EPA and DHA  
14 supplementation dosage.

15 Table 2 about here

16 *Compliance:* The largest AA:EPA reduction for most participants occurred in the first four  
17 weeks (Figure 1). Figure 1 shows that one participant's AA:EPA ratio returned to baseline  
18 levels at week eight following a significant reduction at week four. Furthermore, this  
19 participant's EPA and DHA levels returned to near baseline levels, indicating poor compliance  
20 from week four to eight. A second participant refused to consume the liquid and was switched to  
21 a capsule supplementation and was instructed to consume 24 one-gram capsules (9.6 g EPA  
22 and 4.8 g DHA) per day from week two to week eight. The fatty acid analysis showed less than  
23 100% increase in the isolated plasma phospholipids for EPA and DHA, indicating poor  
24 compliance. All other participants had greater than a 100% increase in both EPA and DHA

1 levels at the conclusion of the study and were considered compliant with study supplementation  
2 protocol.

3

4 *Adverse Effects:* One participant reported mild GI distress while taking 30 ml of the liquid EPA  
5 and DHA concentrate per day. At week four, the dosage was decreased to 15 ml per day with  
6 no subsequent adverse events.

7

Figure 1 about here

8 *Behavioral analysis:* All categories of the ADHD SC-4 significantly improved by week eight  
9 (Table 3). The severity of illness score, assessed by the psychiatrist (blinded to compliance and  
10 dosage adjustments), tended to improve ( $p=0.08$ ) over time. On average, the severity of illness  
11 score decreased by 1 point from 4.4 (moderately symptomatic) to 3.3 (mildly symptomatic). The  
12 two subjects who were identified as non-compliant were the only participants who were scored a  
13 5 (markedly symptomatic) at baseline and week eight.

14

Table 3 about here

15 *Correlations:* There was a significant positive correlation of the percent change in AA:EPA ratio  
16 with the percent change in severity of illness ( $Rho= 0.7638, p=0.027$ ).

17

## 18 **Discussion:**

19       Supplementation with high-dose EPA/DHA concentrate resulted in significant  
20 modifications of fatty acids in the plasma phospholipids and improvements in behavior assessed  
21 by a psychiatrist (blinded to compliance) in this small pilot sample of children with ADHD.

22       At baseline fatty acid analysis of the isolated plasma phospholipids from the children in  
23 this study were similar to that of previous studies of children with ADHD and thirst/skin  
24 symptoms of EFA deficiency [3, 5, 6]. Children with ADHD and thirst/skin symptoms of EFA  
25 deficiency had lower AA and DHA levels in the plasma phospholipids compared to control

1 groups. Both the AA and DHA mean levels from previous studies [3, 5, 6] were within the 95%  
2 CI (8.98-10.05; 1.63-2.97, respectively) of this study's mean AA and DHA levels.

3         Supplementation of high-dose EPA/DHA concentrates resulted in marked changes in  
4 fatty acid levels of the isolated plasma phospholipids. EPA and DHA levels in the isolated  
5 plasma phospholipids and the AA:EPA ratio were used to monitor compliance. We chose the  
6 AA:EPA ratio as a primary marker because of the low levels found in the Japanese population,  
7 and because of noted correlations between the AA:EPA ratio and severity of depression [20],  
8 and depression is often associated with ADHD [21]. In this study, there was indeed a significant  
9 positive correlation between the AA:EPA ratio and severity of illness.

10         Although the EPA and DHA supplementation dosages used in this study were high  
11 compared to previous studies with children, there was no serious adverse effect except one  
12 case of loose stools that was corrected with a lower dose. Young et al [22] supplemented adults  
13 with ADHD with high-dose EPA/DHA concentrates (approximately 36 g EPA and DHA per day)  
14 with no reported serious adverse effects other than loose stools and fishy burps. The average  
15 AA:EPA ratio after 12 weeks of the high-dose EPA/DHA supplementation in adults with ADHD  
16 was  $1.4 \pm 0.6$  [22]. This AA:EPA ratio is slightly lower than our goal of between 1.5 and 3 and  
17 behavior was not assessed.

18         Stevens et al [6] supplemented children with ADHD and thirst/skin symptoms with  
19 480mg DHA, 80mg EPA, 40mg AA and 60mg GLA per day. This dosage significantly increased  
20 DGLA, AA, EPA and DHA levels in the plasma phospholipids of the supplement group;  
21 however, between-group comparisons revealed that AA and DHA significantly increased  
22 compared to placebo, this would suggest that not enough EPA was provided to increase EPA  
23 levels in the plasma phospholipids compared to placebo supplementation. The AA:EPA ratio in  
24 Steven's sample was 15 after four months of supplementation [6], which remains 2.5 times  
25 greater than the mean AA:EPA ratio obtained in this study. Stevens did monitor behavior and

1 found improvements in conduct assessed by the parents and attention assessed by the  
2 teachers. There was no assessment of the children by a psychiatrist [6].

3 This study found a statistically significant improvement in the psychiatrist's report of  
4 inattention, hyperactivity, oppositional/defiant behavior and conduct disorder based on the  
5 ADHD SC-4 questionnaire. The severity illness scale demonstrated a positive improvement  
6 from an average of moderately symptomatic to mildly symptomatic. This improvement was  
7 similar regardless of medication use or lack there of. The percent change in severity of illness  
8 also correlated with percent decrease in the AA:EPA ratio, suggesting a connection between the  
9 clinical improvement observed by the psychiatrist and the improvements in the AA:EPA ratio.

10 Data from Stevens et al [6] in children and Young et al [22] in adults with ADHD suggest  
11 that greater amounts of both EPA and DHA may be required to decrease the AA:EPA ratio to  
12 between 1.5 and 3. The mean AA:EPA ratio at the end of this study was  $6.0 \pm 7.4$  for all  
13 participants. When the two participants who were non-compliant throughout the study were  
14 removed, the AA:EPA ratio was  $2.5 \pm 2.9$ , suggesting a daily dose between 8.1 g and 16.2 g of  
15 EPA/DHA concentrate may be appropriate to decrease the AA:EPA ratio to between 1.5 and 3  
16 and to observe improvements in behavior in children with ADHD.

17 There are a number of limitations to this pilot study and therefore interpretation of results  
18 requires caution. The study is limited in that there was no placebo group for reference  
19 comparisons as this was a pilot study to determine appropriate dosage for tolerability and fatty  
20 acid levels. Dietary intake was not recorded at baseline or monitored throughout the study;  
21 therefore, we are unable to decipher intake of fatty acids from the diet. Also related to diet, we  
22 advised the children to eat more fruits and vegetables and consume meals and snacks that are  
23 balanced with protein, carbohydrates (preferably fruit and vegetables) and "healthy"  
24 monounsaturated fats. Advice for following both a "healthy diet" and high-dose fish oil  
25 supplementation may have been confounding factors. However, the dose-response relationship

1 between percent change in AA:EPA ratio and the reduction in the severity of ADHD suggest the  
2 behavioral changes were due to, at least in part, the intake of high-dose EPA/DHA  
3 concentrates. The lack of behavioral change or regression to pre-study status in those subjects  
4 who were least compliant to supplementation also suggest that behavioral changes were  
5 associated with intake of the LC omega-3 fatty acids.

6 EPA/DHA concentrate dosage adjustments themselves can be viewed as a limitation  
7 since some, but not all participants' daily intake dosage was modified at week four. The  
8 supplement intervention adjustment based on the AA:EPA ratio was to avoid any potential  
9 adverse events. The design to limit adverse events was successful as the one report of a mild  
10 event was alleviated when the participant's dosage was adjusted downward. The lack of a  
11 proper means to monitor supplement intake, such as weight of returned bottles, was also a  
12 limitation of this study. However, this was compensated for by use of isolated plasma  
13 phospholipids levels as a means to monitor compliance.

14

## 15 **Conclusions**

16 Although this was a small, one-arm study, the results are encouraging as they suggest  
17 that high-dose EPA and DHA (up to 16.2 g per day) can be given to children with good  
18 compliance. Also, our results concur with trends and significant findings of some, but not all,  
19 studies of PUFA supplementation in children with ADHD or related symptoms [6, 8, 10]. The  
20 inconsistent findings from previous studies and our results suggest that greater dosages of EPA  
21 are needed to decrease the AA:EPA ratio to levels similar to the Japanese population and to  
22 observe significant behavioral improvements.

23 The preliminary results found in this pilot study warrant future randomized, placebo-  
24 controlled, double blind studies of high-dose EPA/DHA concentrates for adjunct treatment of  
25 ADHD in children.

26

1 **Competing Interests:** BS is a stockholder and president of Zone Labs Inc; HLH is a  
2 stockholder and employee of Zone Labs Inc.

3

4 **Authors' Contributions:** PJS was involved with the design of the study and carried out all  
5 testing psychological testing. EMH was involved with the design of the study. HLH performed  
6 the statistical analysis and drafted the manuscript. BS conceived the study and helped to draft  
7 the manuscript. All authors read and approved the final manuscript.

8

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Table 1. Baseline Characteristics of Study Participants

<sup>a</sup> Reported values are means±SD (n=9) or percentages.

Table 2. Fatty acids from the isolated plasma phospholipids described as means±SD and median.

<sup>a</sup> p<0.01 using Wilcoxon signed rank test to compare to baseline. LA, linoleic acid; DGLA, dihomogammalinolenic acid; AA, arachidonic acid; LNA, linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Table 3. Behavioral Assessment by psychiatrist

\* Values are mean±SD (n=9) ADHD SC-4, Attention Deficit Hyperactivity Disorder Symptom Checklist 4. <sup>a</sup> p<0.01, <sup>b</sup> p<0.05 using Wilcoxon signed rank test to compare to baseline; <sup>c</sup> p=0.08 using Friedman test to compare to baseline.

Figure 1. AA: EPA Ratio Changes at Week 0, Week 4 and Week 8.

Each line represents a participant's AA:EPA ratio from baseline to week 4 and week 8.

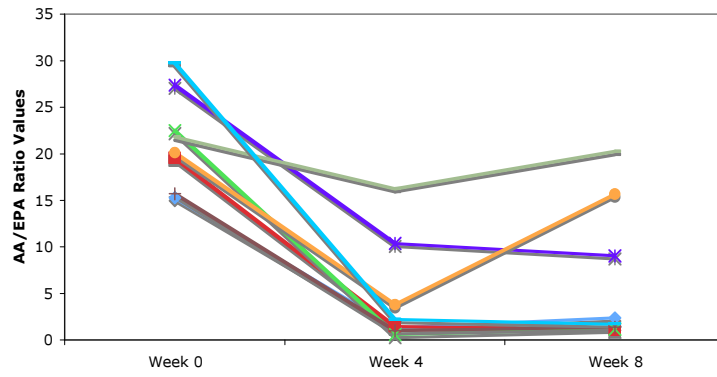
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Figure 1

AA/EPA Ratio Changes at week 0, week 4 and week



**Additional files provided with this submission:**

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Additional file 3: table 3.doc, 36K

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