# The Omega Protocol for treating ADHD

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## The effect of fish oil and vitamin E on the omega 3 index and on symptom severity in ADHD children

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The authors declare no conflict of interest

**Background:** Attention deficit hyperactivity disorder (ADHD) is a common developmental disorder in children. Studies suggest an association between consumption of low levels of polyunsaturated fatty acids especially omega 3 and an increased incidence of ADHD. An index of the level of omega 3 (EPA and DHA) in Red Blood Cell (RBC) has been developed by Harris and Von Schacky (HS Omega 3 IndexTM (O3I)).

ADHD children in general have lower omega 3 indices (1) Oxidized omega 3 is less effective in diseases that involve high oxidative stress (2,3). ADHD children in general have a higher oxidative stress (4). Omega 3 supplementation studies with high DHA content have failed to show significant benefit (5).

We therefore hypothesized that inconsistent results of past omega 3 studies in ADHD may be due to:

- Fixed omega 3 dose, not normalized to body mass
- Insufficient dose
- Inappropriate EPA to DHA ratio
- Low antioxidant capacity in the blood
- Oxidized (rancid) oil

We attempted to overcome these limitations by providing an omega 3 dose normalized to body mass (100 mg/kg/d) with an EPA:DHA ratio of 2:1 while ensuring low oil oxidation before consumption and low oxidative stress by vitamin E (VE) supplementation.

**Target:** In order to come up with a verified omega 3 treatment protocol (The Omega Protocol) for ADHD we tried to correlate 3 factors:

- Severity of ADHD symptoms before during and after the trial
- O3I at time 0, 3 and 6 months
- Dose response before during and after the trial

**Methods:** The study was authorized by the Ziv Helsinki Committee and the Israel Ministry of Health. The study was open label self-controlled of ADHD children (n=33, ages 6-14) diagnosed according to DSM-5 and control group without ADHD or related neuropsychiatric syndromes (n=26, age and gender matched). The ADHD group was supplemented with 100mg/kg of Fish Oil (FO) (400mg EPA+ 200mg DHA per capsule) plus 400 IU alpha tocopherol per 3000 mg O3 to eliminate peroxidation in the lipoprotein in the serum. The FO was from a fresh 3 months old batch with initial oxidation values pAv 10, POv 2, TOTOX 14. The FO capsules were stored at 7°c to ensure freshness before and during the trial.

At 0, 3 and 6 months, each child had a clinical examination and provided a 3ml blood sample. RBCs were isolated at 2,500g for 10 min and frozen at -80°C immediately after collection.

**Omega 3 Index** was analyzed by GC according to O3I methodology.

**ADHD severity** was assessed by a psychiatrist based on CGI-S questionnaire on a scale of 1 to 7 where 1 is normal and 7 is extremely severe ADHD. Improvement was assessed by CGI-I also on a 1-7 scale.

**Results:** The initial omega 3 index in ADHD children's RBC was 4.45%, significantly lower (p=0.037) than the 5.1% in the children control group and 6.4% in the general population in Israel (Fig 1). The omega 3 index increased very significantly in the ADHD group after 3 months and leveled off after 6 months (Fig 2).

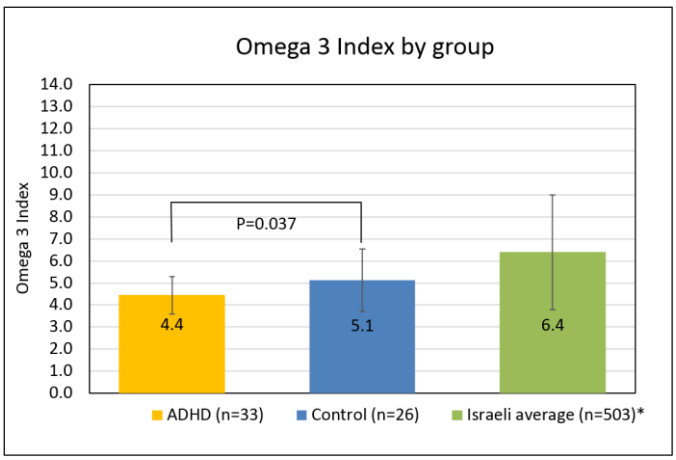


Figure 1 – omega 3 index in the ADHD children, control group of children and general Israeli population (* 503 adult Israelis who sent their blood to be tested privately at Ziv research center and who are not regular users of fish oil supplements).

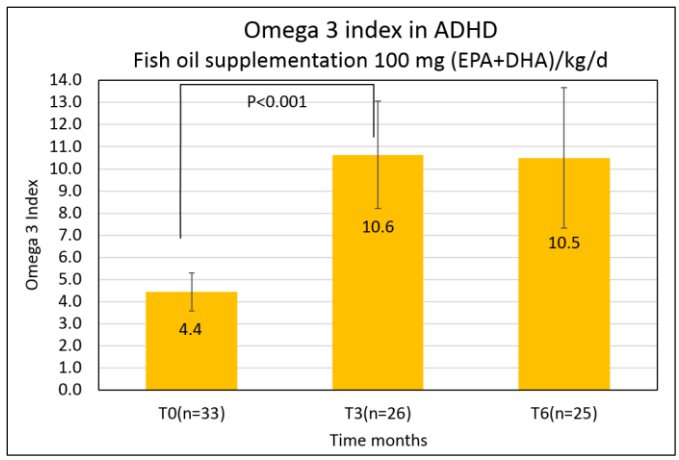


Figure 2 – omega 3 index at 0, 3 and 6 months of supplementation with 100mg/kg EPA+DHA per day.

The ADHD symptoms on the CGI-S improved significantly in the treated population. We found 3 populations of responders. Fully compliant, partially compliant and non responders. Most of the subjects responded positively with a significant reduction which was correlated to the increase in the O3I (Fig 3). However, a minority of compliant subjects did not respond and their CGI-S value did not change (Fig 4). No subject had a worsening of symptoms.

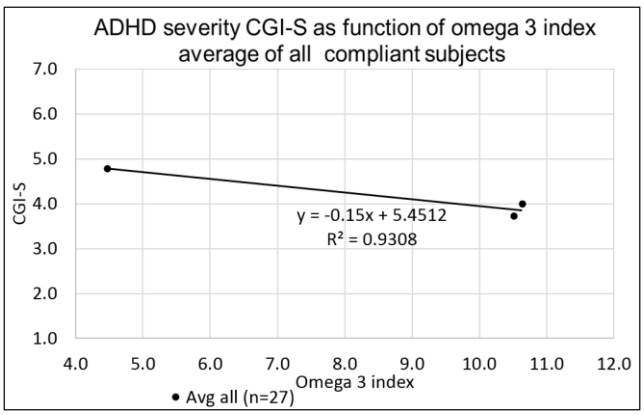


Figure 3– CGI-S is correlated to the omega 3 index. The slope y shows that for the whole group each 1% index was correlated to a reduction of 0.15 point of CGI-S.

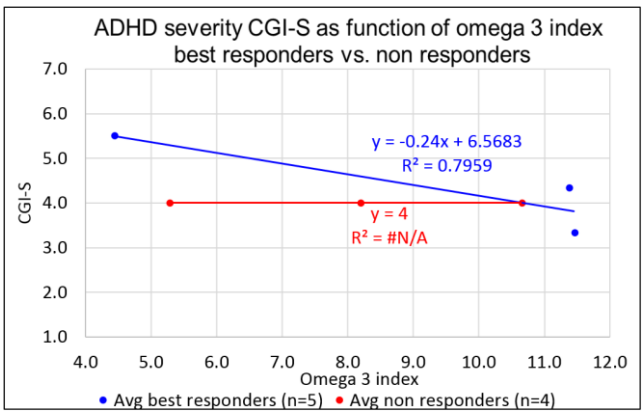


Figure 4– CGI-S is strongly correlated to the omega 3 index in the best responders and not correlated at all ($R^2$ <0.1) in the non responders. This means there are at least two distinct responses to an increased O3I.

Looking at the O3I increase between the best responders and no responders shows that the best responders had the lowest initial O3I, the largest increase in O3I (Fig 5) and the best improvement in CGI (Fig 6). This clearly shows that there is a subset of children for whom the low level of omega 3 is not the cause (or not the only cause) of ADHD.

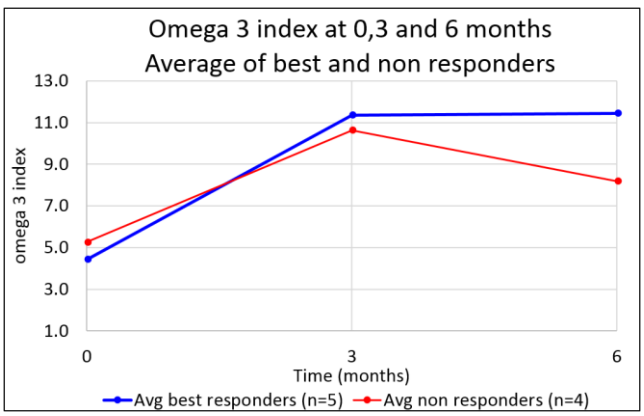


Figure 5- Omega 3 index at 0,3 and 6 months of the best responders and non responders. The index in the non responders declined due to non compliance.

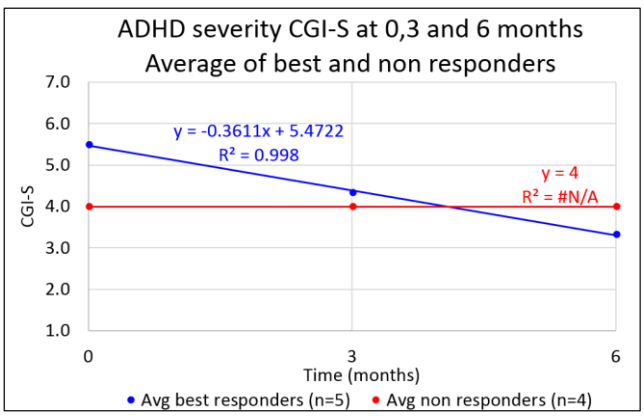


Figure 6 - CGI-S at 0,3 and 6 months of the best responders and non responders. The best responders enjoyed a CGI-S reduction from 5.6 to 3.4 which is very significant while the non responders saw no improvement at all.

Notes: 1) CGI-I (ADHD symptom improvement scale) showed similar results to CGI-S and was left out of this report for brevity. 2) Antioxidant capacity- We are conducting antioxidant capacity analysis from serum samples that will be published later on.

**Discussion:** Previous inconsistent results of ADHD omega 3 trials may have been due to a combination of factors: Too low dose, not normalized dose, not fresh (oxidized) oil, too high oxidative stress in the subject blood. Our study shows that 100 mg/kg/d fish oil + VE both increases the O3I and correlates to a significant reduction in ADHD symptoms at 3 and 6 months. We identified a group of subjects who were compliant as evident by the increased O3I but who did not improve on the CGI-S scale at all. This correlates with previous experience that shows that ~15% of ADHD children do not respond to fish oil even if fresh oil and antioxidant status is maintained. This fact is worth further study. Detailed analysis showed that a few subjects saw a continuous improvement in CGI-S even when their O3I reduced at 6 months after increasing at 3 months (due to non-compliance after 3 months). This shows that the effect on the nervous system might be slower than on RBC and may require elevated omega 3 levels for a longer time than it takes for RBC levels to reach equilibrium (~90 days).

**Conclusions and recommendations**:

**Omega 3 at 100 mg/kg/d + 400 IU VE was an effective treatment for 85% (23 out of 27) of ADHD compliant children. 4 (15%) of the 27 were non responsive. This shows that there are at least two distinct sub-populations of ADHD subjects, one which responds well and another that does not respond at all to omega 3. The positive effect on symptoms persisted for 6 months in responsive subjects and the trends predicts further improvement.**

**We recommend that future trials shall use a weight normalized dose; use an EPA:DHA ratio of 2:1; control freshness (TOTOX) value; include vitamin E and extend for 6 months at least.**


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2. Gumpricht E et al: **Can omega-3 fatty acids and tocotrienol-rich vitamin E reduce symptoms of neurodevelopmental disorders?** *Nutrition* 2014, **30**(7-8).
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# The Omega Protocol for treating ADHD

The effect of fish oil and vitamin E on the omega 3 index and on symptom severity in ADHD children

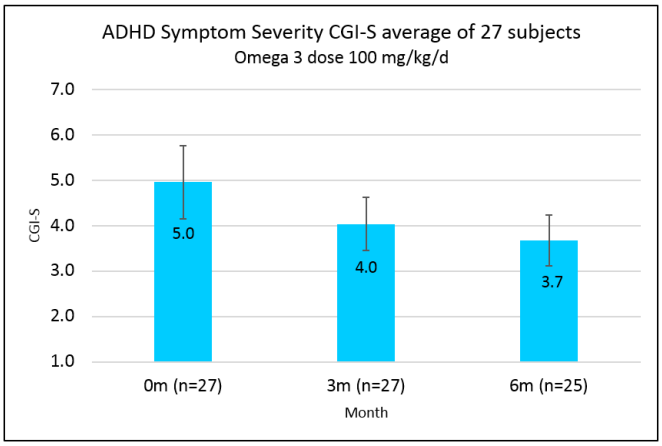
## Supplemental materials

| | O3 index | | | CGI-S | | | CGI-I | |
|---|---|---|---|---|---|---|---|---|
| Time month | 0 | 3m | 6m | 0 | 3m | 6m | 3m | 6m |
| Subject no | (n=27 | (n=27 | (n=25 | (n=27 | (n=27 | (n=25 | (n=27 | (n=25 |
| 1 | 4.2 | 7.4 | 7.6 | 6 | 5 | 4 | 3 | 3 |
| 2 | 5.3 | 11.9 | 12.0 | 5 | 4 | 4 | 2 | 3 |
| 3 | 4.4 | 13.4 | 15.1 | 6 | 4 | 4 | 1 | 2 |
| 4 | 4.5 | 10.2 | 11.5 | 4 | 3 | 3 | 2 | 2 |
| 6 | 5.1 | 10.0 | | 4 | 4 | | 3 | |
| 9 | 5.1 | 14.3 | 13.2 | 6 | 5 | 4 | 2 | 2 |
| 10 | 3.8 | 10.4 | 8.9 | 5 | 4 | 3 | 2 | 2 |
| 12 | 2.5 | 11.9 | 10.0 | 4 | 4 | 3 | 2 | 2 |
| 13 | 3.6 | 13.7 | 16.2 | 5 | 5 | 4 | 4 | 2 |
| 17 | 4.1 | 6.4 | 5.7 | 6 | 4 | 4 | 3 | 3 |
| 18 | 3.8 | 6.7 | 5.4 | 5 | 4 | 3 | 2 | 2 |
| 19 | 4.0 | 6.5 | 5.5 | 4 | 4 | 4 | 4 | 4 |
| 20 | 3.4 | 7.2 | 5.4 | 6 | 5 | 5 | 3 | 3 |
| 23 | 4.4 | 11.8 | 12.2 | 5 | 4 | 4 | 3 | 3 |
| 27 | 3.7 | 8.7 | 9.8 | 4 | 3 | 3 | 2 | 3 |
| 28 | 5.8 | 11.4 | 11.6 | 6 | 3 | 4 | 3 | 2 |
| 29 | 4.1 | 10.2 | 11.7 | 4 | 4 | 4 | 2 | 3 |
| 30 | 2.9 | | 8.3 | 4 | 3 | 3 | 2 | 2 |
| 31 | 5.9 | 12.4 | 14.5 | 5 | 4 | 4 | 3 | 2 |
| 34 | 4.6 | 8.0 | 10.6 | 6 | 4 | 4 | 3 | 3 |
| 38 | 4.4 | 11.7 | 9.6 | 5 | 5 | 4 | 2 | 3 |
| 40 | 4.3 | 11.8 | 13.4 | 5 | 4 | 3 | 2 | 2 |
| 41 | 4.6 | 10.1 | 10.8 | 5 | 4 | 3 | 3 | 2 |
| 45 | 4.6 | 14.2 | 14.9 | 6 | 4 | 3 | 2 | 2 |
| 47 | 5.2 | 11.4 | 10.8 | 5 | 4 | 4 | 3 | 3 |
| 48 | 6.3 | 11.7 | 7.8 | 4 | 4 | 4 | 4 | 4 |
| 50 | 5.6 | 13.2 | | 4 | 4 | | 3 | |
| **Avg** | **4.5** | **10.6** | **10.5** | **5.0** | **4.0** | **3.7** | **2.6** | **2.6** |
| n | 27.0 | 26.0 | 25.0 | 27.0 | 27.0 | 25.0 | 27.0 | 25.0 |
| Min | 2.5 | 6.4 | 5.4 | 4.0 | 3.0 | 3.0 | 1.0 | 2.0 |
| Max | 6.3 | 14.3 | 16.2 | 6.0 | 5.0 | 5.0 | 4.0 | 4.0 |
| Range | 3.7 | 8.0 | 10.9 | 2.0 | 2.0 | 2.0 | 3.0 | 2.0 |
| Std | 0.9 | 2.4 | 3.2 | 0.8 | 0.6 | 0.6 | 0.7 | 0.7 |

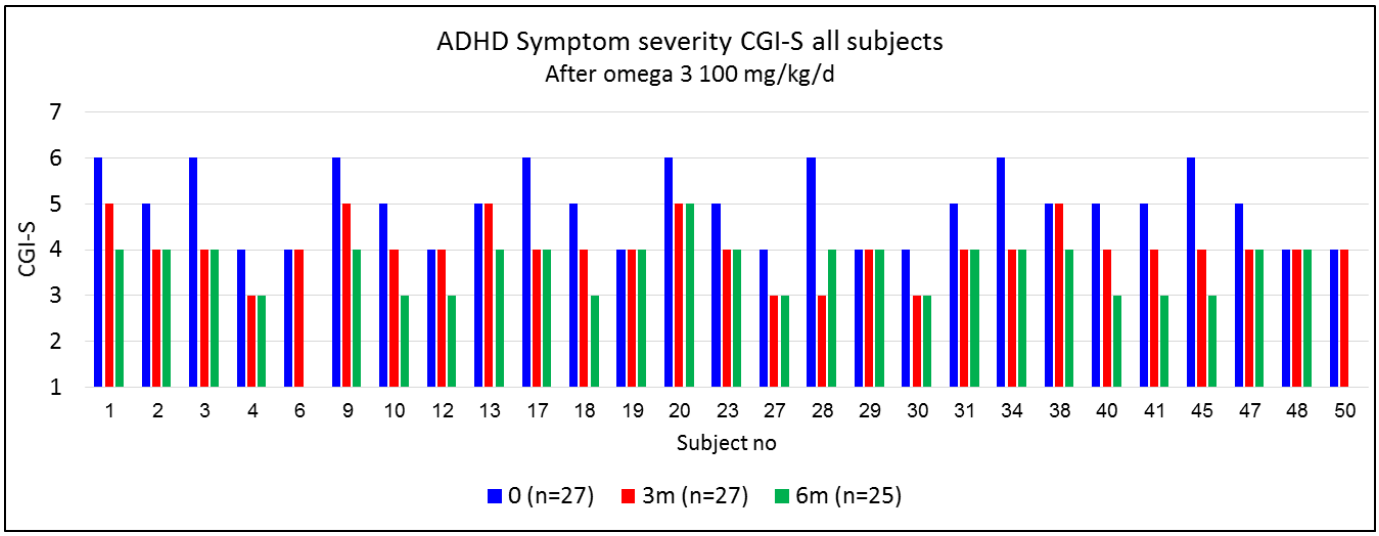
Omega 3 Index, and ADHD symptom severity at 0, 3 and 6 months. The table includes data of all 27 subjects that were compliant for at least 3 months.

| Omega 3 Index before supplementation | | | |
|---|---|---|---|
| | Control (n=26) | ADHD (n=33) | Israeli average (n=503)* |
| n | 26 | 33 | 503 |
| Avg O3I | 5.1 | 4.4 | 6.4 |
| min | 2.4 | 2.5 | 1.7 |
| max | 7.8 | 6.3 | 16.6 |
| Range | 5.3 | 3.7 | 14.9 |
| Stdv | 1.42 | 0.86 | 2.6 |

Omega 3 index in ADHD , control and general Israeli population that reported not using omega 3 supplements on a regular basis.




ADHD symptom severity at 0, 3 and 6 months.
Average for all 27 compliant subjects after 3 and 6 months fish oil supplementation at a dose of 100 mg/kg/d of EPA+DHA.




ADHD symptom severity at 0, 3 and 6 months. Detailed data for all subjects.
Note that no. 19, 29 and 48 were fully compliant for 6 months but saw no improvement in symptoms.