Effect of 1 year krill oil supplementation on depression and self-esteem in typically developing Dutch adolescents: Preliminary results

ISM van der Wurff, C von Schacky, T Bergeland, R Leontjevas, MP Zeegers, PA Kirschner, RHM de Groot
Research Question

What is the influence of 1 year of krill oil supplementation in 13-15 year old adolescents attending lower general secondary education on:

- Cognitive functioning and academic achievement?
- Mood and self-esteem?
- Sleep quality and quantity and visual processing?
Study design

Inclusion

Omega-3 Index < 5%

Krill:
520mg EPA p/day
280mg DHA p/day

Placebo:
0 mg EPA p/day
0 mg DHA p/day

baseline
3 months
6 months
12 months

Dose adjustment
Unique characteristics

- Adolescents
- Lower general secondary education (TL/MAVO)
- Selection <5% Omega-3 Index
- Personalised dose-adjustment after 3 months
- Supplement consumed at dinner time
## Mood and Self-esteem

<table>
<thead>
<tr>
<th>Test</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center of Epidemiology Studies Depression Scale – Dutch version</td>
<td>Depression</td>
</tr>
<tr>
<td>Rosenberg Self-esteem questionnaire</td>
<td>Self-esteem</td>
</tr>
</tbody>
</table>
Assessed for eligibility (n=286)

- Excluded (n=19)
  - Not meeting inclusion criteria (n=17)
  - Declined to participate (n=1)
  - Other reasons (n=2)

Randomized (n = 267)

Placebo (n =133)
- Lost to follow-up (n=25)
  - Forgetting (n=8)
  - Difficulty swallowing (n=6)
  - Motivation (n=4)
  - Reason not given (n=4)
  - Dose adjustment (n=3)
- Discontinued intervention (n=38)
  - Forgetting (n=7)
  - Difficulty swallowing (n=9)
  - Motivation (n=11)
  - Reason not given (n=2)
  - Dose adjustment (n=4)
  - Personal (n=1)
  - Other (n=2)

Analysed intention to treat (n=106)
- Excluded from analysis (n=3)
  - Included in RCT but Omega-3 Index >5% (n =3)

Krill (n = 134)
- Lost to follow-up (n=31)
  - Forgetting (n=2)
  - Difficulty swallowing (n=8)
  - Motivation (n=15)
  - Reason not given (n=3)
  - Dose adjustment (n=1)
  - Personal (n=1)
  - Other (n=1)
- Discontinued intervention (n=49)
  - Forgetting (n=13)
  - Difficulty swallowing (n=5)
  - Motivation (n=15)
  - Reason not given (n=3)
  - Dose adjustment (n=3)
  - Personal (n=3)
  - Other (n=7)

Analysed intention to treat (n=97)
- Excluded from analysis (n=7)
  - Included in RCT but Omega-3 Index >5% (n =6)
  - Quit during test moment 1 (n =1)

withdraw consent (n =1)
Statistics baseline

• Bayesian analyses

• Baseline data corrected for:
  – CESD: smoking, sex and BMI
  – RSE: smoking, diagnosis and sex

• CESD used as a continuous variable, for descriptive purposes CESD > 16 as depressed.
Frequentist vs Bayesian

- Frequentist analyses non-significant result:
  - There is evidence for the $H_0$ (i.e. there is no association) or
  - The data are insensitive in distinguishing the $H_1$ from the $H_0$ (i.e. nothing follows from the data)

- Bayesian analyses, Bayes Factor
  - There is evidence for $H_0$ ($BF > 3$)
  - There is evidence for $H_1$ ($BF < 0.33$)
  - Data is not sensitive (i.e. nothing follows from the data; $BF = 0.33-1$)
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Fatty acid (%wt/wt of total FA, except for O3I)</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>257</td>
<td>14.11</td>
<td>0.50</td>
<td>Omega-3 Index</td>
<td>257</td>
<td>3.78</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Male/Female</strong></td>
<td>257</td>
<td>124/133 [48.2/51.8%]</td>
<td>-</td>
<td>DHA 22:6n-3</td>
<td>257</td>
<td>2.55</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Smoking no/yes(^1)</strong></td>
<td>255</td>
<td>231/24 [89.9/9.3%]</td>
<td>-</td>
<td>EPA 20:5n-3</td>
<td>257</td>
<td>0.38</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>240</td>
<td>19.98</td>
<td>3.00</td>
<td>DPA 22:5n-3</td>
<td>257</td>
<td>1.22</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Alcohol units per week(^2)</strong></td>
<td>256</td>
<td>0.47</td>
<td>1.80</td>
<td>AA 20:4n-6</td>
<td>257</td>
<td>11.15</td>
<td>1.27</td>
</tr>
<tr>
<td><strong>LPE</strong></td>
<td>240</td>
<td>5.05</td>
<td>1.5</td>
<td>ObA 22:5n-6</td>
<td>257</td>
<td>0.44</td>
<td>0.10</td>
</tr>
</tbody>
</table>

\(^1\) Smoking ‘yes’ was defined as anybody who indicated to smoke more than 0 cigarettes per week.

\(^2\) Diagnosis was indicated by students themselves and included (but not limited to) dyslexia, dyscalculia, depression, autism and ADHD.

3 Alcohol consumption was asked as how many times per week and units per consumption moment, alcohol per week is defined as these factors multiplied.
Depression

• 29.4% scored CESD ≥16
  – Girls: 42.3% ≥16
  – Boys: 15.6% ≥16

• 17.1% scored CESD ≥22

• Those with depression: more girls, higher BMI, further in puberty, lower self-esteem.
Baseline results

<table>
<thead>
<tr>
<th>Predictor fatty acid</th>
<th>One fatty acid</th>
<th>All fatty acids in 1 model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient</td>
<td>95% credibility interval</td>
</tr>
<tr>
<td>Omega-3 Index</td>
<td>-0.016</td>
<td>-0.14;0.11</td>
</tr>
<tr>
<td>DHA</td>
<td>-0.04</td>
<td>-0.16;0.08</td>
</tr>
<tr>
<td>EPA</td>
<td>0.06</td>
<td>-0.06;0.18</td>
</tr>
<tr>
<td>AA</td>
<td>-0.13</td>
<td>-0.25;-0.02</td>
</tr>
<tr>
<td>DPA</td>
<td>-0.13</td>
<td>-0.24;-0.02</td>
</tr>
<tr>
<td>ObA</td>
<td>-0.16</td>
<td>-0.28;-0.04</td>
</tr>
</tbody>
</table>

O3I = Omega-3 Index

One fatty acid model, is a model in which only one predictor of interest is entered (Omega-3 Index, DHA, EPA, AA, DPA, or ObA). All fatty acids model is a model in which all fatty acids (DHA, EPA, AA, DPA, and ObA) are entered, i.e. for example the association between DHA and self-esteem is corrected for the other fatty acids (EPA, AA, DPA, ObA).

All analyses were adjusted for BMI, smoking (yes/no), and sex.

1 Credibility intervals are analogous to confidence intervals in traditional statistics.

2 BF<sub>10</sub> refers to the evidence for the model with the specific fatty acid compared to a model with only covariates.

3 BF<sub>omit</sub> indicates whether the model improves with the omission of that specific fatty acid. BF<sub>omit</sub> numbers above 3 indicate that keeping the variable in the model is not preferable.
Self-esteem

<table>
<thead>
<tr>
<th>Predictor fatty acid</th>
<th>One fatty acid</th>
<th>All fatty acids in one model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient</td>
<td>95% credibility interval</td>
</tr>
<tr>
<td>Omega-3 Index</td>
<td>-0.05</td>
<td>-0.18;0.08</td>
</tr>
<tr>
<td>DHA</td>
<td>-0.03</td>
<td>-0.15;0.10</td>
</tr>
<tr>
<td>EPA</td>
<td>-0.09</td>
<td>-0.20;0.03</td>
</tr>
<tr>
<td>AA</td>
<td>0.008</td>
<td>-0.12;0.10</td>
</tr>
<tr>
<td>DPA</td>
<td>-0.02</td>
<td>-0.09;0.14</td>
</tr>
<tr>
<td>ObA</td>
<td>0.09</td>
<td>-0.03;0.20</td>
</tr>
</tbody>
</table>

O3I = Omega-3 Index

One fatty acid model, is a model in which only one predictor of interest is entered (Omega-3 Index, DHA, EPA, AA, DPA, or ObA). All fatty acids model is a model in which all fatty acids (DHA, EPA, AA, DPA, and ObA) are entered, i.e. for example the association between DHA and self-esteem is corrected for the other fatty acids (EPA, AA, DPA, ObA).

All analyses were adjusted for BMI, smoking (yes/no), and sex.

1 Credibility intervals are analogous to confidence intervals in traditional statistics.
2 BF_{10} refers to the evidence for the model with the specific fatty acid compared to a model with only covariates.
3 BF_{omit} indicates whether the model improves with the omission of that specific fatty acid. BF_{omit} numbers above 3 indicate that keeping the variable in the model is not preferable.
Intervention
## Change in fatty acids (ITT)

<table>
<thead>
<tr>
<th>fatty acid (%wt/wt of total FA)</th>
<th>condition</th>
<th>baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA 20:4n-6</td>
<td>Placebo</td>
<td>11.19 ± 1.36</td>
<td>10.97 ± 1.18</td>
<td>11.02 ± 1.49</td>
<td>11.15 ± 1.30</td>
</tr>
<tr>
<td></td>
<td>Krill</td>
<td>11.12 ± 1.18</td>
<td>10.26 ± 1.13*</td>
<td>10.28 ± 1.41 *</td>
<td>10.702 ± 1.49*</td>
</tr>
<tr>
<td>EPA 20:5n-3</td>
<td>Placebo</td>
<td>0.38 ± 0.14</td>
<td>0.43 ± 0.15</td>
<td>0.41 ± 0.14</td>
<td>0.40 ± 0.12</td>
</tr>
<tr>
<td></td>
<td>Krill</td>
<td>0.38 ± 0.15</td>
<td>0.93 ± 0.58*</td>
<td>0.95 ± 0.69*</td>
<td>0.75 ± 0.58*</td>
</tr>
<tr>
<td>ObA 22:5n-6</td>
<td>Placebo</td>
<td>0.43 ± 0.11</td>
<td>0.41 ± 0.17</td>
<td>0.42 ± 0.09</td>
<td>0.38 ± 0.12</td>
</tr>
<tr>
<td></td>
<td>Krill</td>
<td>0.45 ± 0.10</td>
<td>0.32 ± 0.12*</td>
<td>0.32 ± 0.11*</td>
<td>0.34 ± 0.13*</td>
</tr>
<tr>
<td>DPA 22:5n-3</td>
<td>Placebo</td>
<td>1.22 ± 0.20</td>
<td>1.29 ± 0.23</td>
<td>1.30 ± 0.20</td>
<td>1.30 ± 0.19</td>
</tr>
<tr>
<td></td>
<td>Krill</td>
<td>1.22 ± 0.17</td>
<td>1.58 ± 0.34*</td>
<td>1.54 ± 0.35*</td>
<td>1.47 ± 0.31 *</td>
</tr>
<tr>
<td>DHA 22:6n-3</td>
<td>Placebo</td>
<td>2.60 ± 0.44</td>
<td>2.61 ± 0.52</td>
<td>2.69 ± 0.53</td>
<td>2.72 ± 0.54</td>
</tr>
<tr>
<td></td>
<td>Krill</td>
<td>2.49 ± 0.46</td>
<td>3.25 ± 0.73*</td>
<td>3.40 ± 0.90*</td>
<td>3.20 ± 0.84*</td>
</tr>
</tbody>
</table>

* Krill oil and placebo condition are significantly different p<0.05
Change in Omega-3 Index over time

* Krill oil and placebo condition are significantly different p<0.05
In comparison

<table>
<thead>
<tr>
<th>Target group</th>
<th>Omega-3 index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unselected Japanese men (n 262)</td>
<td>9.58</td>
</tr>
<tr>
<td>Unselected Germans (n 5000)</td>
<td>7.15 ± 2.19</td>
</tr>
<tr>
<td>Unselected Europeans (n 10000)</td>
<td>6.96 ± 2.15</td>
</tr>
<tr>
<td>Framingham-Offspring (n 3196)</td>
<td>4.90 ± 2.10</td>
</tr>
<tr>
<td>American adolescents with major depression (n 150)</td>
<td>3.46</td>
</tr>
<tr>
<td>Americans with major depression (n 118)</td>
<td>2.90 ± 1.50</td>
</tr>
</tbody>
</table>

# Depression

<table>
<thead>
<tr>
<th>Depression &gt;15</th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>70.6%</td>
<td>78.7%</td>
<td>73.5%</td>
</tr>
<tr>
<td>Yes</td>
<td>29.4%</td>
<td>21.3%</td>
<td>26.5%</td>
</tr>
<tr>
<td>Depression &gt;21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>82.9%</td>
<td>88%</td>
<td>81.4%</td>
</tr>
<tr>
<td>Yes</td>
<td>17.1%</td>
<td>12%</td>
<td>18.6%</td>
</tr>
</tbody>
</table>
Analyses

- Multilevel analyses – with person as unit
- Intention to treat and according to blood Omega-3 Index
- Correction for covariates
  - Drinking (units per week)
  - Smoking (yes/no)
  - Age at baseline
  - BMI (self-reported at baseline)
  - Sex
  - Cohort number
  - Diagnosis which can influence learning (yes/no)
  - Test moment
  - Level of parental education (low/high)
  - In condition analyses: condition*test moment
Results depression

ITT analyses:
B = -0.64
p = 0.624
95% CI: -3.19 to 1.90
Results depression

Omega-3 Index: B = 0.38, p = 0.264, 95% CI: -0.28 to 1.30
Other fatty acids

<table>
<thead>
<tr>
<th>CES-D</th>
<th>Beta</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA</td>
<td>-0.17</td>
<td>0.749</td>
<td>[-1.17; 0.84]</td>
</tr>
<tr>
<td>EPA</td>
<td>0.68</td>
<td>0.399</td>
<td>[-0.88; 2.23]</td>
</tr>
<tr>
<td>DPA</td>
<td>-0.71</td>
<td>0.604</td>
<td>[-3.36; 1.94]</td>
</tr>
<tr>
<td>AA</td>
<td>-0.36</td>
<td>0.165</td>
<td>[-0.86; 0.14]</td>
</tr>
<tr>
<td>OBA</td>
<td>-4.07</td>
<td>0.198</td>
<td>[-10.19; 2.06]</td>
</tr>
</tbody>
</table>
Results: self-esteem

ITT analyses:
B = 0.28
p = 0.721
95% CI: -1.22; 1.77
Results: self-esteem

Omega-3 Index:
B = -0.03
p = 0.866
95% CI: -0.38 to 0.32
Other fatty acids

<table>
<thead>
<tr>
<th>RSE</th>
<th>Beta</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA</td>
<td>0.08</td>
<td>0.761</td>
<td>[-0.45; 0.61]</td>
</tr>
<tr>
<td>EPA</td>
<td>-0.14</td>
<td>0.736</td>
<td>[-0.96; 0.68]</td>
</tr>
<tr>
<td>DPA</td>
<td>-0.41</td>
<td>0.573</td>
<td>[-1.83; 1.00]</td>
</tr>
<tr>
<td>AA</td>
<td>-0.13</td>
<td>0.367</td>
<td>[-0.39; 0.14]</td>
</tr>
<tr>
<td>OBA</td>
<td>-1.61</td>
<td>0.333</td>
<td>[-4.85; 1.62]</td>
</tr>
</tbody>
</table>
Discussion (1)

• Depression is very common in adolescents.
• No significant effects of supplementation on depression and self-esteem.
• Even analyses according to omega-3 fatty acid status did not show effects.
• 1 year of krill oil, still low Omega-3 Index
  – Did not take capsules – compliance
  – Factors associated with metabolism
  – Krill oil
Discussion (2)

• Important to take blood values!
Funding

• Study was funded by:
  – Grant of Dutch Scientific Organisation
  – Aker Biomarine
  – Omegametrix
Publications


