Information brief: 
Omega-3 Fatty Acids

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NIAAA, NIH, Rockville, MD

14 NOV 2011
Defense Medical Board
Arlington, VA

This presentation does not represent any policy or position of the US Federal Government. It is solely the scientific opinion of the presenter.
From Fish Oil to Medicine

By Bernadine Healy, M.D.

Dr. Bernadine Healy served as director of the NIH and president and CEO of the American Red Cross.


- No nutrient is more important for decreasing cardiovascular death—and more lacking—than omega-3
- We have failed to take seriously a significant nutritional fat deficiency that afflicts most Americans: We have too little omega-3s of the kind found in oily fish...
- This deficiency significantly increases the risk of heart attacks and sudden cardiac death, and mounting evidence suggests omega-3 shortages contribute to problems as disparate as premature birth, neurological disorders, mental illness, autoimmune disease, obesity, and certain cancers. This is no fish story: Raising omega-3s could be as important to public health as lowering cholesterol.
Mortality Rates

Hibbeln et al Am J Clin Nutr 2006; 83; 1483S-93S
American Heart Assoc. recommends eating fish 2-3 times/week or 1g/day omega-3 HUFA.

Omega-3 HUFA:
- prevent plaque formation
- prevent plaque bursting
- prevent clotting

Result:
- Arrhythmias
- Death
Surgical Recommendations for Omega-3’s for the Most Severe Subjects

Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

- Immune-modulating enteral formulations (supplemented with agents such as arginine, glutamine, nucleic acid, omega-3 fatty acids, and antioxidants) should be used for the appropriate patient populations

- major elective GI surgery,
- trauma (abdominal trauma index scores >20),
- burns (total body surface area >30%), head and neck cancer, and critically ill patients on mechanical ventilation
- (For surgical ICU patients, Level of Recommendation - Grade: A)

J Parenteral Enteral Nutrition 2009 (33) 3, 277-316
250 M years ago

**n-3 rich diets**
- ALA (18:3 n-3)
- EPA (20:5 n-3)
- DHA (22:6 n-3)

**Omega-3 HUFA MARINE OILS**

% n-3 in HUFA rich membranes

**Flux**

% n-6 in HUFA rich membranes

**n-6 rich diets**
- LA (18:2 n-6)
- AA (20:4 n-6)

**Equation**

Lands

**20th Century**

**diets**

**“Marijuana-like” molecules**

COX

PGE\textsubscript{2} TXA\textsubscript{2}

PGE\textsubscript{3} TXA\textsubscript{3}

Impaired satiety ↑
↑ obesity
↑ suicide risk?

↑ substance use?

Respiratory cytokine storms - Impaired wound healing - thrombosis – headache - pain
Changes in Oils in the US Food Supply in the 20th Century

Disappearance (kg/person/y)

Year


Soybean
Cottonseed
Corn
Olive
Coconut
Canola
Peanut
Palm/Palm Kernel
Safflower
Sunflower
Sesame

Will \( \text{\( \uparrow \)} \omega \text{-3 HUFAs} \) also Reduce High Risk Behaviors?

Major depression, Substance abuse, Violence and Suicidal behavior

**Health Promotion by \( \text{\( \uparrow \)} \omega \text{-3 HUFAs} \) is already recommended by** more than 30 international scientific and government bodies

- e.g. USDA 2010 dietary guidelines: - Cardiovascular, stroke, immunological, surgical survival, ect

Publications ~90,000 basic science, ~9,000 human studies, 1,889 clinical trials
DHA dietary deficiency impairs synapse development

<table>
<thead>
<tr>
<th></th>
<th>Adequate</th>
<th>Deficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampal Fatty Acids</td>
<td></td>
<td></td>
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<tr>
<td>DHA</td>
<td>6.6 ± 0.7%</td>
<td>0.5 ± 0.1%</td>
</tr>
<tr>
<td>DPAn-6</td>
<td>0.4 ± 0.1%</td>
<td>4.7 ± 0.1%</td>
</tr>
</tbody>
</table>

Mother mice fed adequate or deficient diets, embryo neurons harvested day 18

Do deficiencies in n-3 HUFAs increase likelihood of high risk behaviors?
Overview of human data

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Plausible mechanism</th>
<th>Epidemiological Ecological</th>
<th>Case control (Tissue)</th>
<th>RCT’s</th>
<th>Meta analyses</th>
<th>Positive clinical effect? Size?</th>
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</thead>
<tbody>
<tr>
<td>Major depression</td>
<td>Yes</td>
<td>54</td>
<td>16</td>
<td>34</td>
<td>5</td>
<td>Yes Similar to anti-depressants</td>
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<tr>
<td>ADHD</td>
<td>Yes</td>
<td>6</td>
<td>12</td>
<td>10</td>
<td>1</td>
<td>Yes Less than stimulants</td>
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<tr>
<td>Aggression/violence/conduct</td>
<td>Yes</td>
<td>8</td>
<td>5</td>
<td>8</td>
<td>-</td>
<td>Probable Large effect ↓37% in felony violence</td>
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<tr>
<td>Anxiety</td>
<td>Yes</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>-</td>
<td>Probable -</td>
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<tr>
<td>Alcohol/Sub. use</td>
<td>Yes</td>
<td>-</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>Hopeful Large effect</td>
</tr>
<tr>
<td>Suicide</td>
<td>Yes</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td>Hopeful -</td>
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</tbody>
</table>
Omega-3 treatment of childhood depression: a controlled, double-blind pilot study.

Age range = 8-12.5
Monotherapy

400 mg/d EPA + 200 mg/d DHA vs. Safflower placebo

*p<0.05

Major Depressive Symptoms RCT meta-analysis

EPA+DHA vs. EPA predominant interventions - Forest Plot

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Point Est</th>
<th>SE</th>
<th>Var Limit</th>
<th>Low Limit</th>
<th>Up Limit</th>
<th>Z</th>
<th>P</th>
<th>Point Est and 95% CI</th>
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<tr>
<td>Frangou06 1</td>
<td>-0.580</td>
<td>0.283</td>
<td>0.081</td>
<td>-1.138</td>
<td>-0.022</td>
<td>-2.038</td>
<td>0.042</td>
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<tr>
<td>Frangou00 m high dose</td>
<td>-0.440</td>
<td>0.279</td>
<td>0.078</td>
<td>-0.917</td>
<td>0.107</td>
<td>-1.575</td>
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<td>Hallahan D</td>
<td>-0.860</td>
<td>0.296</td>
<td>0.087</td>
<td>-1.439</td>
<td>-0.281</td>
<td>-2.910</td>
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<td>Jazayeri</td>
<td>-1.040</td>
<td>0.369</td>
<td>0.136</td>
<td>-1.762</td>
<td>-0.318</td>
<td>-2.822</td>
<td>0.005</td>
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<td>Lesperance10</td>
<td>-0.190</td>
<td>0.096</td>
<td>0.009</td>
<td>-0.379</td>
<td>-0.001</td>
<td>-1.974</td>
<td>0.048</td>
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<td>Michoulon09</td>
<td>-0.660</td>
<td>0.338</td>
<td>0.114</td>
<td>-1.223</td>
<td>0.103</td>
<td>-1.655</td>
<td>0.098</td>
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<td>Nements06 ch</td>
<td>-3.670</td>
<td>0.721</td>
<td>0.220</td>
<td>-5.053</td>
<td>-2.257</td>
<td>-5.090</td>
<td>0.000</td>
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<td>Nements02 dep</td>
<td>-1.800</td>
<td>0.520</td>
<td>0.276</td>
<td>-2.904</td>
<td>-0.916</td>
<td>-2.957</td>
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<td>Peet02 1</td>
<td>-1.150</td>
<td>0.485</td>
<td>0.235</td>
<td>-2.107</td>
<td>-0.193</td>
<td>-2.356</td>
<td>0.018</td>
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<td>Peet02 2</td>
<td>0.070</td>
<td>0.455</td>
<td>0.207</td>
<td>-0.822</td>
<td>0.962</td>
<td>0.154</td>
<td>0.878</td>
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<td>Peet02 4</td>
<td>-0.350</td>
<td>0.461</td>
<td>0.212</td>
<td>-1.253</td>
<td>0.543</td>
<td>-0.781</td>
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<td>Moncanneau adj</td>
<td>-0.720</td>
<td>0.305</td>
<td>0.093</td>
<td>-1.317</td>
<td>-0.123</td>
<td>-2.364</td>
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<td>Stro1996</td>
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<td>0.418</td>
<td>0.175</td>
<td>-1.779</td>
<td>-0.141</td>
<td>-2.297</td>
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<td>Sub</td>
<td>-3.160</td>
<td>0.653</td>
<td>0.433</td>
<td>-4.500</td>
<td>-1.870</td>
<td>-4.801</td>
<td>0.000</td>
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<tr>
<td>Tad ad 25%</td>
<td>-0.370</td>
<td>0.321</td>
<td>0.103</td>
<td>-0.998</td>
<td>0.258</td>
<td>-1.154</td>
<td>0.249</td>
<td></td>
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<tr>
<td>Tad no ad 25%</td>
<td>-0.770</td>
<td>0.287</td>
<td>0.082</td>
<td>-1.333</td>
<td>-0.207</td>
<td>-2.683</td>
<td>0.007</td>
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<td>EPA +DHA</td>
<td>-0.500</td>
<td>0.067</td>
<td>0.035</td>
<td>-0.628</td>
<td>-0.364</td>
<td>-7.370</td>
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<td>Bot a</td>
<td>0.330</td>
<td>0.307</td>
<td>0.157</td>
<td>-0.477</td>
<td>1.077</td>
<td>0.757</td>
<td>0.440</td>
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<td>Carmay10</td>
<td>-0.210</td>
<td>0.130</td>
<td>0.033</td>
<td>-0.564</td>
<td>0.114</td>
<td>-1.154</td>
<td>0.245</td>
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<td>Froman03</td>
<td>0.100</td>
<td>0.277</td>
<td>0.077</td>
<td>-0.443</td>
<td>0.643</td>
<td>0.361</td>
<td>0.718</td>
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<td>Lucas NII</td>
<td>-0.260</td>
<td>0.233</td>
<td>0.060</td>
<td>-0.697</td>
<td>0.167</td>
<td>-1.121</td>
<td>0.262</td>
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<tr>
<td>Rest08 n III</td>
<td>-0.203</td>
<td>0.216</td>
<td>0.046</td>
<td>-0.622</td>
<td>0.222</td>
<td>-0.928</td>
<td>0.353</td>
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<tr>
<td>Rest08 inIMAD</td>
<td>-0.060</td>
<td>0.216</td>
<td>0.046</td>
<td>-0.462</td>
<td>0.362</td>
<td>-0.278</td>
<td>0.781</td>
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<tr>
<td>EPA predom</td>
<td>-0.120</td>
<td>0.094</td>
<td>0.009</td>
<td>-0.307</td>
<td>0.062</td>
<td>-1.303</td>
<td>0.193</td>
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<tr>
<td>Overall</td>
<td>-0.370</td>
<td>0.055</td>
<td>0.003</td>
<td>-0.477</td>
<td>-0.262</td>
<td>-5.750</td>
<td>0.000</td>
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</table>
Omega-3 supplements are effective for reducing ADHD in children
Moderate effect size, with low heterogeneity

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voigt 2001</td>
<td>8.0%</td>
<td>0.04 [-0.49, 0.58]</td>
<td>2001</td>
</tr>
<tr>
<td>Richardson 2002</td>
<td>4.1%</td>
<td>0.38 [-0.37, 1.13]</td>
<td>2002</td>
</tr>
<tr>
<td>Stevens 2003</td>
<td>4.8%</td>
<td>0.40 [-0.29, 1.09]</td>
<td>2003</td>
</tr>
<tr>
<td>Richardson 2005</td>
<td>17.3%</td>
<td>0.36 [-0.00, 0.73]</td>
<td>2005</td>
</tr>
<tr>
<td>Sinn 2007</td>
<td>11.6%</td>
<td>0.58 [0.13, 1.02]</td>
<td>2007</td>
</tr>
<tr>
<td>Vaisman 2008 fishoil</td>
<td>6.3%</td>
<td>0.17 [-0.44, 0.77]</td>
<td>2008</td>
</tr>
<tr>
<td>Johnson 2008</td>
<td>11.1%</td>
<td>0.35 [-0.11, 0.81]</td>
<td>2008</td>
</tr>
<tr>
<td>Vaisman 2008 omega-3</td>
<td>5.7%</td>
<td>0.41 [-0.22, 1.05]</td>
<td>2008</td>
</tr>
<tr>
<td>Raz 2009</td>
<td>9.6%</td>
<td>0.13 [-0.36, 0.62]</td>
<td>2009</td>
</tr>
<tr>
<td>Gustafsson 2009</td>
<td>13.8%</td>
<td>0.22 [-0.19, 0.62]</td>
<td>2009</td>
</tr>
<tr>
<td>Belanger 2010</td>
<td>7.7%</td>
<td>0.40 [-0.15, 0.95]</td>
<td>2010</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% [0.31 [0.16, 0.47]]

Heterogeneity: Chi^2 = 3.68, df = 10 (P = 0.96); I^2 = 0%
Test for overall effect: Z = 4.04 (P < 0.0001)

Bloch and Qawasmi J Am Acad Child Adol Psych, e pub 2011

10 trials, n=699 children%
Anybody can become angry - that is easy,
but to be angry
with the right person
and to the right degree
and at the right time
and for the right purpose,
and in the right way
that is not within everybody's power
and is not easy.

- Aristotle
Low serotonergic function is a common mechanism underlying high risk-impulsive disorders.

Infant formula supplemented with DHA and AA increases serotonin and dopamine in piglet frontal cortex after 18 days of life.

de la Pressa Owens and Innis 2000 Peds Research 48:1:125-130
Reduced Felony Violent Offences Among Prisoners with recommended daily amounts of vitamins, minerals and essential fatty acids

Active -37.0%  
\( p < 0.005 \)
Placebo -10.1%  
\( p = \text{ns} \)

UK maximum security prison - 338 offences among 172 prisoners over 9 months treatment in a compared to 9 months baseline.  
Suicide?
Deliberate Self-Harm

• Subjects n= 49
• Recruited from a Dublin emergency room
• 12 week, double-blind, placebo-controlled trial
• 2.1 g/d, (1.2 g/d EPA, 0.9 g/d DHA)
• (EPAX 5500, Pronova Biocare, Norway)

• Results
  • 50% reduction in depression (Beck)
  • 45% reduction in suicidal thinking (OAS)
  • 33% reduction in perception of stress (PSS)
  • 30% improvement in “happiness” (DHUS)
  • (perception of daily events as uplifting)

Hallahan, Hibbeln, Davis, Garland, Br J Psychiatry, 2006
Low omega-3 HUFA status and increased risk of suicide deaths for US Military

All US Active Duty Military 2002-2008

- Suicide Deaths n=800
- Matched Controls n=800
- Matched by:
  - age, gender, rank, duty category,
- Serum - previously collected and repository stored at -80C
  - drawn within 12 m for cases /controls
  - evaluated for collection /storage artifacts
  - high throughput robotic GC analysis
- Armed Forces Health Surveillance Center (AFHSC) data
  - Suicide death confirmation
  - All medical visits with a ICD-9 psychiatric diagnostic code
  - Post deployment form DD2796


Funded by DARPA, Dr. Amy Kruse, Program Manager
Risk of Suicide and low DHA status
Among Male US Military and Chinese populations

OR = 1.82, p<0.007
95% CI (1.10-2.47)

OR = 1.63, p<0.016
95% CI (1.04-1.93)

Medians of DHA (%):
- US Mil. ref: 0.7
- China ref: 2.7
- 1.1
- 1.4
- 2.7
- 4.2
- 5.4
- 6.9

p for trend < 0.001
p for trend < 0.002

Funded by DARPA, Dr. Amy Kruse, Program Manager
Nutritional Armor for the Warfighter: Can Omega-3 Fatty Acids Enhance Stress Resilience, Wellness and Military Performance?
13-14 OCT 2009

CAPT Joseph R. Hibbeln, M.D., NIAAA
Bernadette Marriott, Ph.D., Samueli Institute
DARPA

Dominant Themes -

• 1. Immediately educate Senior Military personnel on omega-3 heart benefits

• **Key man insurance** - protecting your hearts and your brains best protects us.

• 2. Conduct large suicide prevention and mental health outcome studies.

• 3. Change the US Military diet and do the research at the same time.

• 4. Trust, but verify- institute programs to measure omega-3 HUFA blood levels.
Blood levels of omega-3 HUFAs and health

- 17% US MILITARY ACTIVE DUTY
- 20% TAKE URGENT REMEDIAL ACTION
- 30% TAKE REMEDIAL ACTION
- 40% REMEDIAL ACTION BENIFICIAL
- 50% HEALTHY OMEGA-3 LEVEL
- 60% ADJUST FOR OPTIMAL HEALTH
- 70% OPTIMAL HEALTH
How can we increase omega-3 HUFA levels?

Provide and promote

1. Supplements in capsules (easy, but problematic)

2. Fresh seafood (hard)

3. Omega-3 enriched manufactured food products (expensive)

4. Stealth health
   - **SUPER CHICKEN/ SUPER EGGS/ SUPER PORK**
   - High omega-3 HUFA/ low omega-6
Super Chicken Project

Bernadette P. Marriott, Ph.D.
Vice President, Health Research and Education
Samueli Institute

CAPT Joseph R. Hibbeln, M.D., USPHS
Acting Chief, Section on Nutritional Neurosciences
LMBB, NIAAA, NIH

This project is supported in part by Award Number: W81XWH-06-2-0009 from U.S. Army Medical Research Acquisition Activity (USAMRAA) and Military Operational Medicine Research Programs (MOMRP) to the Samueli Institute; the National Institute on Alcohol Abuse and Alcoholism, the U.S. Army Natick Soldier Systems Center (NSSC); and in kind contributions from Wenger® Feeds, Development and Management Frontiers (DMF), and Pioneer Hi-Bred - a DuPont Business.
# Super chicken #2 - Human Diet Study

No capsules – Stealth health ingredients in main line Military garrison menus

<table>
<thead>
<tr>
<th>Diet</th>
<th>Chicken, Eggs, Pork, Bacon</th>
<th>Oils Frying, baking, salad dressing</th>
<th>Smoothie</th>
<th>Enriched foods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Current DoD</strong></td>
<td>“Standard”</td>
<td>High n-6 Soy (std)</td>
<td>Placebo</td>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>2. Swapped DoD</strong></td>
<td>“Super Foods”</td>
<td>Low n-6 Soy (Plenish)</td>
<td>Placebo</td>
<td>-------------------------------</td>
</tr>
<tr>
<td></td>
<td>high n-3 HUFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low n-6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3. Swapped DoD + enrichment</strong></td>
<td>“Super Foods”</td>
<td>Low n-6 Soy (Plenish)</td>
<td>Smart fish 500 mg/d</td>
<td>Enriched mayo pasta sauce chocolate, etc</td>
</tr>
<tr>
<td></td>
<td>high n-3 HUFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low n-6</td>
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**Study Design:** 12 week complete dietary intervention

– Pennington metabolic kitchen. Military age population.
Promoting Health in the Army: A Holistic Approach

The Army recognizes that a healthy balanced diet, to include appropriate nutrients such as Vitamin D and Omega-3 fatty acids, is important to promoting health. They are addressing this through a three-prong, holistic approach:

1. **Educate**: Support a comprehensive public health campaign to stress the importance of a healthy, balanced diet.

2. **Nutrition**: Provide appealing, nutrient-rich foods to Soldiers to encourage healthy eating habits.

3. **Research**: Encourage research to examining the health benefits of Omega-3 fatty acids, including a possible link to behavioral health.
Critical mental health research gaps

1. **Prevention of Severe Suicidal Episodes**
   - High risk subjects representative of US Military personnel (OIF/OEF Vets?)
   - In emergency room or admitted for suicide attempt/risk
   - 4 g/d omega-3 HUFA compared to placebo - 12 month follow up

2. **Treatment of Resistant Major Depression**
   - Large and unequivocal trial
   - Significant symptoms despite medications and psychotherapy
   - 4 g/d omega-3 HUFA compared to placebo

3. **Prevention of Combat Stress Induced-Anxiety/Depression/PTSD**
   - Rangers or SEALs before and during extreme “combat like” training
   - 4 g/d omega-3 HUFA compared to placebo

4. **Military Families**
   - improve mental health of military children and spouses?
Acknowledgements

• Bernadette Mariott, Ph.D. Samuei Institute

• Prof. John Davis, MD, Univ. of Illinois ChicagDoD
• COL Michael Lewis, M.D.
• COL Mark Rubitone, M.D.
• DARPA

• Columbia, Univ.
• M Elizabeth Sublette, M.D.

• Ireland
• Brian Hallahan, M.D.
• Malcolm Garland, M.D.

• Superchicken
• Michael Hawes, DMF Frontiers
• Fabian DeMester, DMF Frontiers
• Kevin Herkelman, Wenger Feeds
• Janet Collins, Ph.D., Dupont/Pioneer
• Susan Knowlton, Ph.D., Dupont/Pioneer
• Catherine Champane, Ph.D. Pennington, LA
• Andrew Young, Ph.D., USARIUM, DoD

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