Information brief: Omega-3 Fatty Acids

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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.

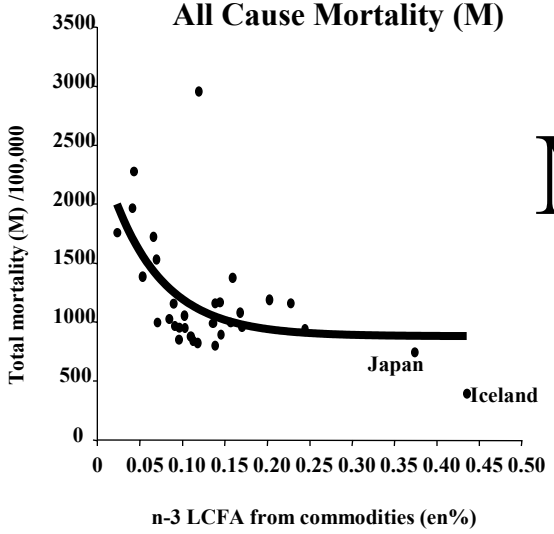
Dr. Bernadine Healy served as director of the NIH and president and CEO of the American Red Cross.

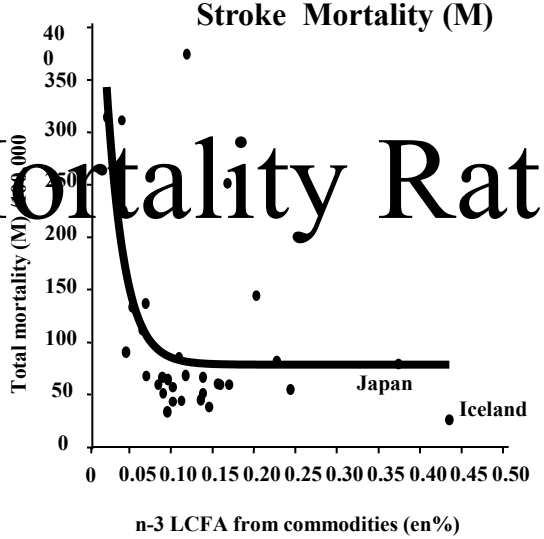
US News and World Report August 7, 2008

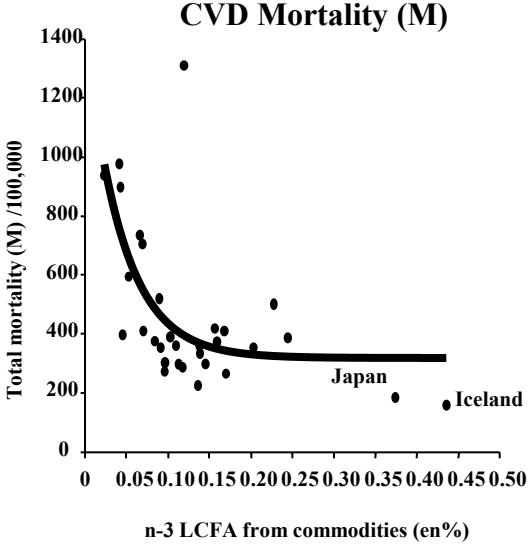
- **No nutrient is more important for decreasing cardiovascular death—and more lacking—than omega-3**

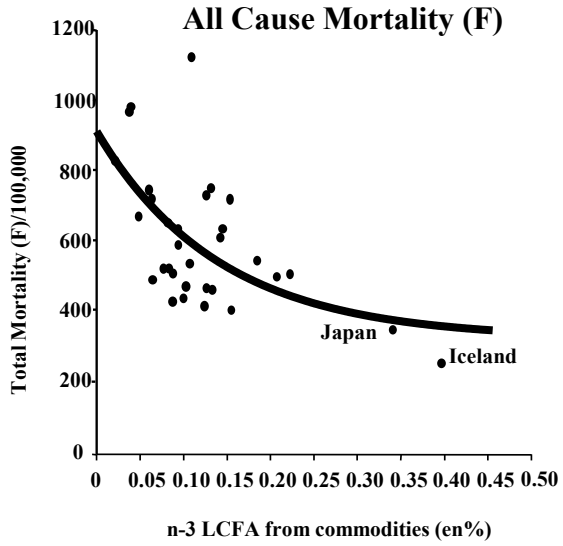
- We have failed to take seriously a significant nutritional fat *deficiency* that afflicts most Americans: We have too little omega-3s of the kind found in oily fish…
- This deficiency significantly increases the risk of heart attacks and sudden cardiac death, and mounting evidence suggests omega-3 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.**

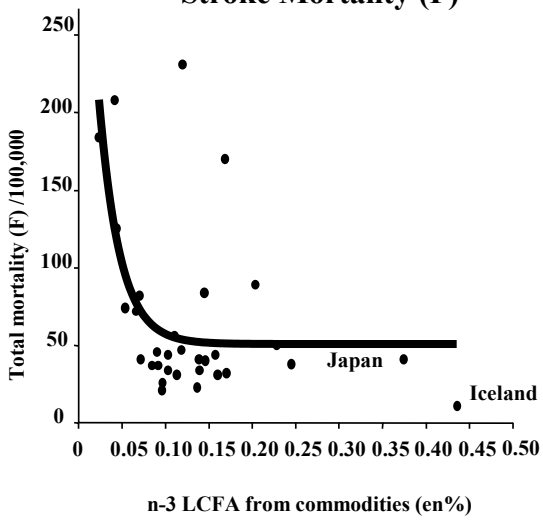
Mortality Rates

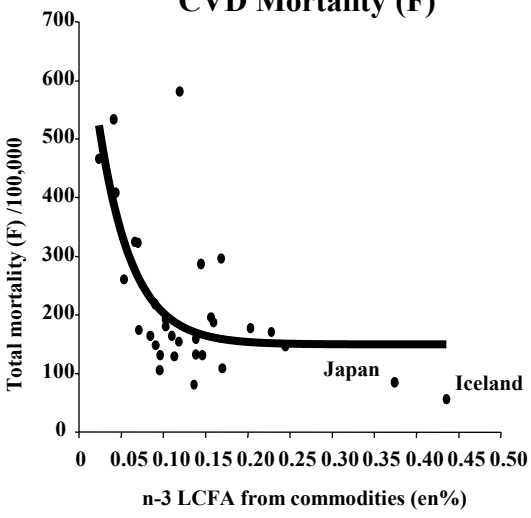






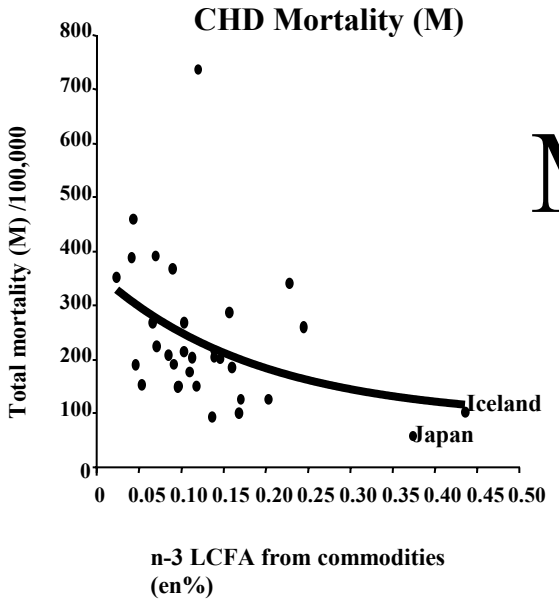


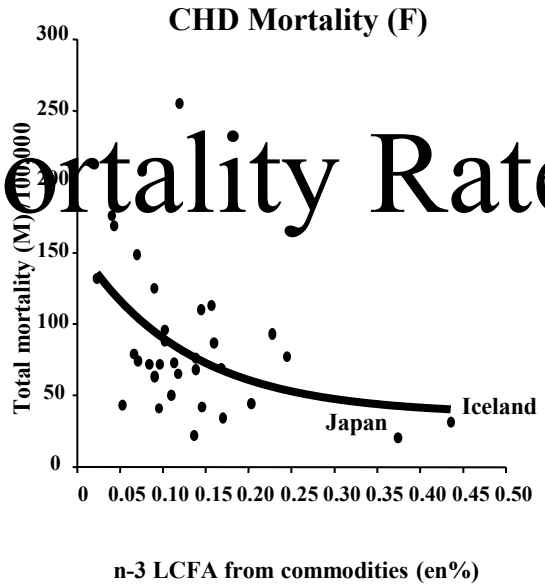


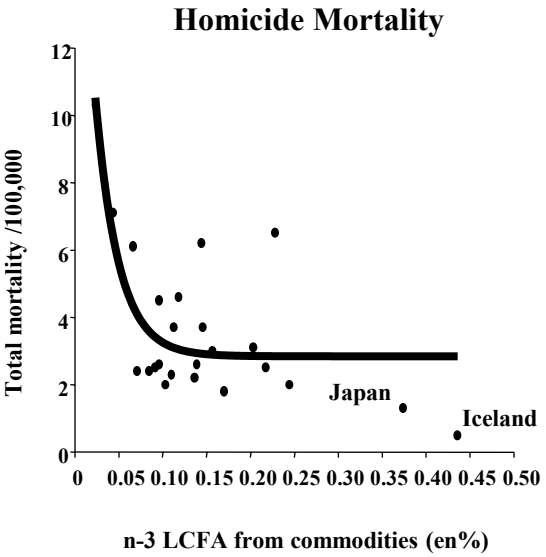


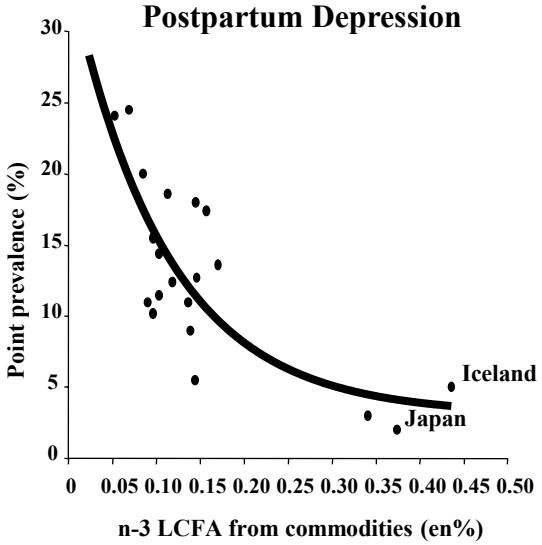
Hibbeln et al Am J Clin Nutr 2006; 83; 1483S-93S

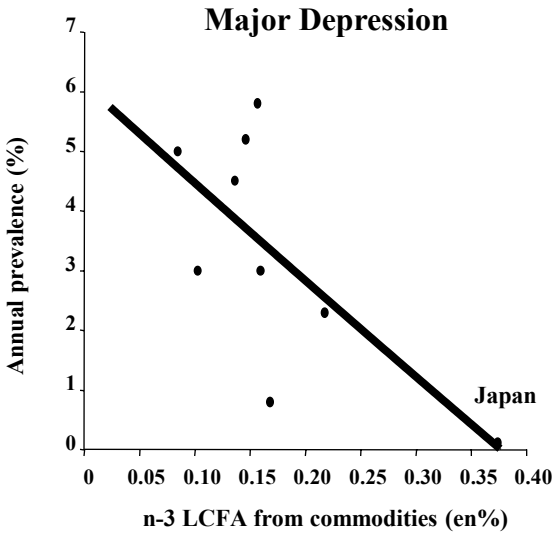
Mortality Rates

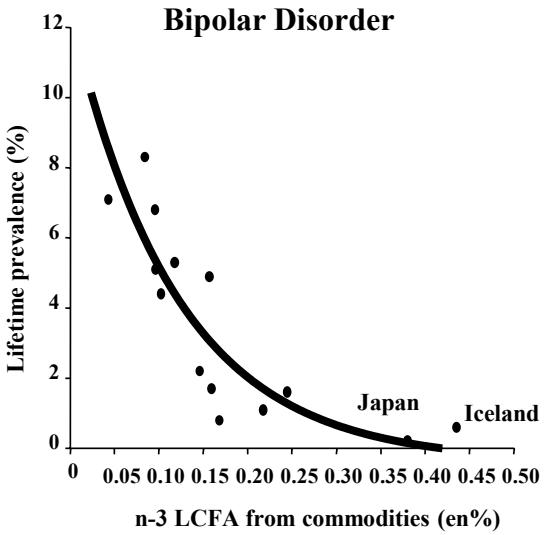






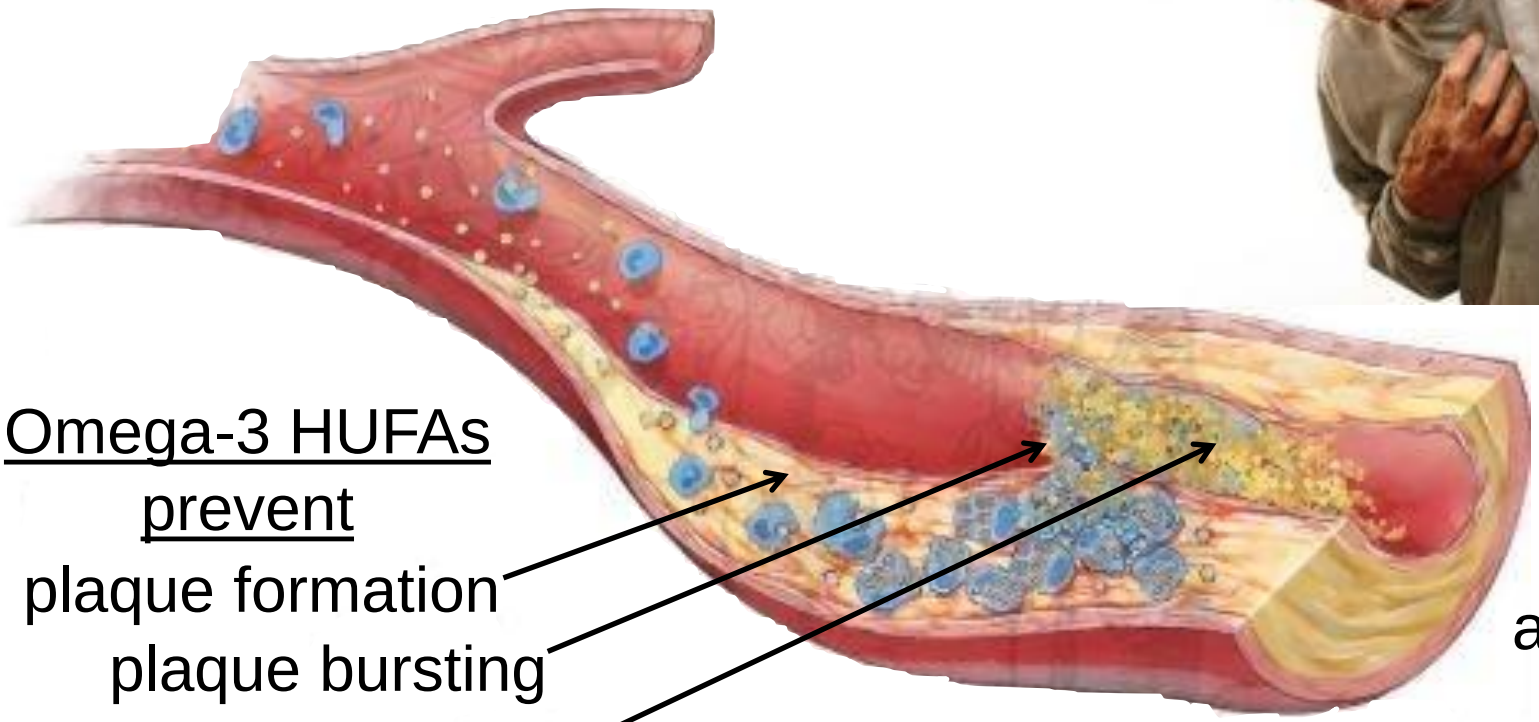






Hibbeln et al Am J Clin Nutr 2006; 83; 1483S-93S

American Heart Assoc. recommends eating fish 2-3 times/week or 1g/day omega-3 HUFA



Omega-3 HUFAs prevent

plaque formation

plaque bursting

clotting

arrythmias and death

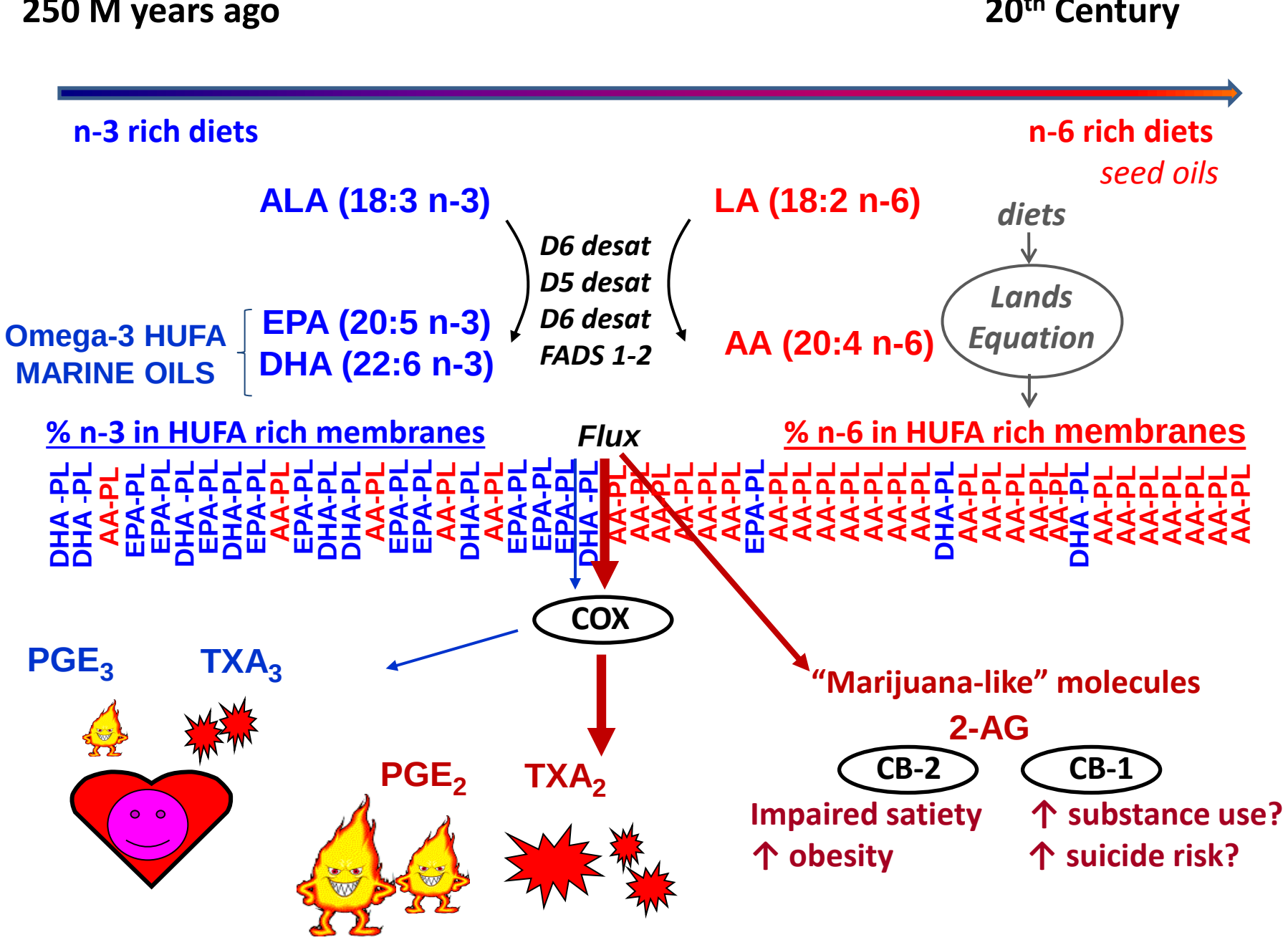
Surgical Recommendations for Omega-3's for the Most Severe Subjects

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

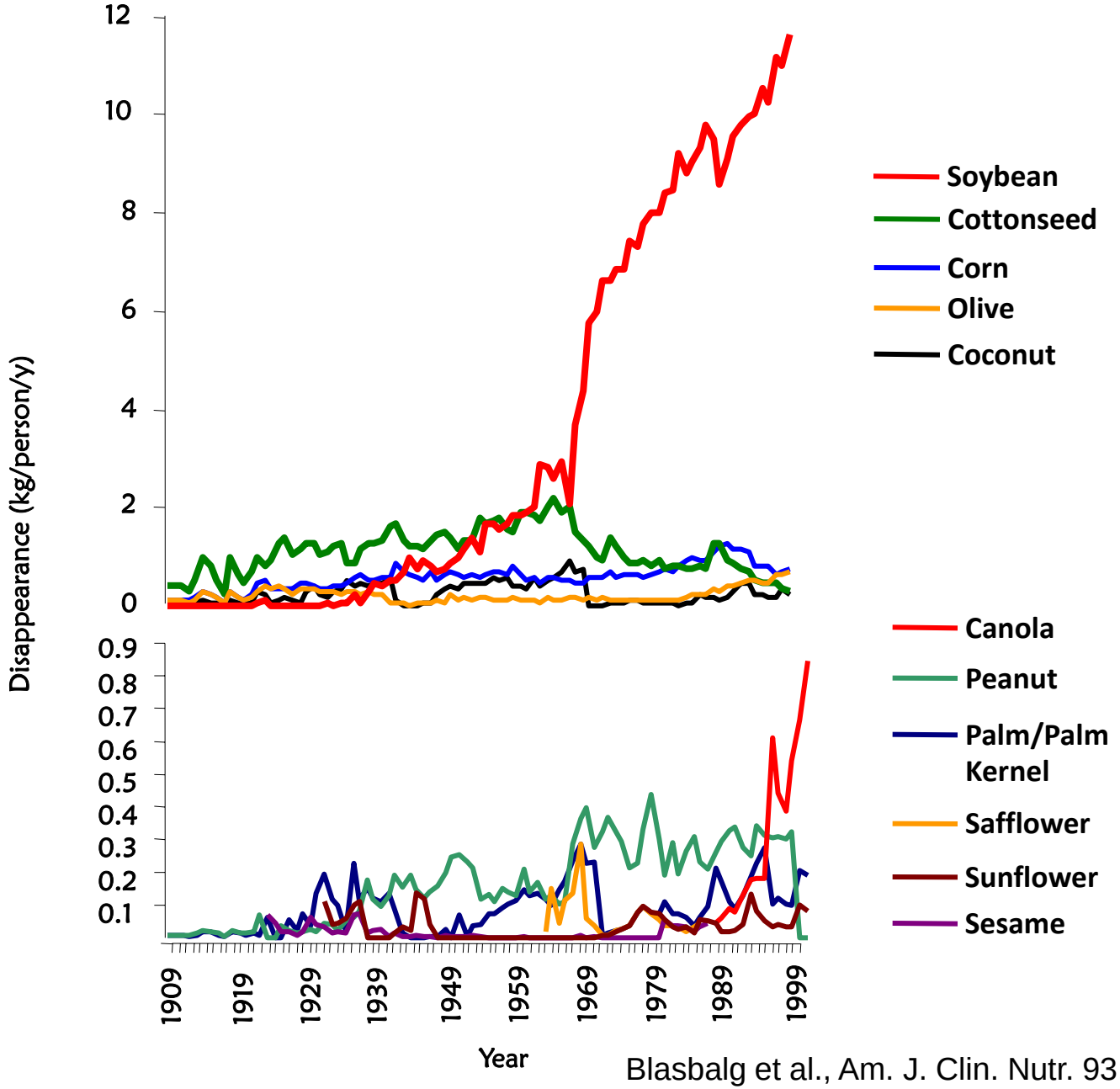
- **Immune-modulating enteral formulations (supplemented with agents such as arginine, glutamine, nucleic acid, omega-3 fatty acids, and antioxidants) should be used for the appropriate patient populations**

- **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

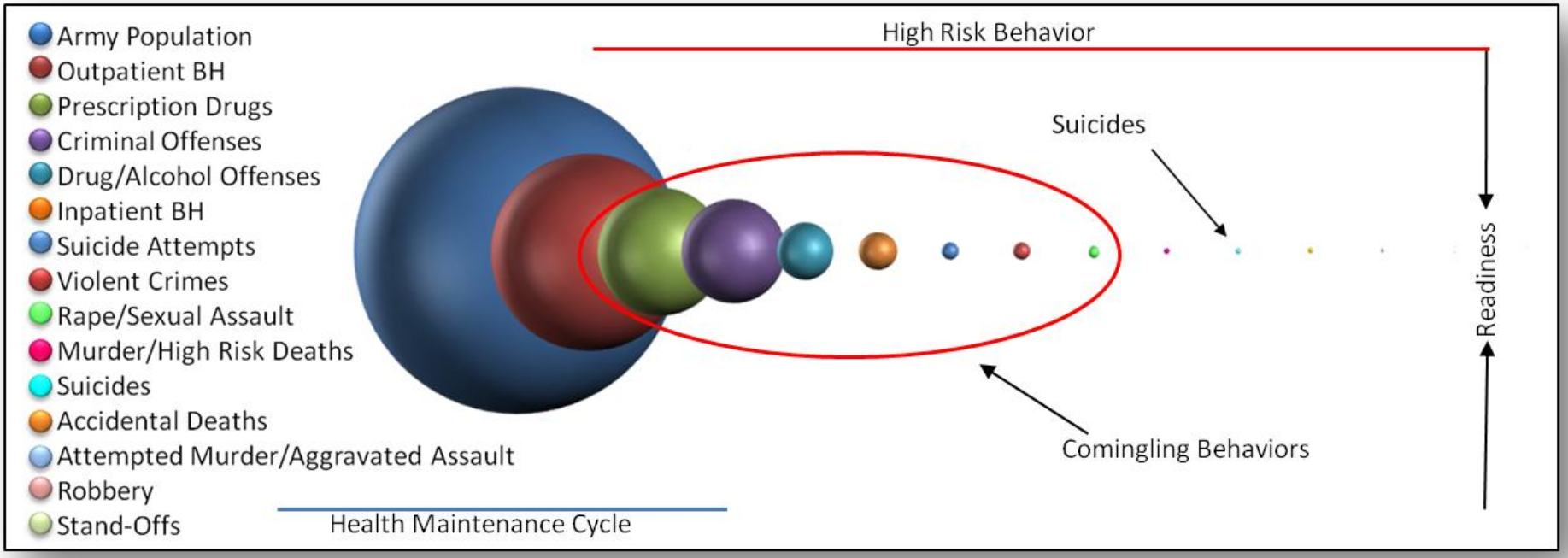

250 M years ago
20th Century
n-3 rich diets
n-6 rich diets
seed oils
ALA (18:3 n-3)
LA (18:2 n-6)
diets
D6 desat
D5 desat
D6 desat
FADS 1-2
Lands Equation
Omega-3 HUFA MARINE OILS
EPA (20:5 n-3)
DHA (22:6 n-3)
AA (20:4 n-6)
% n-3 in HUFA rich membranes
Flux
% n-6 in HUFA rich membranes
DHA -PL
AA-PL
EPA-PL
COX
PGE3
TXA3
PGE2
TXA2
"Marijuana-like" molecules
2-AG
CB-2
CB-1
Impaired satiety
↑ obesity
↑ substance use?
↑ suicide risk?
Respiratory cytokine storms - Impaired wound healing - thombosis – headache - pain

Changes in Oils in the US Food Supply in the 20th Century



Blasbalg et al., Am. J. Clin. Nutr. 93: 950-962, 2011.

Will ↑omega-3 HUFAs also Reduce High Risk Behaviors? Major depression, Substance abuse, Violence and Suicidal behavior



Health Promotion by ↑omega-3 HUFAs is already recommended by more than 30 international scientific and government bodies

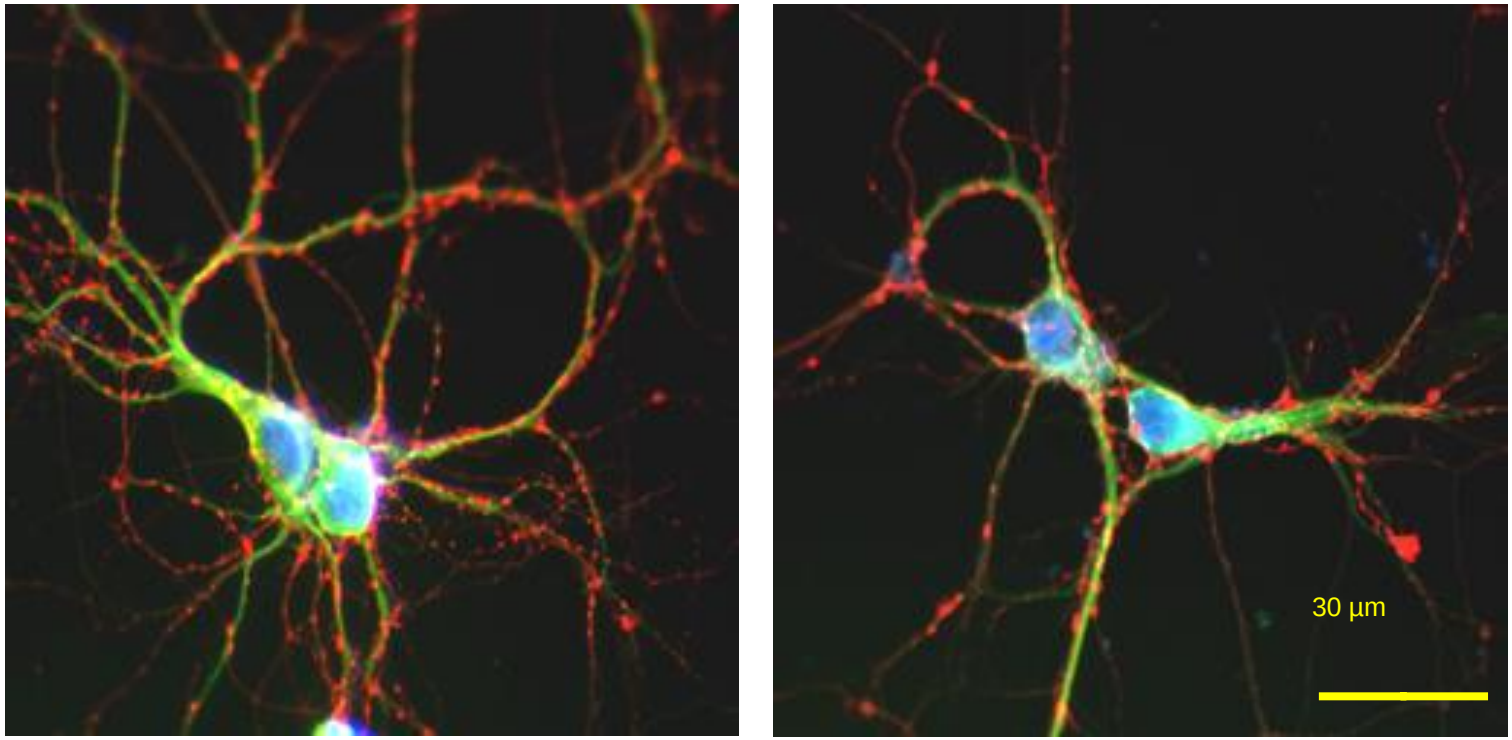
- e.g. USDA 2010 dietary guidelines: - Cardiovascular, stroke, immunological, surgical survival, ect

Publications ~90,000 basic science, ~ 9,000 human studies, 1,889 clinical trials

DHA dietary deficiency impairs synapse development

	Adequate	Deficient
Hippocampal Fatty Acids	DHA 6.6 ± 0.7%	0.5 ± 0.1%
	DPAn-6 0.4 ± 0.1%	4.7 ± 0.1%

Synapes in Hippocampal Neurons



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

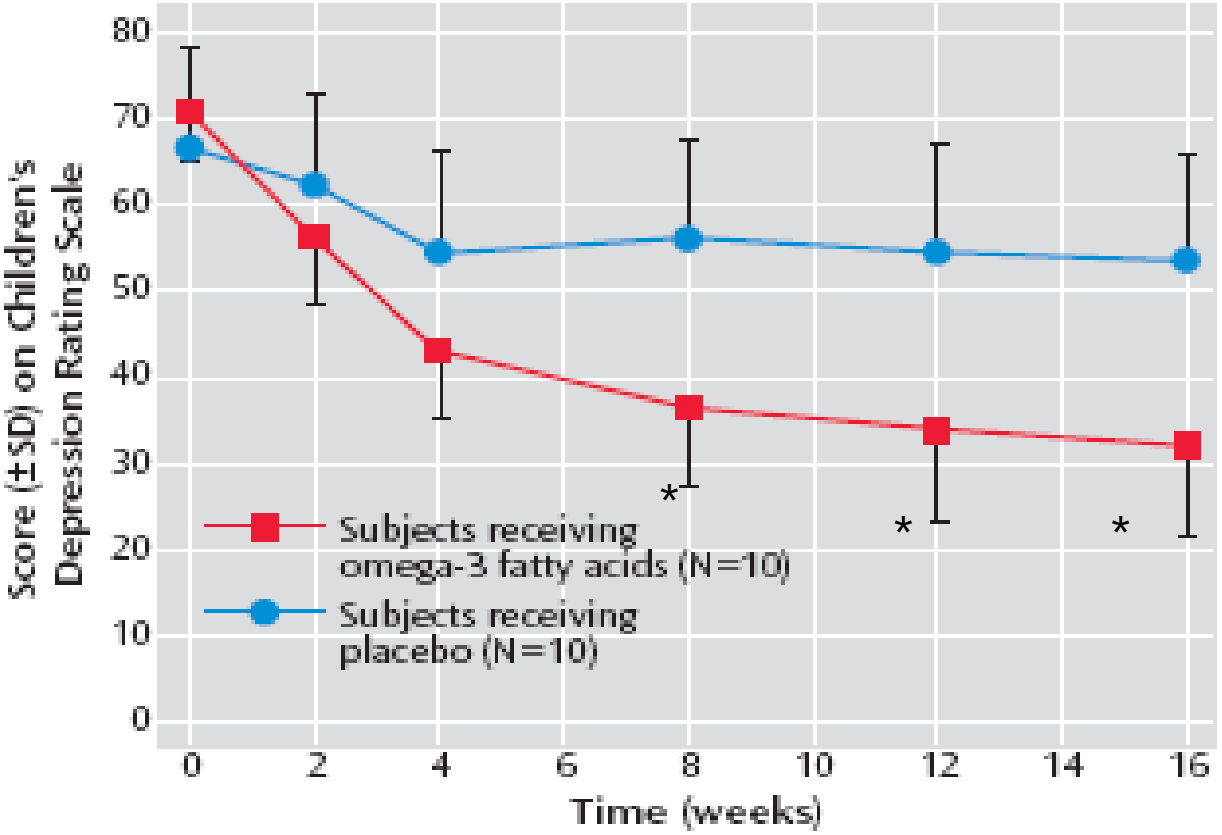
Cao et al. *J. Neurochem.* 2009

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

Disorder	Plausible mechanism	Epidemiological Ecological	Case control (Tissue)	RCT's	Meta analyses	Positive clinical effect? Size?
Major depression	Yes	54	16	34	5	Yes Similar to anti-depressants
ADHD	Yes	6	12	10	1	Yes Less than stimulants
Aggression/ violence/conduct	Yes	8	5	8	-	Probable Large effect ↓37% in felony violence
Anxiety	Yes	2	5	3	-	Probable -
Alcohol/Sub. use	Yes	-	4	1	-	Hopeful Large effect
Suicide	Yes	6	3	1	-	Hopeful -

Omega-3 treatment of childhood depression: a controlled, double-blind pilot study.

FIGURE 1. CDRS During 16 Weeks of Omega-3 or Placebo Treatment[a]



Age range= 8-12.5
Monotherapy

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

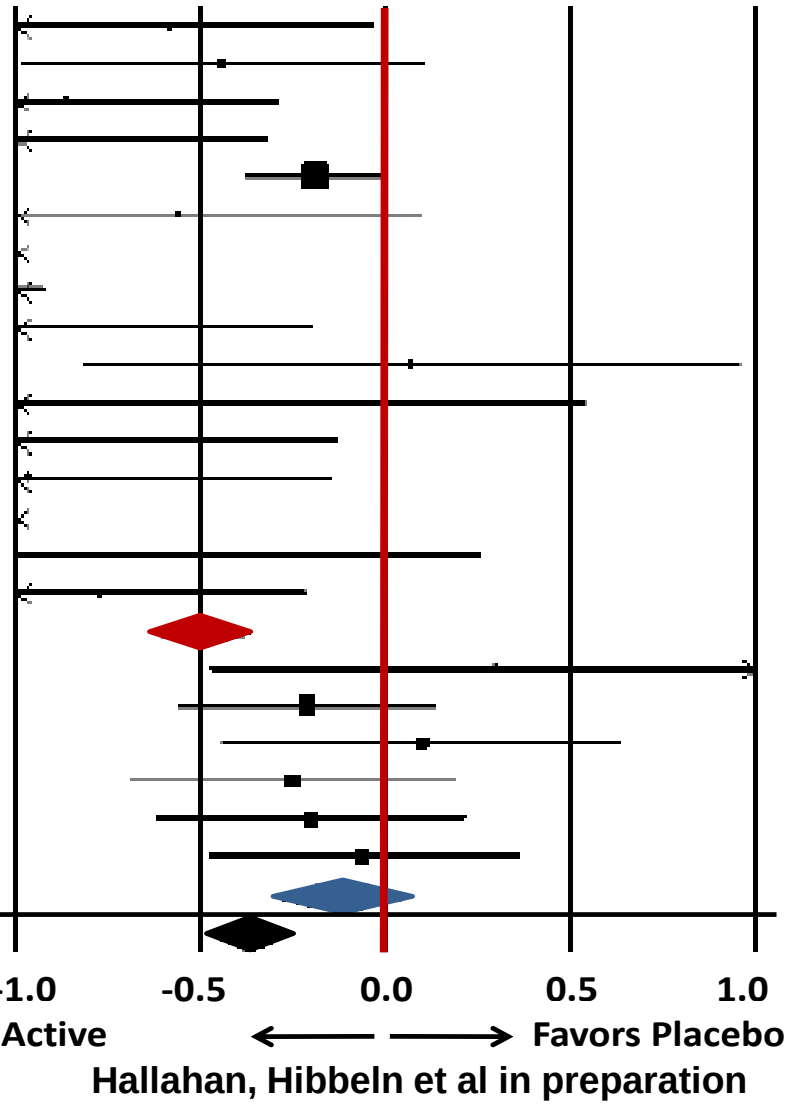
*p<0.05

Nemets et al Am J Psychiatry. 2006 Jun;163(6):1098-100.

Major Depressive Symptoms RCT meta-analysis

EPA+DHA vs. EPA predominant interventions - Forest Plot

Study Name	Point Est	SE	Var	Low Limit	Up Limit	Z	P
Frangou06 1	-0.580	0.285	0.081	-1.138	-0.022	-2.038	0.042
Frangou06 m high dose	-0.440	0.279	0.078	-0.987	0.107	-1.575	0.115
Hallahan 0	-0.860	0.296	0.087	-1.439	-0.281	-2.910	0.004
Jazayeri	-1.040	0.369	0.136	-1.762	-0.318	-2.822	0.005
Lesperance10	-0.190	0.096	0.009	-0.379	-0.001	-1.974	0.048
Mischoulon09	-0.560	0.338	0.114	-1.223	0.103	-1.655	0.098
Nemets06 ch	-3.670	0.721	0.520	-5.083	-2.257	-5.090	0.000
Nemets02_dep	-1.950	0.528	0.278	-2.984	-0.916	-3.697	0.000
Peet02 1	-1.150	0.488	0.238	-2.107	-0.193	-2.356	0.018
Peet02 2	0.070	0.459	0.207	-0.822	0.962	0.154	0.878
Peet02 4	-0.360	0.461	0.212	-1.263	0.543	-0.781	0.435
Roncaneteadj	-0.720	0.305	0.093	-1.317	-0.123	-2.364	0.018
Stoll99	-0.960	0.418	0.175	-1.779	-0.141	-2.297	0.022
Su 0	-3.160	0.658	0.433	-4.450	-1.870	-4.801	0.000
Tad ad 25%	-0.370	0.321	0.103	-0.998	0.258	-1.154	0.249
Tad no ad 25%	-0.770	0.287	0.082	-1.333	-0.207	-2.683	0.007
EPA +DHA	**-0.50**	0.067	0.005	-0.628	-0.364	-7.370	**0.000**
Bot a	0.300	0.397	0.157	-0.477	1.077	0.757	0.449
Carney10	-0.210	0.180	0.033	-0.564	0.144	-1.164	0.245
Freeman08	0.100	0.277	0.077	-0.443	0.643	0.361	0.718
LucasNI	-0.260	0.223	0.050	-0.697	0.177	-1.121	0.262
Rest08 n ni	-0.200	0.216	0.046	-0.622	0.222	-0.926	0.353
Rest08 niMAD_	-0.060	0.216	0.046	-0.482	0.362	-0.278	0.781
EPA predom	**-0.12**	0.094	0.009	-0.307	0.062	-1.303	**0.193**
Overall	**-0.37**	0.055	0.003	-0.477	-0.262	-6.750	**0.000**



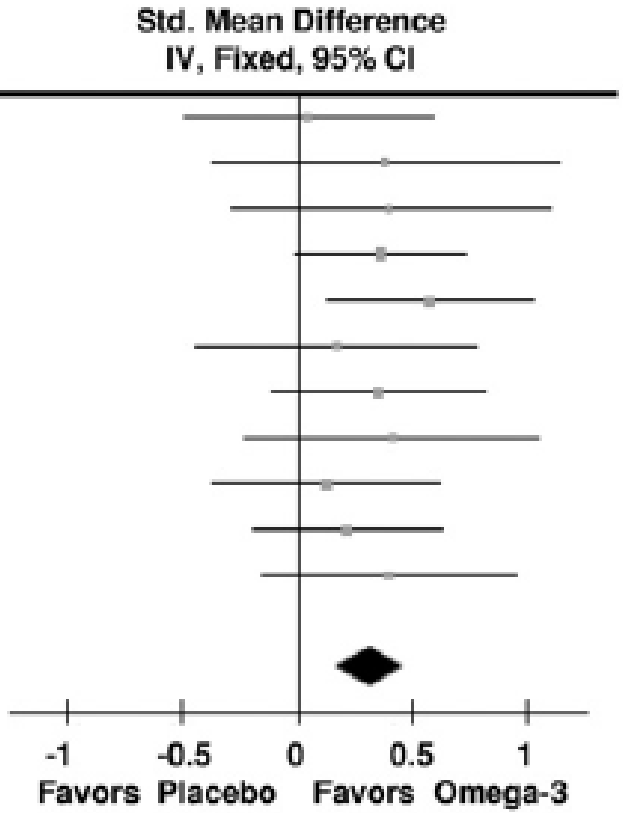
Hallahan, Hibbeln et al in preparation

Omega-3 supplements are effective for reducing ADHD in children
Moderate effect size, with low heterogeniety

Study or Subgroup	Weight	Std. Mean Difference IV, Fixed, 95%CI	Year
Voigt 2001[44]	8.0%	0.04 [-0.49, 0.58]	2001
Richardson 2002[42]	4.1%	0.38 [-0.37, 1.13]	2002
Stevens 2003[25]	4.8%	0.40 [-0.29, 1.09]	2003
Richardson 2005[41]	17.3%	0.36 [-0.00, 0.73]	2005
Sinn 2007[45]	11.6%	0.58 [0.13, 1.02]	2007
Vaisman 2008[43] fishoil	6.3%	0.17 [-0.44, 0.77]	2008
Johnson 2008[39]	11.1%	0.35 [-0.11, 0.81]	2008
Vaisman 2008[43] omega-3	5.7%	0.41 [-0.22, 1.05]	2008
Raz 2009[40]	9.6%	0.13 [-0.36, 0.62]	2009
Gustafsson 2009[46]	13.8%	0.22 [-0.19, 0.62]	2009
Belanger 2010[47]	7.7%	0.40 [-0.15, 0.95]	2010
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)



10 trials, n=699 children%

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

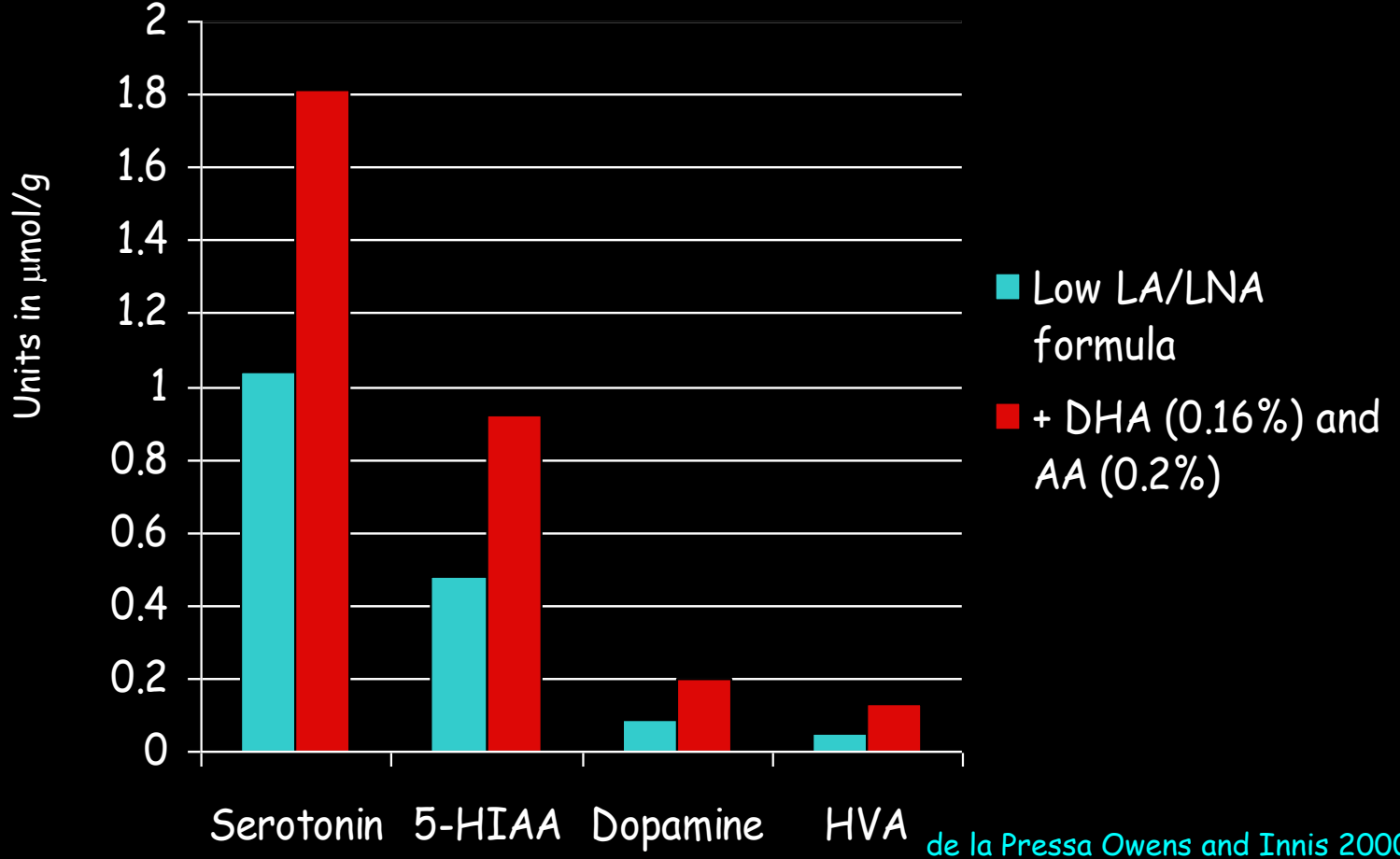
Anybody can become angry - that is easy,

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

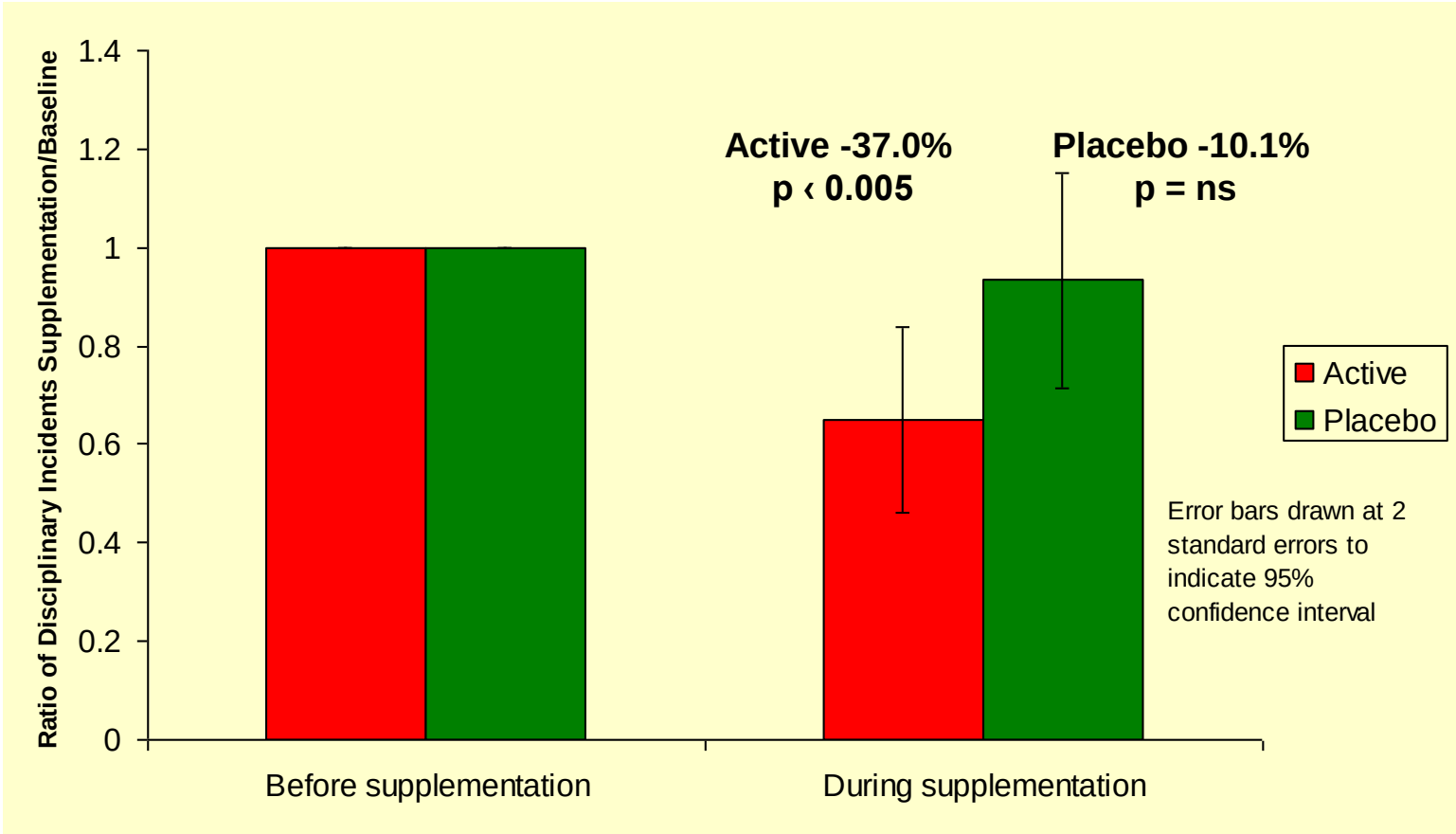
Infant formula supplemented with DHA and AA increases serotonin and dopamine in piglet frontal cortex after 18 days of life



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



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

Gesch et al. Br J Psychiatry 2002, 181:22-28

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

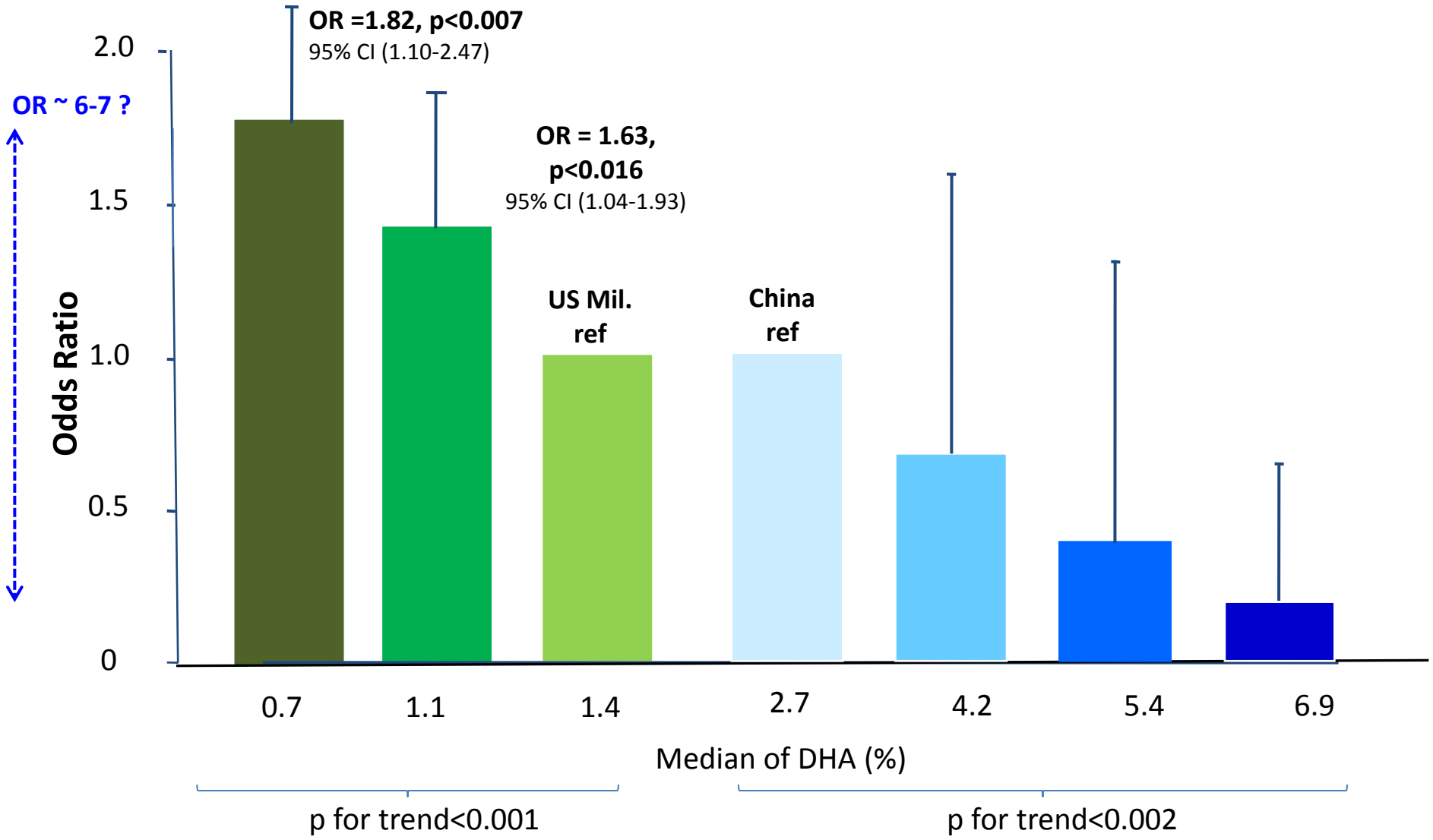
- **Armed Forces Health Surveillance Center (AFHSC) data**

- Suicide death confirmation
- All medical visits with a ICD-9 psychiatric diagnostic code
- Post deployment form DD2796

Lewis, Hibbeln et al J Clin Psych, 2011

Funded by DARPA, Dr. Amy Kruse, Program Manager

Risk of Suicide and low DHA status Among Male US Military and Chinese populations



Funded by DARPA, Dr. Amy Kruse, Program Manager

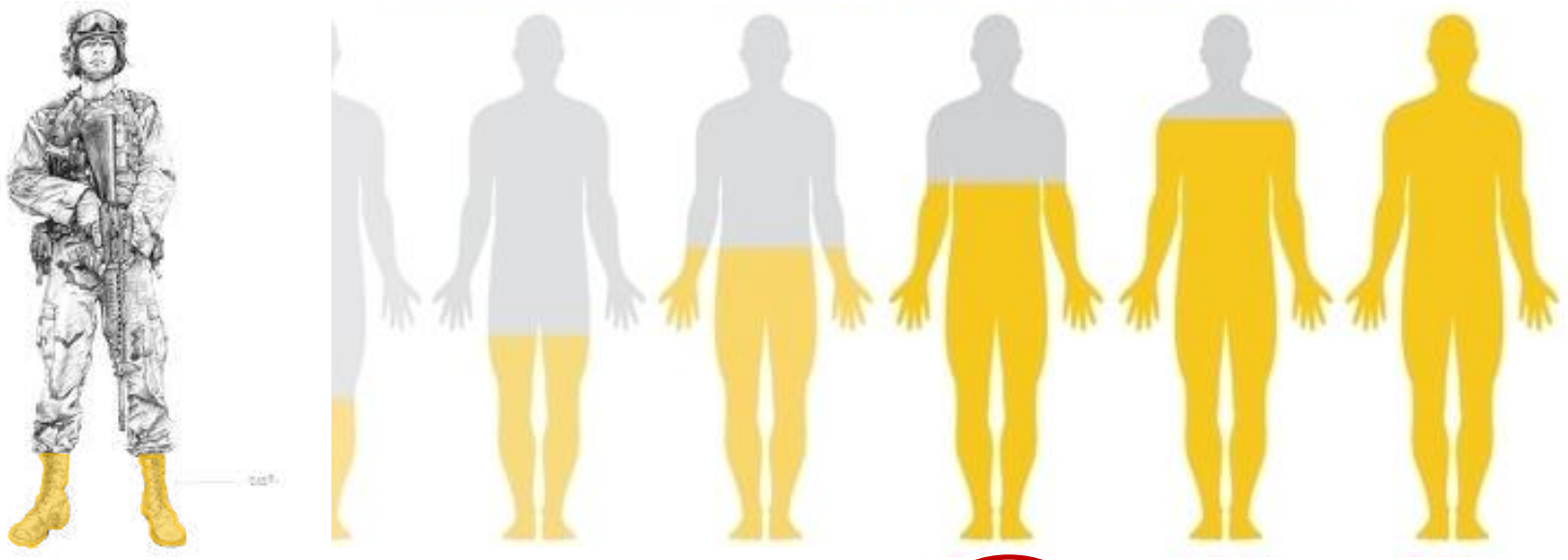
Nutritional Armor for the Warfighter:
Can Omega-3 Fatty Acids Enhance Stress Resilience, Wellness and Military Performance?
13-14 OCT 2009

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%	20%	30%	40%	50%	60%	70%
US MILITARY ACTIVE DUTY	TAKE URGENT REMEDIAL ACTION	TAKE REMEDIAL ACTION	REMEDIAL ACTION BENIFICIAL	HEALTHY OMEGA-3 LEVEL	ADJUST FOR OPTIMAL HEALTH	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

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Super chicken #2 - Human Diet Study

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

Diet	Chicken, Eggs, Pork, Bacon	Oils Frying, baking, salad dressing	Smoothie	Enriched foods
1. Current DoD	"Standard"	High n-6 Soy (std)	Placebo	----------
2. Swapped DoD	"Super Foods" high n-3 HUFA Low n-6	Low n-6 Soy (Plenish)	Placebo	----------
3. Swapped DoD + enrichment	"Super Foods" high n-3 HUFA Low n-6	Low n-6 Soy (Plenish)	Smart fish 500 mg/d	Enriched mayo pasta sauce chocolate, ect

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?

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