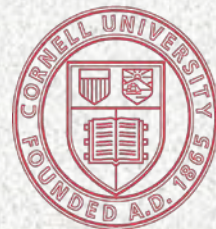


# *Nutrition Above the Neck: Emerging Results on Seafood Nutrients for Brain Development and Health*

Tom Brenna

Dell Pediatric Research Institute  
Departments of *Pediatrics*, of *Chemistry*,  
and of *Nutrition*



Cornell University  
Division of  
Nutritional Sciences



The University of Texas at Austin  
College of Natural Sciences



# Disclosure/Conflict of Interest - Tom Brenna

- Scientific Advisory Council member
  - Nature's Bounty, Dietary Supplement manufacturer; Seafood Nutrition Partnership, charitable non-profit
- Research Grants (all >3 years ago)
  - National Cattleman's Beef Association
  - (Mostly NIH)
- Recent Advisory Groups
  - DMI = Dairy Management, Inc
  - Texas Beef Council, Austin, TX
- Shareholder
  - Retrotope, biotech startup
- Editorial Board
  - Fats of Life Newsletter, published by GOED = Global Organization for EPA and DHA

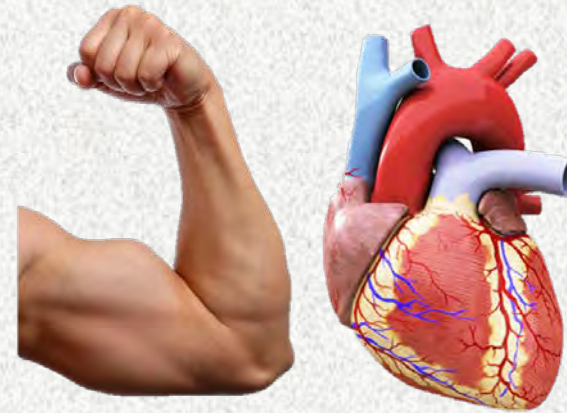
# Outline

- Dietary guidelines recommend more seafood
- Human development emphasizes brain development.
- Brain composition is unique: omega-3
- High omega-6 creates a metabolic demand for preformed omega-3 EPA and DHA
- A few clinical results relevant to babies and moms
- Seafood is safe



# Nutrition Recommendations Historically Focus on Brawn, Not Brain

- Nutritional recommendations expressly and implicitly address prevention of **premature death** afflicting 50-something men.
  - Cardiovascular disease
  - Cancer
  - More recently, as waist lines expand
    - Diabetes
    - Obesity (a risk factor or a disease?)
- In other words, the focus has been **brawn** not **brain**.
- However,
  - Omega-6 for bodies
  - Omega-3 for brains



# 2010

Key  
Recommendations



Recommendations for specific population groups

*Women capable of becoming pregnant?*

- Increase foods with heme iron and enhancers of iron absorption such as vitamin C-rich foods
- 400 micrograms/d folate

*Women who are pregnant or breastfeeding?*

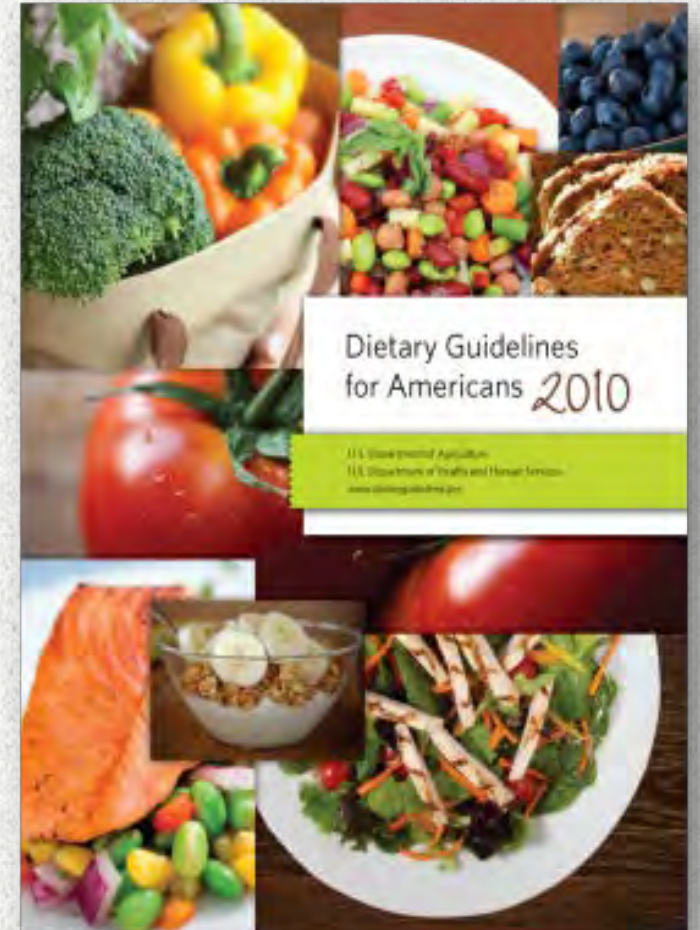
- 8-12 oz/week seafood. Limit albacore tuna to 6 oz/week
- Pregnant – take an iron supplement

*Individuals ages 50 years and older*

- Consume foods with vitamin B12, cereals or supplements

## A break

*Seafood in pregnancy is for DHA,  
for baby brain*



# 2015-2020 Shift to Under Consumed Foods

DIETARY GUIDELINES  
2015-2020

## Key Recommendations

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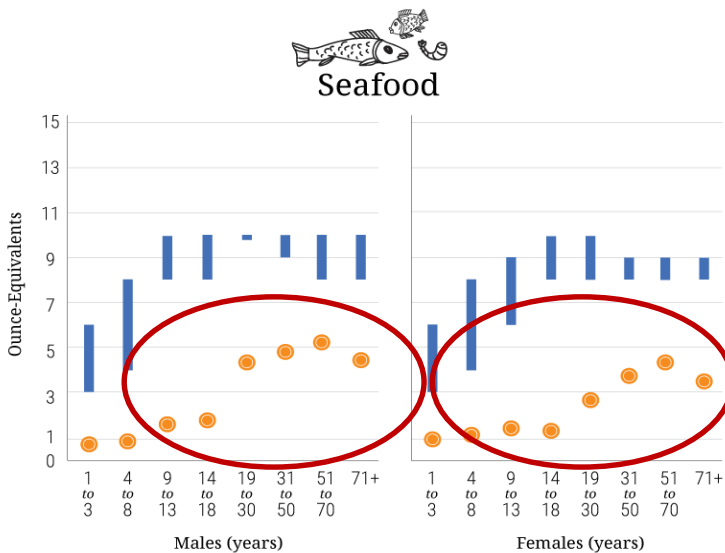
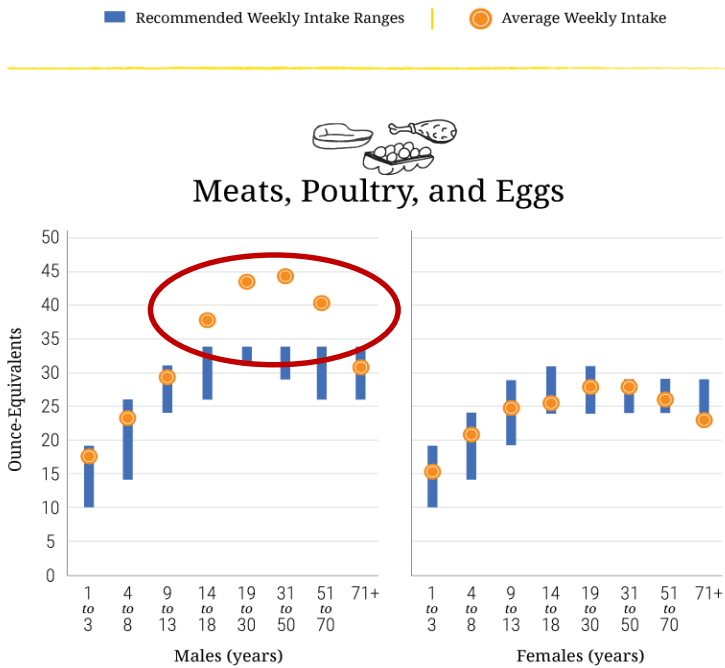
Consume a healthy eating pattern that accounts for all foods and beverages within an appropriate calorie level.

A healthy eating pattern includes:<sup>[2]</sup>

- A variety of vegetables from all of the subgroups—dark green, red and orange, legumes (beans and peas), starchy, and other
- Fruits, especially whole fruits
- Grains, at least half of which are whole grains
- Fat-free or low-fat dairy, including milk, yogurt, cheese, and/or fortified soy beverages
- A variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), and nuts, seeds, and soy products
- Oils



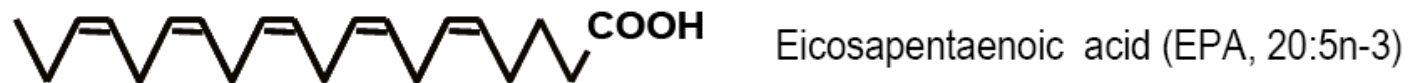
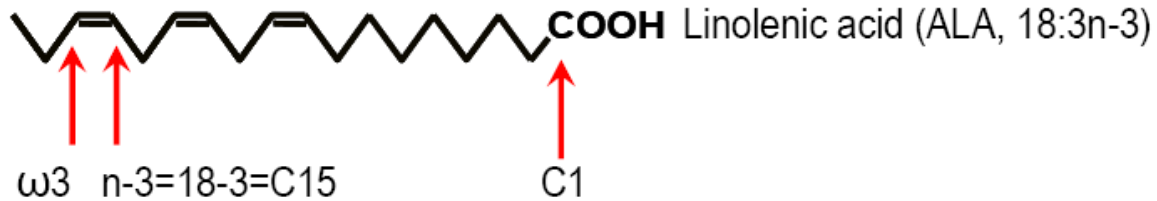
- Guidelines recommend dairy and/or fortified soy
- A variety of protein-rich foods
- 2015 DGA
  - No recommendation to eliminate meat/animal foods
  - Emphasis is on **shift** in consumption from excess amounts of some foods to underconsumed other foods.



# Consumption Patterns: Americans Don't Eat Enough Seafood

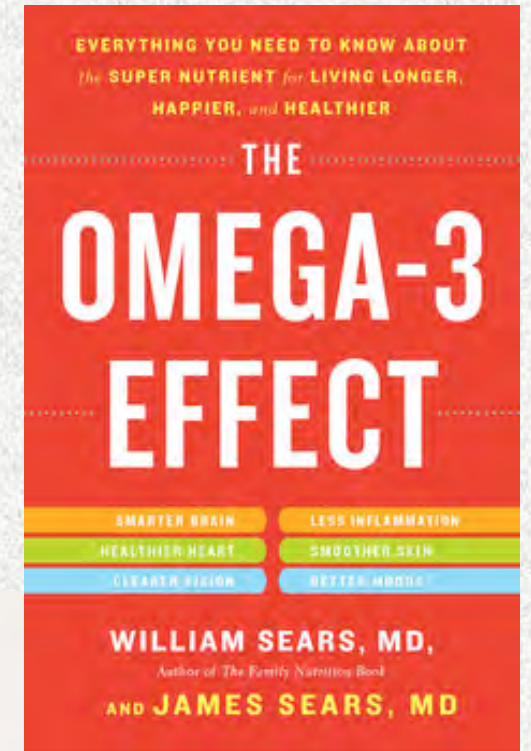
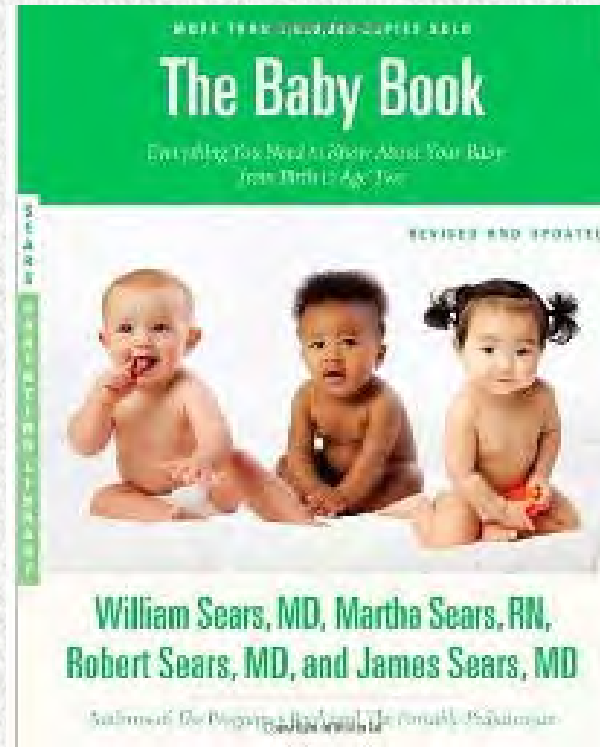
- The 2015 Dietary Guidelines for Americans considered US surveys called “What we eat in America”
  - Men over consume meat/poultry and eggs
  - All Americans under consume seafood
- Shift from meat to seafood is recommended.
- No recommendation was made to *eliminate*
  - meat
  - dairy

# Omega-3 ( $\omega$ 3) and Omega-6 ( $\omega$ 6) fatty acids





*“As calcium is to the bones,  
DHA is to the brain.”*





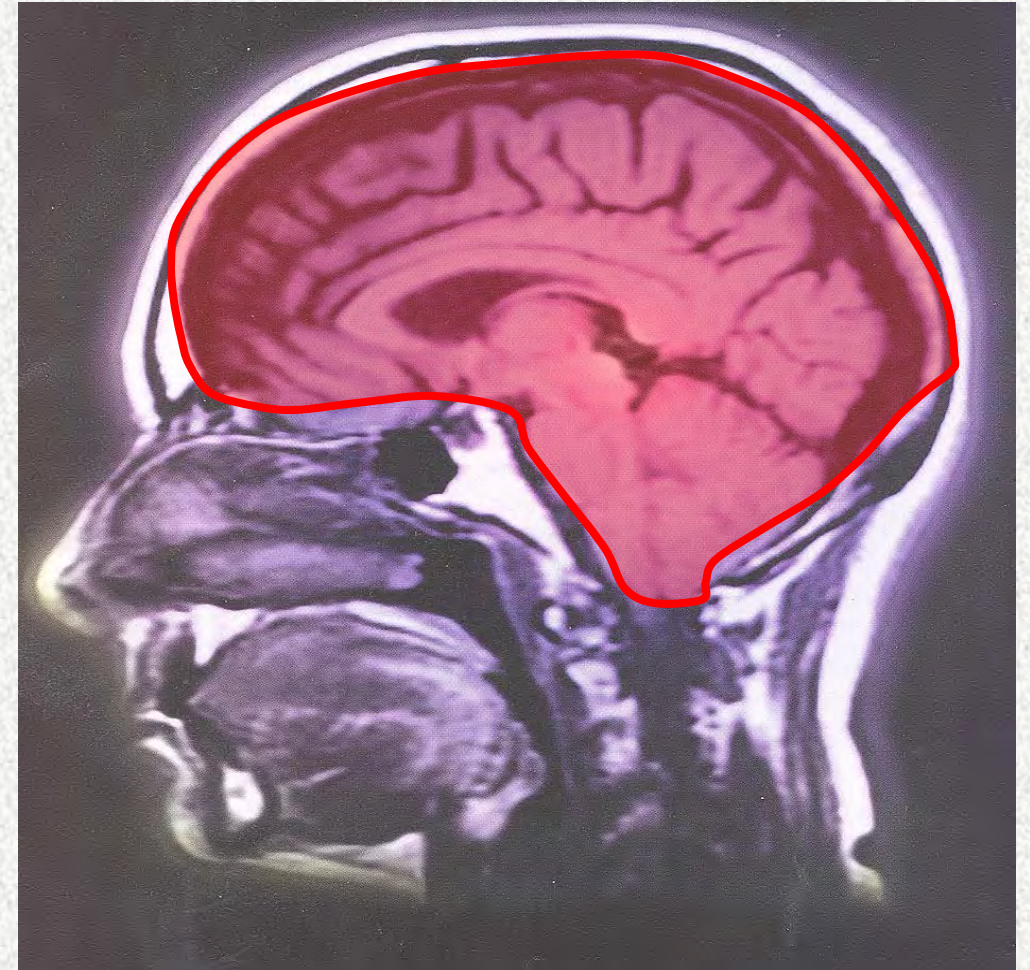
# Early Human Development Emphasizes Brain Growth

- The priority of early human development is the brain.
  - Arrows of a color are identical length, sized to daughter's dimensions
  - Compare Mom and daughter's
    - Arm length
    - Head width
- 60% of the brain's building material is lipid.
  - Uniquely concentrated highly unsaturated fatty acids

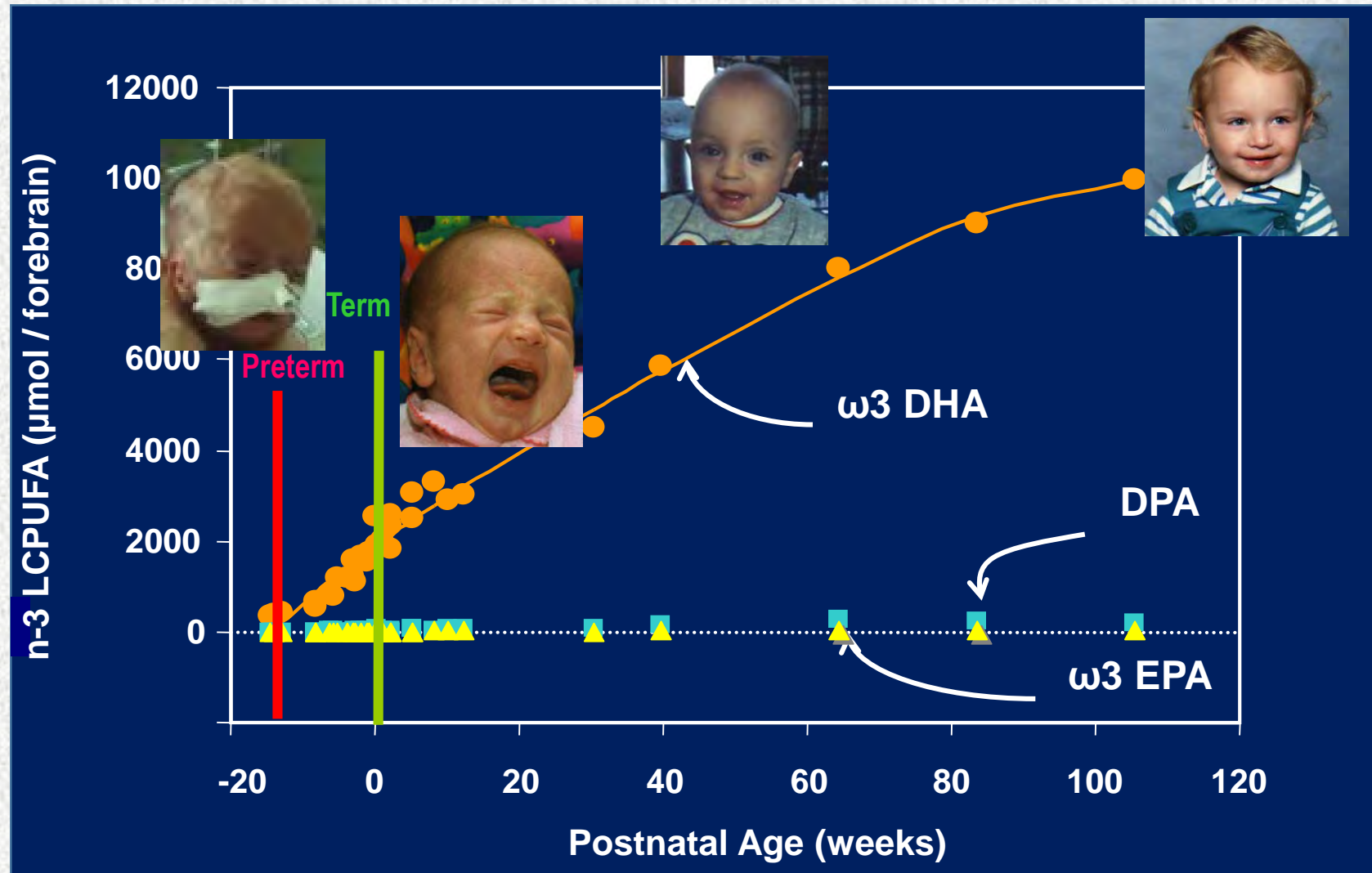
**A mother feeding her kids peanut-based RUTF in Malawi.**

*Photo by Indi Trehan for Mother Jones*

*Which mammal has a greater requirement for components to support its brain?*

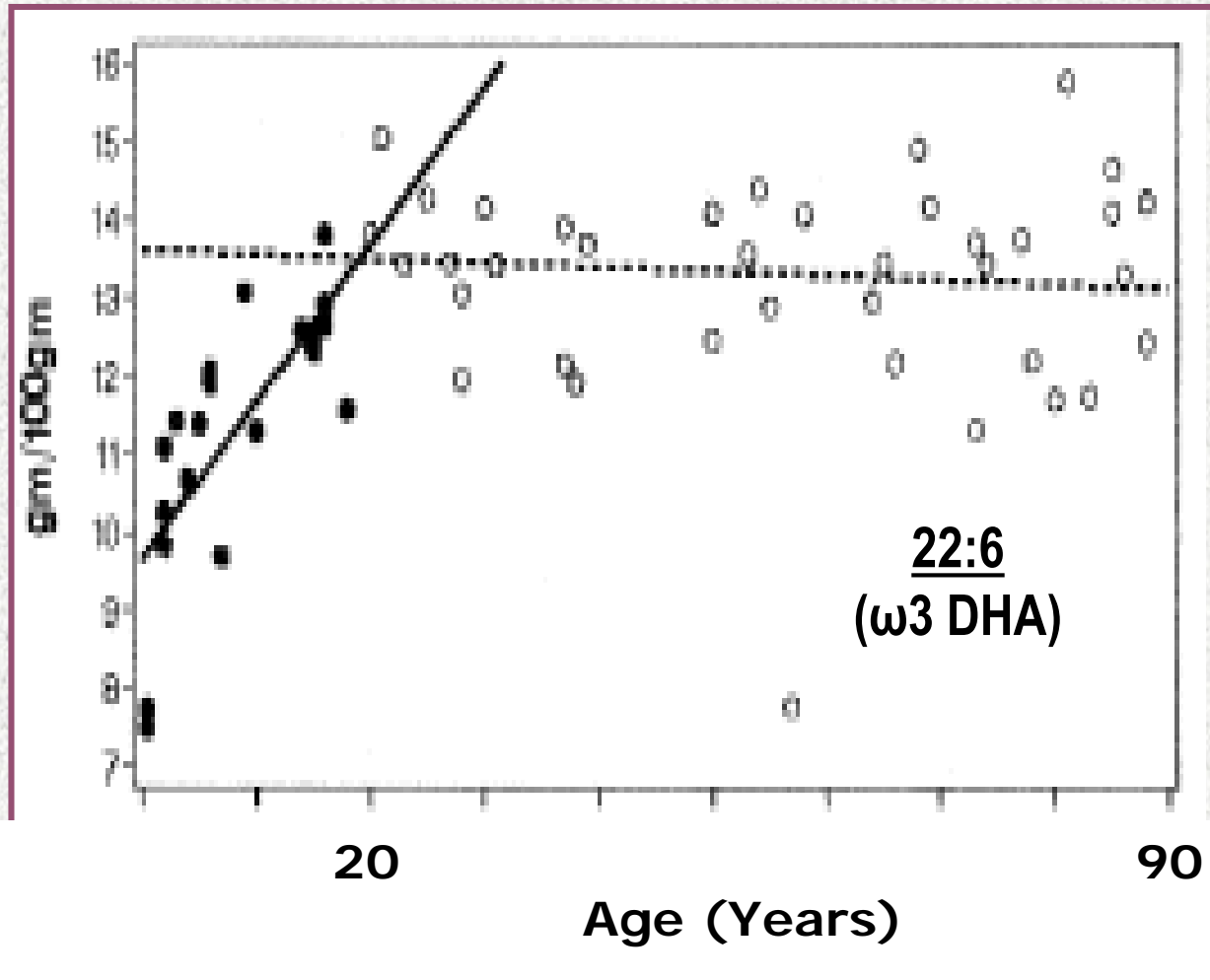


# Omega-3 DHA Accumulates in the Brain Early and Rapidly



- $\omega$ 3 DHA is the only  $\omega$ 3 that accumulates at high levels in the brain.
- The retina, the light detectors in the eye, are similarly rich in  $\omega$ 3 DHA



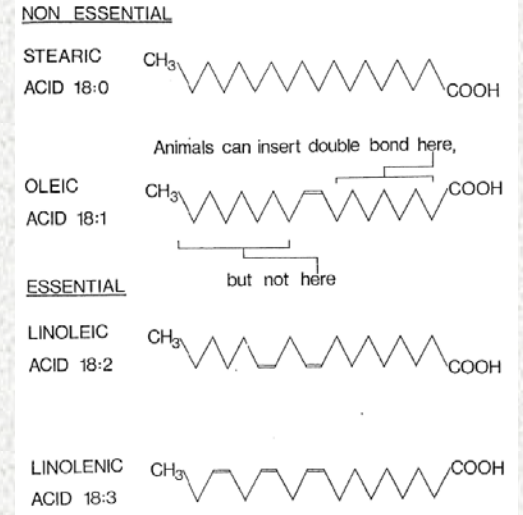
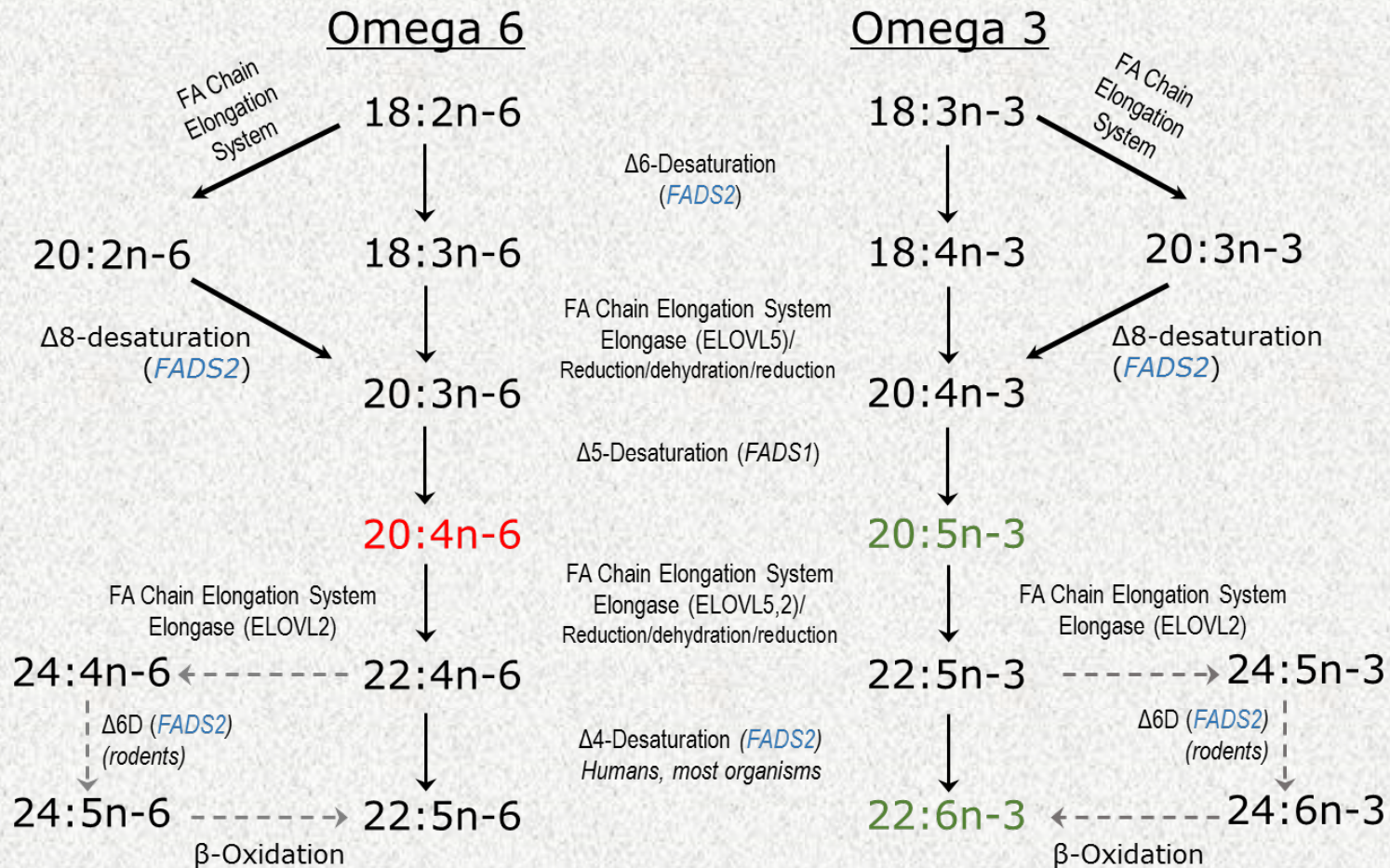


## Cerebral cortex Fatty Acid

- N=58 **humans**, birth to age 88
- $\omega$ 3 DHA
  - rises to age 18
  - Stabilizes to age 88

*Omega-3 is key to the  
BRAIN*

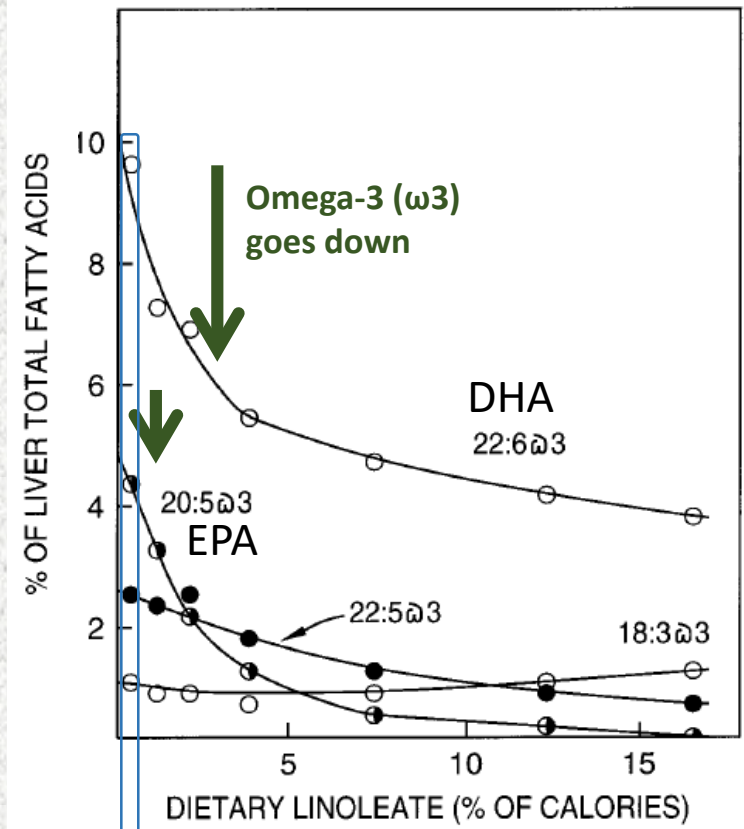
# LCPUFA Endogenous Synthesis



Crawford & Sinclair, 1972

FADS1. 11-20:1 → 7,11-20:2  
 FADS2. 16:0 → 6-16:1

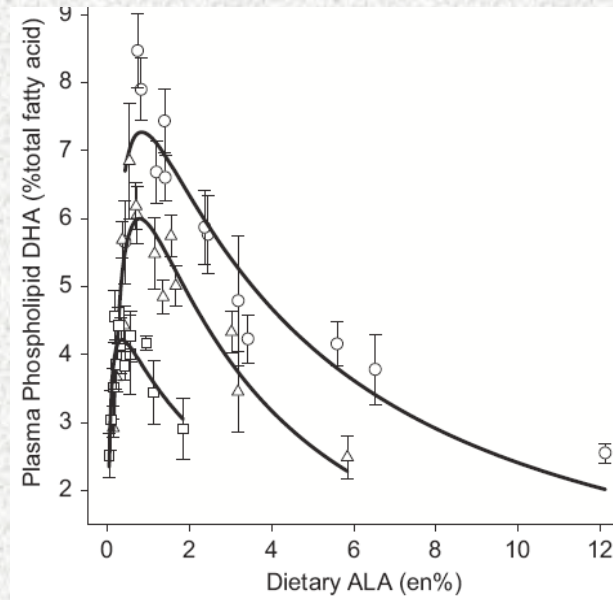
# Diet and Liver Fatty Acid: Greater diet $\omega 6$ LA creates a metabolic demand for $\omega 3$ DHA



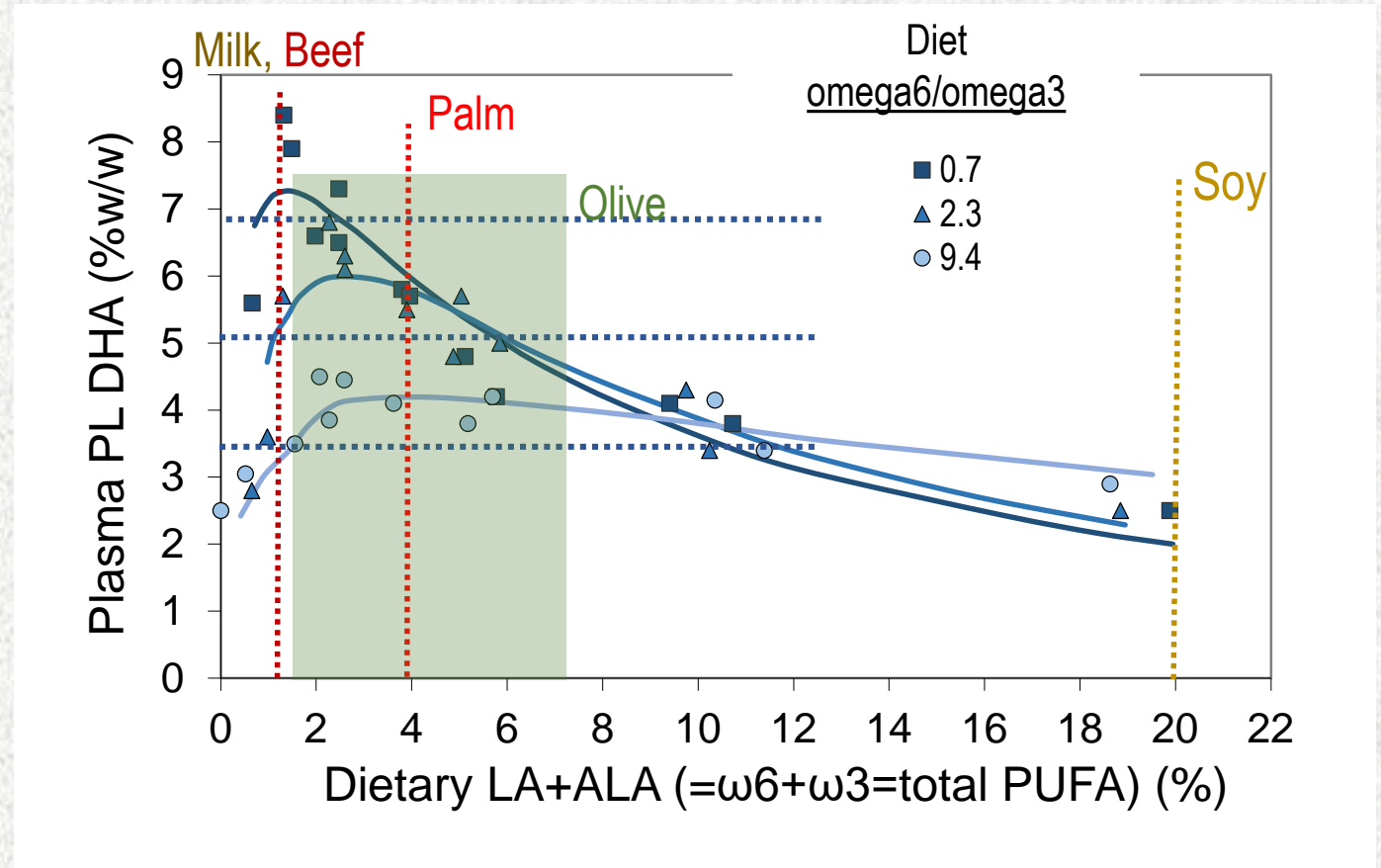
- At low  $\omega 6$  linoleate, DHA (22:6 $\omega 3$ ) and EPA (20:5 $\omega 3$ ) are maximal.
- As omega-6 linoleic acid increases, the omega-3 fatty acids decrease
- To reduce omega-6, replace it with omega-9 = Oleic acid. HI OLEIC !

From 1963! 

# Dietary Control of LCPUFA Synthesis



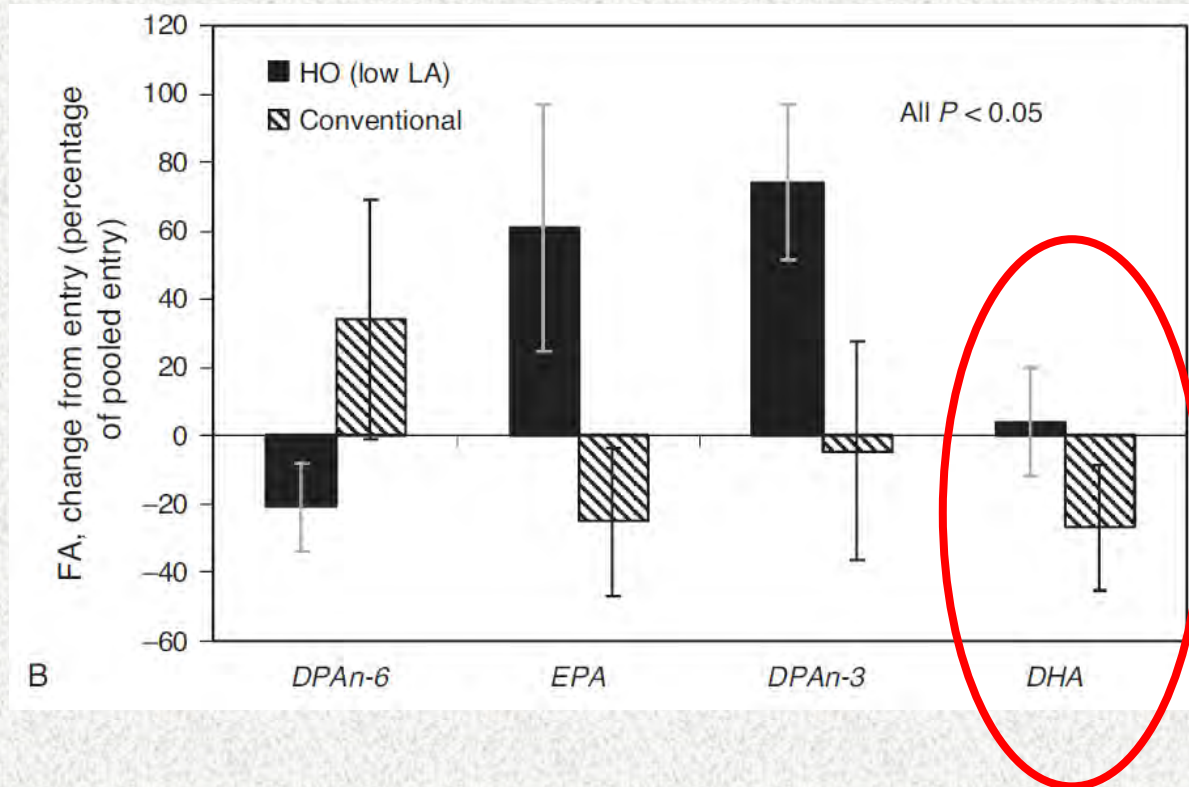
- 54 diets fed to rats for 3 weeks
  - $\omega 6$  LA and  $\omega 3$  ALA \*only\*
  - $\omega 3/ \omega 6$  ratio
  - %energy as fat
- Key outcome is plasma PL DHA because it is most complex and slowest made LCPUFA



18:3 → 18:4 → 20:4 → 20:5 → 22:5 → 22:6 (DHA)



# High Oleic peanuts

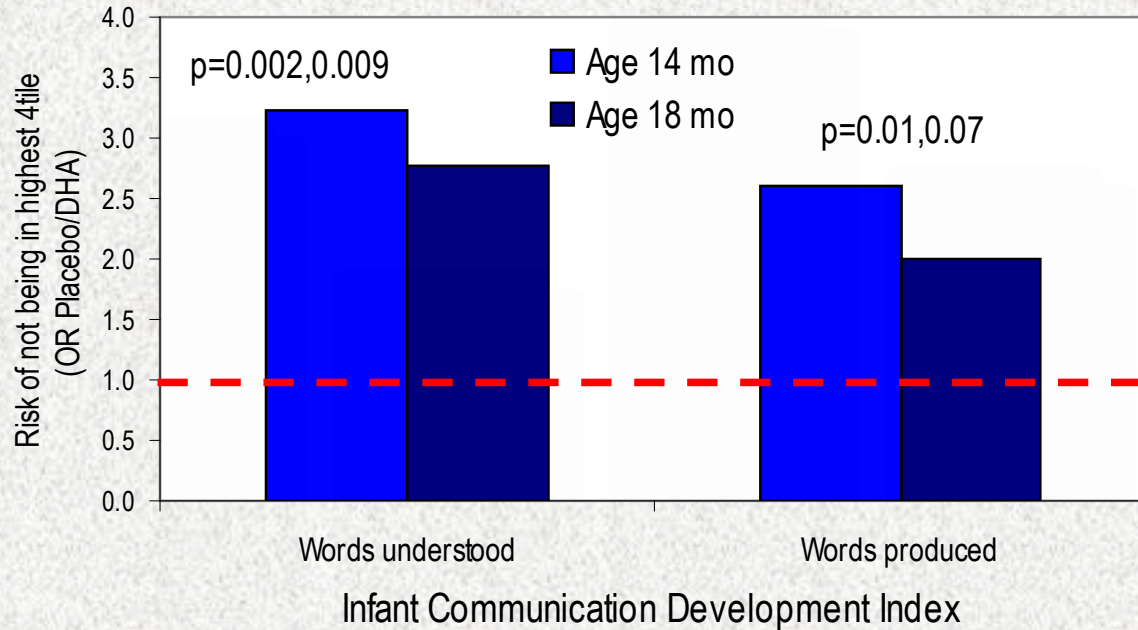


- Severely malnourished children on a high  $\omega 6$  linoleic acid oil experience a precipitous decline (-25%) in circulating DHA in four weeks.
- Reformulated RUTF with lower LA (and higher ALA) enables maintenance of circulating DHA.
  - Endogenous synthesis keeps up with demand.
- Note: Zero diet DHA.
- Driving LA lower would increase DHA according to the animal data.



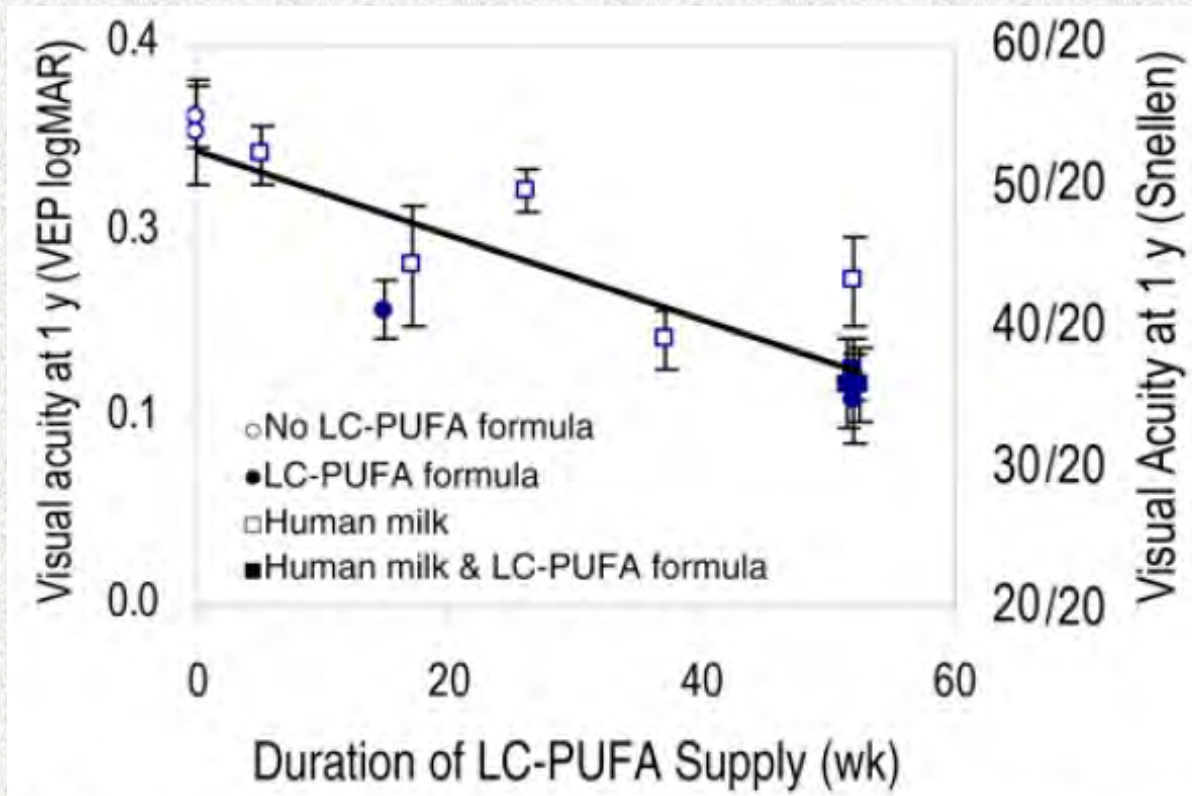
*Does  $\omega_3$  DHA improve child  
development?*

# Childhood Development Outcomes



- Pregnant moms supplemented with  $\omega$ 3 DHA or placebo.
- Placebo toddlers (14 and 18 months) are at **higher risk of not being the highest quartile** for
  - Words understood
  - Words produced
- ***In other words, toddler whose moms did not receive  $\omega$ 3 DHA were much less likely to excel.***
- *What big problem might they not solve?*

# Duration of DHA intake causally related to enhanced neural development



Better vision (& brain)

- 243 infants enrolled in 4 different studies show.
- Visual acuity in infants is a measure of **neural development**.
- Greater duration of DHA intake, better visual acuity/neural development at 1 year of age
- Effect is independent of source (breastmilk or formula).

Brenna, JT. Long-chain polyunsaturated fatty acids and the preterm infant: a case study in developmentally sensitive nutrient needs in the United States. *Am J Clin Nutr.* 2016 Feb; 103(2): 606S–615S. PMID: 26791188

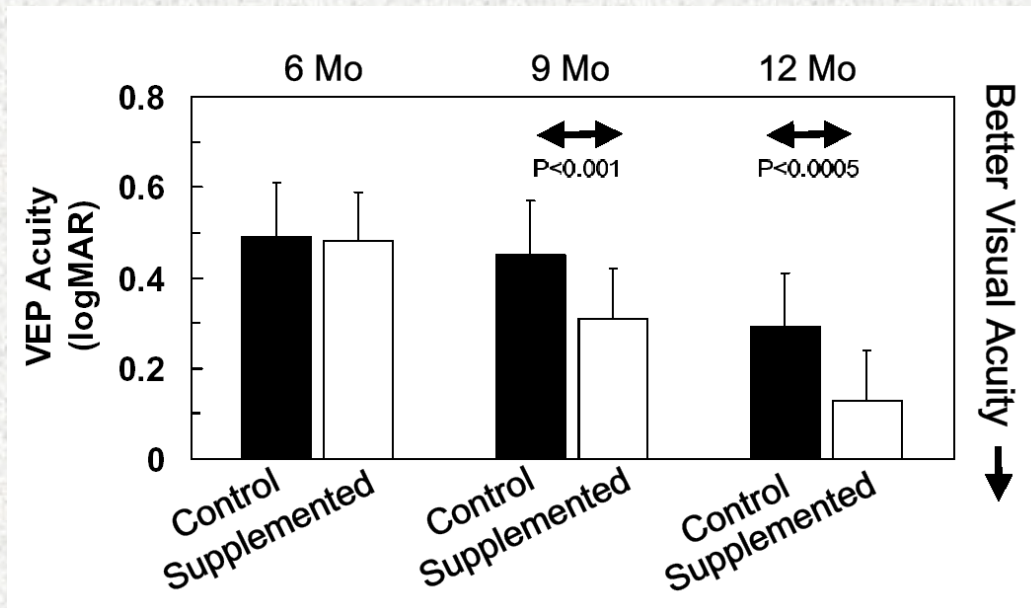
Morale SE, Hoffman DR, Castañeda YS, Wheaton DH, Burns RA, Birch EE. Duration of long-chain polyunsaturated fatty acids availability in the diet and visual acuity. *Early Hum Dev.* 2005 Feb;81(2):197-203.

# DHA Containing Infant Foods Accelerate Visional (and therefore neural) Development

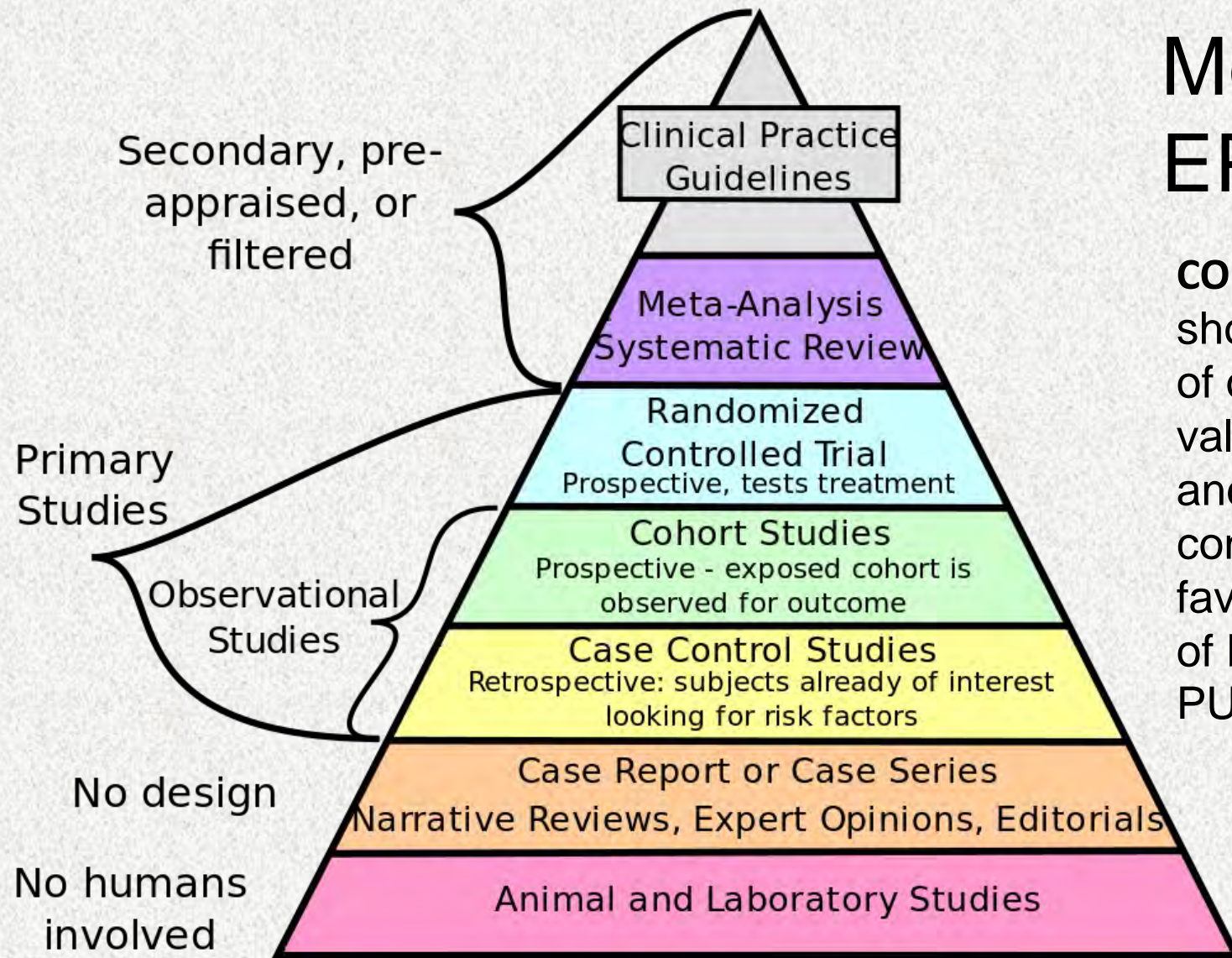


← **Regular**  
← **DHA**

- Randomized trial of DHA-containing baby food fed to **breastfed** infants from about 6 months to 12 months.
- Visual acuity improved such that DHA supplemented infants could see **1.5 lines farther down the eye chart** than unsupplemented infants.



# Meta-analyses of RCTs, EPA & depression



**CONCLUSIONS:** Although our meta-analysis showed significant antidepressant efficacy of omega-3 PUFAs, it is still premature to validate this finding due to publication bias and heterogeneity. More large-scale, well-controlled trials are needed to find out the favorable target subjects, therapeutic dose of EPA, and the composition of omega-3 PUFAs in treating depression.

# EPA for Depression

## Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression\*

Brian Hallahan, Timothy Ryan, Joseph R. Hibbeln, Ivan T. Murray, Shauna Glynn, Christopher E. Ramsden, John Paul SanGiovanni and John M. Davis

Among participants with diagnosed depression, EPA-predominant formulations (450% EPA) demonstrated clinical benefits compared with placebo ..., whereas DHA-predominant formulations (450% DHA) did not. EPA failed to prevent depressive symptoms among populations not diagnosed for depression.

## Meta-Analysis of the Effects of Eicosapentaenoic Acid (EPA) in Clinical Trials in Depression

M. Elizabeth Sublette, MD, PhD; Steven P. Ellis, PhD; Amy L. Geant, BA; and J. John Mann, MD

**Conclusions:** Supplements containing EPA ≥ 60% of total EPA + DHA, in a dose range of 200 to 2,200 mg/d of EPA in excess of DHA, were effective against primary depression. Translational studies are needed to determine the mechanisms of EPA's therapeutic benefit.

*J Clin Psychiatry* 2011;72(12):1577–1584

Journal of the American College of Nutrition, Vol. 28, No. 5, 525–542 (2009)

Review

## EPA but Not DHA Appears To Be Responsible for the Efficacy of Omega-3 Long Chain Polyunsaturated Fatty Acid Supplementation in Depression: Evidence from a Meta-Analysis of Randomized Controlled Trials

Julian G. Martins, MA, MBBS

symptoms of depression were significantly reduced in 13 studies using supplements containing greater than 50% EPA...and in 8 studies using pure ethyl-EPA.

## A Meta-Analytic Review of Double-Blind, Placebo-Controlled Trials of Antidepressant Efficacy of Omega-3 Fatty Acids

Pao-Yen Lin, M.D., Ph.D., and Kuan-Pin Su, M.D.

**Conclusions:** Although our meta-analysis showed significant antidepressant efficacy of omega-3 PUFAs, it is still premature to validate this finding due to publication bias and heterogeneity. More large-scale, well-controlled trials are needed to find out the favorable target subjects, therapeutic dose of EPA, and the composition of omega-3 PUFAs in treating depression. (*J Clin Psychiatry* 2007;68:1056–1061)

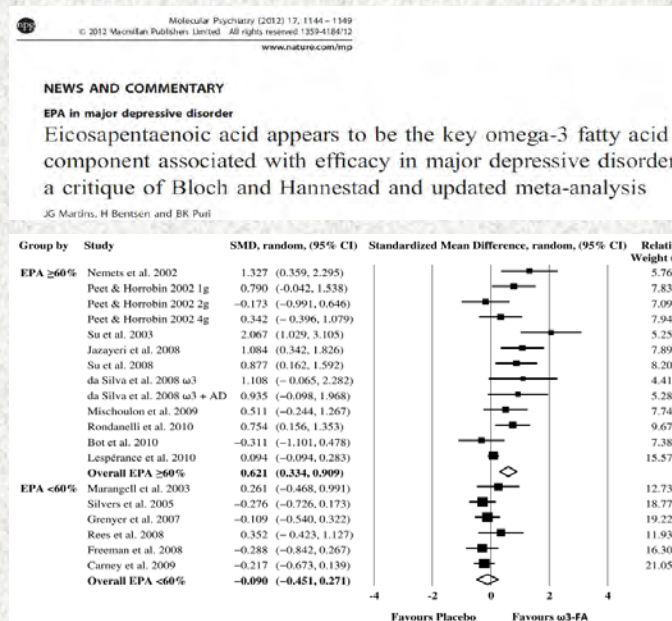
2016



## Role of Omega-3 Fatty Acids in the Treatment of Depressive Disorders: A Comprehensive Meta-Analysis of Randomized Clinical Trials

Giuseppe Grosso<sup>1\*</sup>, Andrzej Pajak<sup>2</sup>, Stefano Marventano<sup>3</sup>, Sabrina Castellano<sup>1</sup>, Fabio Galvano<sup>1</sup>, Claudio Bucolo<sup>1</sup>, Filippo Drago<sup>1</sup>, Filippo Caraci<sup>4,5</sup>

**Conclusions:** The use of omega-3 PUFA is effective in patients with diagnosis of MDD and on depressive patients without diagnosis of MDD.



OPEN

Citation: *Transl Psychiatry* (2016) 6, e756; doi:10.1038/tp.2016.29

www.nature.com/tp

ORIGINAL ARTICLE

## Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder

RJT Mocking<sup>1</sup>, I Harmsen<sup>1</sup>, J Assies<sup>1</sup>, MWJ Koeter<sup>1</sup>, HG Ruhe<sup>1,2,5</sup> and AH Schene<sup>3,4,5</sup>

In conclusion, present meta-analysis suggested a beneficial overall effect of omega-3 PUFA supplementation in MDD patients, especially for higher doses of EPA and in participants taking antidepressants.

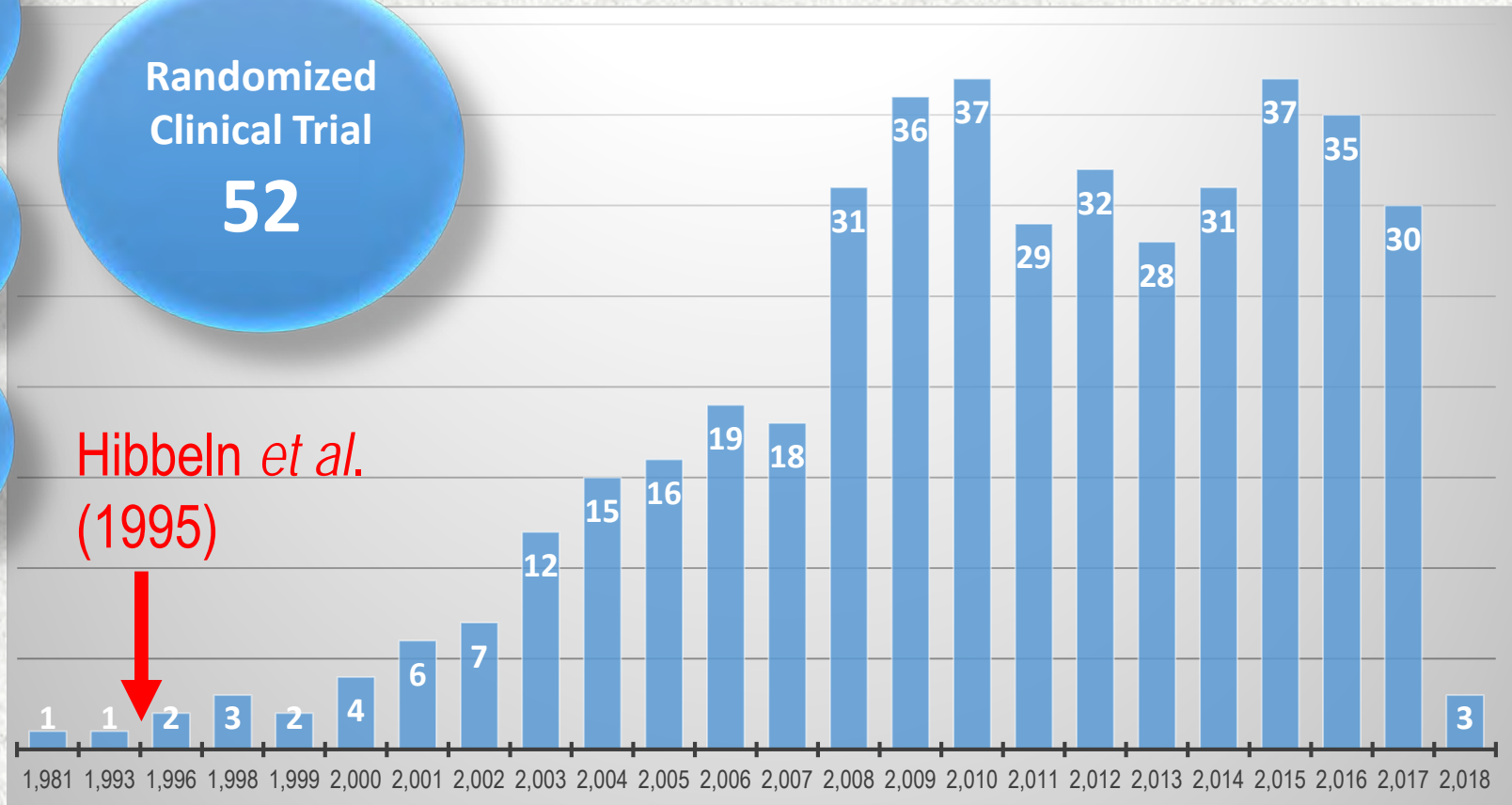
# Publications on Omega-3 Fatty Acids and Major Depression, as of early 2018

Ecological  
54

Case-Control  
17

Meta-Analysis  
6

Randomized  
Clinical Trial  
52



Hibbeln *et al.*  
(1995)

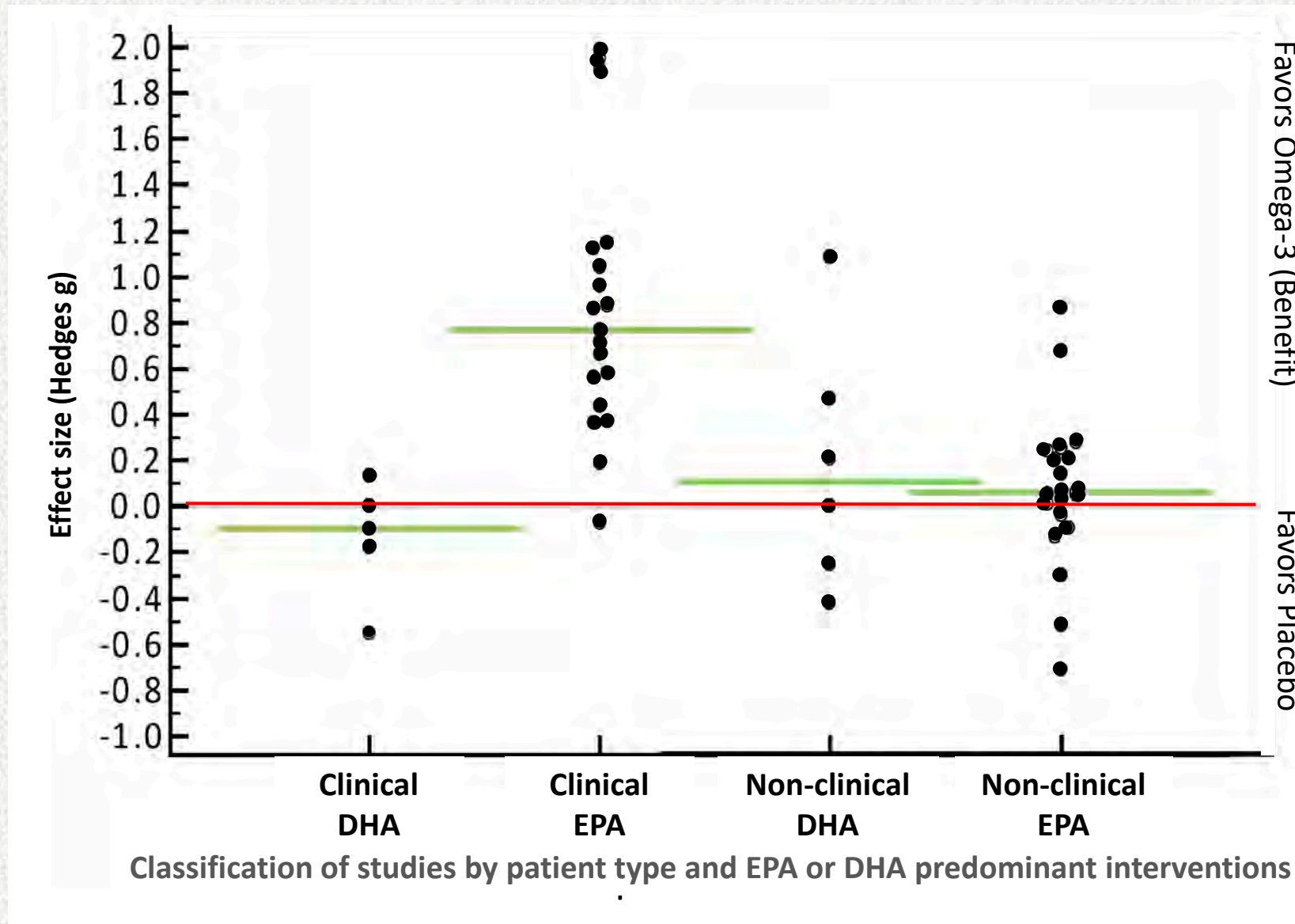
- Interest in adult nutritional neuroscience started in the mid-1990s
- Depression is among the most costly maladies in the modern medicine



Dr Joseph R. Hibbeln, MD, Captain, US Public Health Service,  
Principal Investigator, NIH

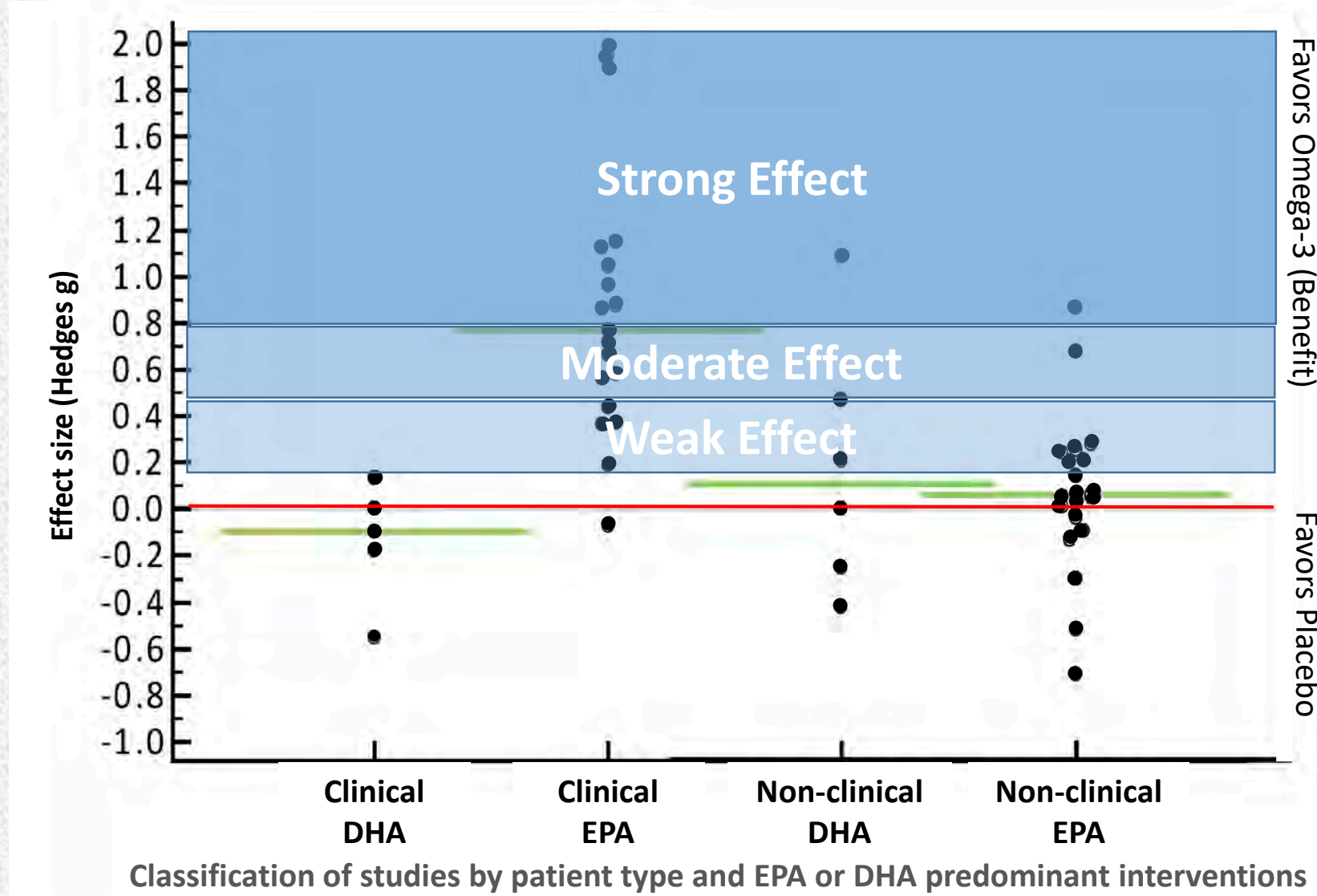


# Effect Sizes of Studies of Omega-3 Fatty Acids for Major Depression



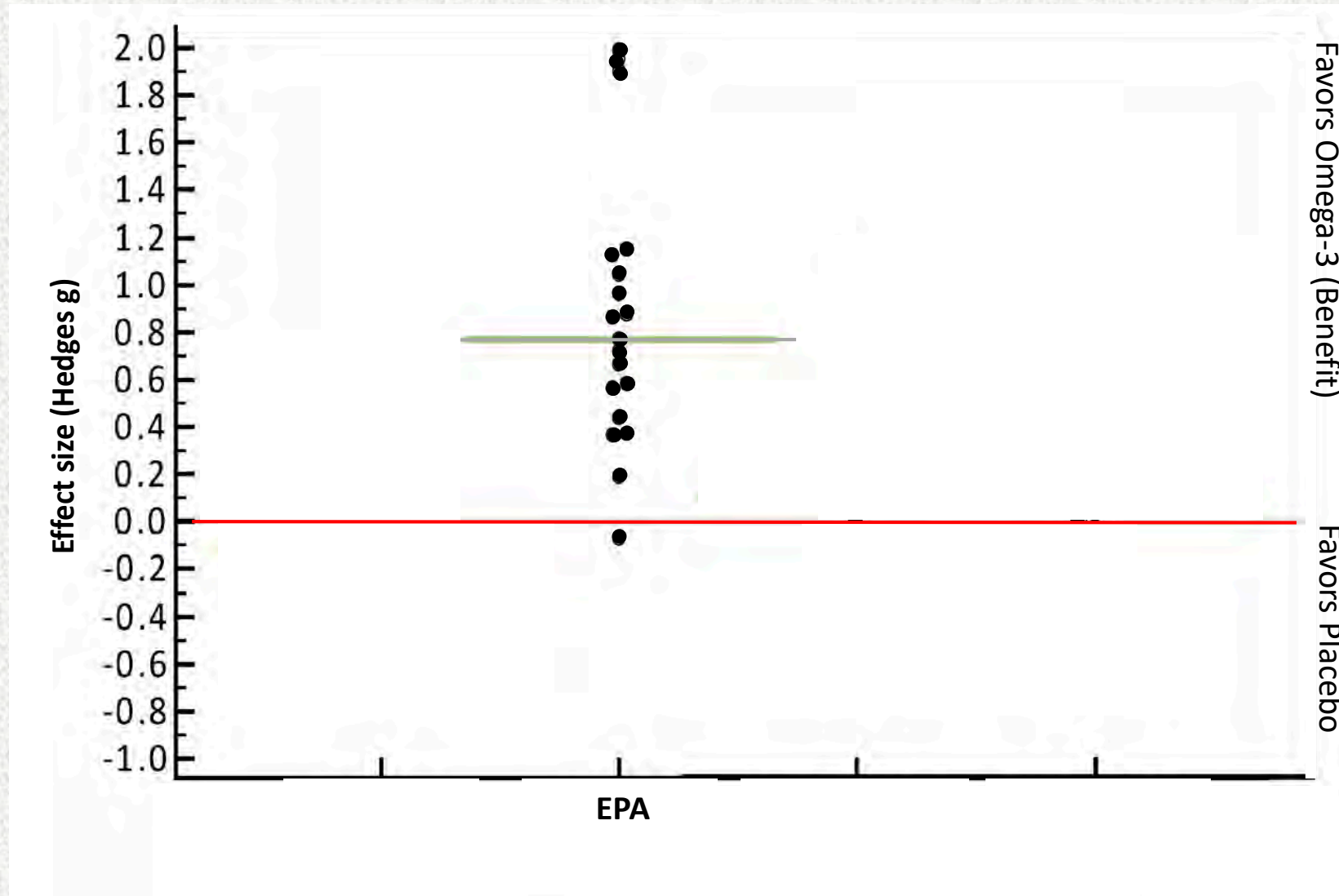
Slide courtesy of  
JR Hibbeln and  
JP San Giovanni

# Effect Sizes of Studies of Omega-3 Fatty Acids for Major Depression



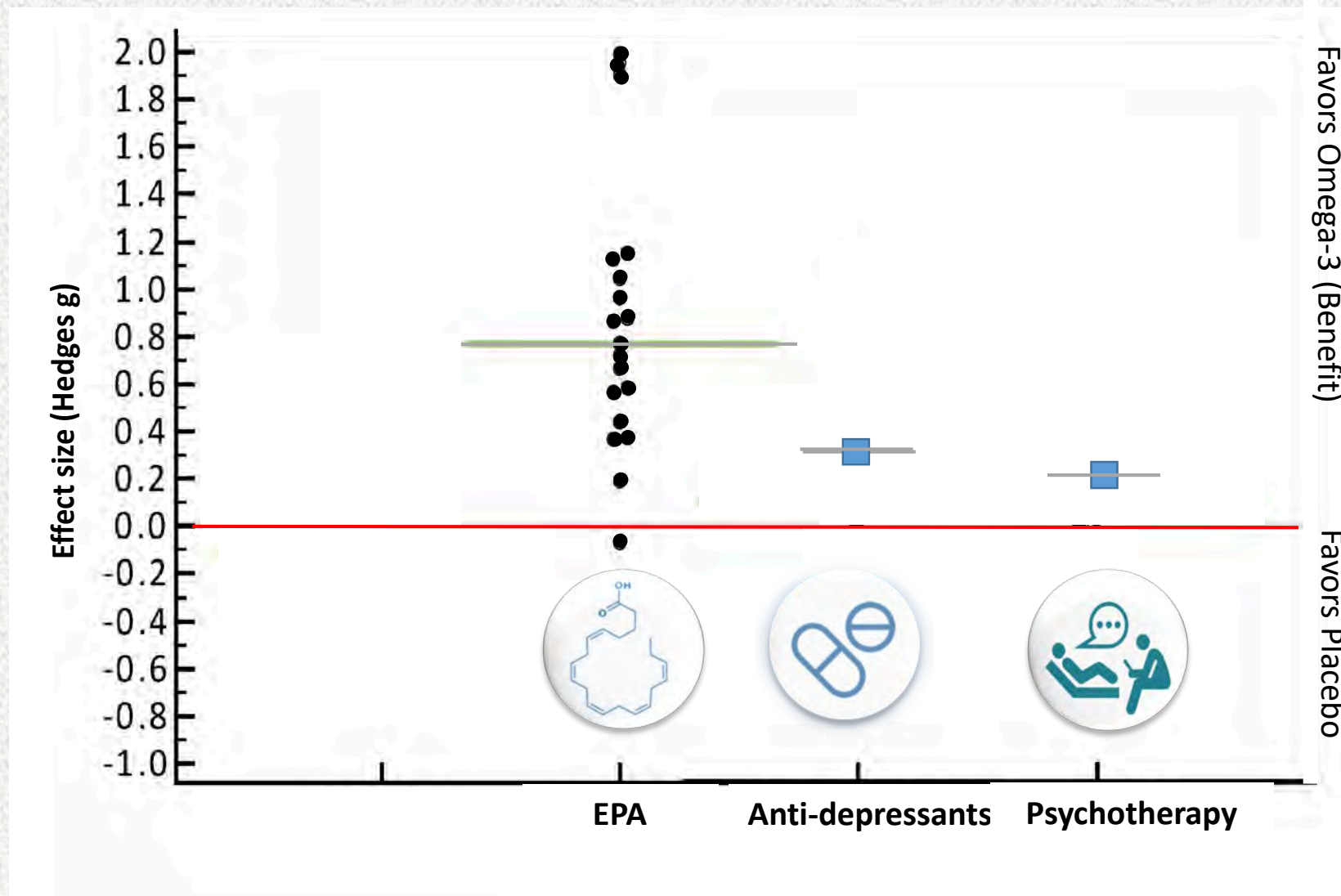
Slide courtesy of  
JR Hibbeln and  
JP San Giovanni

# Effect Sizes of Studies of Omega-3 Fatty Acids for Major Depression



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JP San Giovanni

# Effect Sizes of Therapies for Clinically Significant Major Depression



Slide courtesy of  
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JP San Giovanni

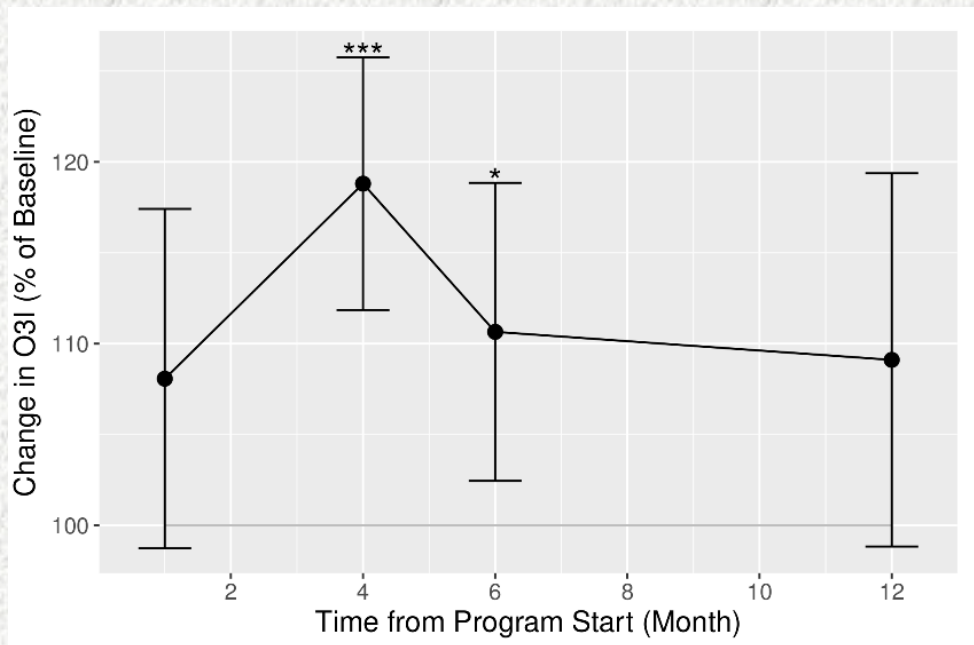
# Seafood Facts

# Eating Heart Healthy program



*“I wish I was taught the importance of good nutrition, especially seafood nutrition, for my children’s brain and heart health. After attending Seafood Nutrition Partnership’s nutrition education workshops in our community I now make sure my grandson eats seafood at least twice a week---and he loves it!”*

Ms. Jacquie B., EHH Program Graduate, Resident of Roxbury Tenants of Harvard

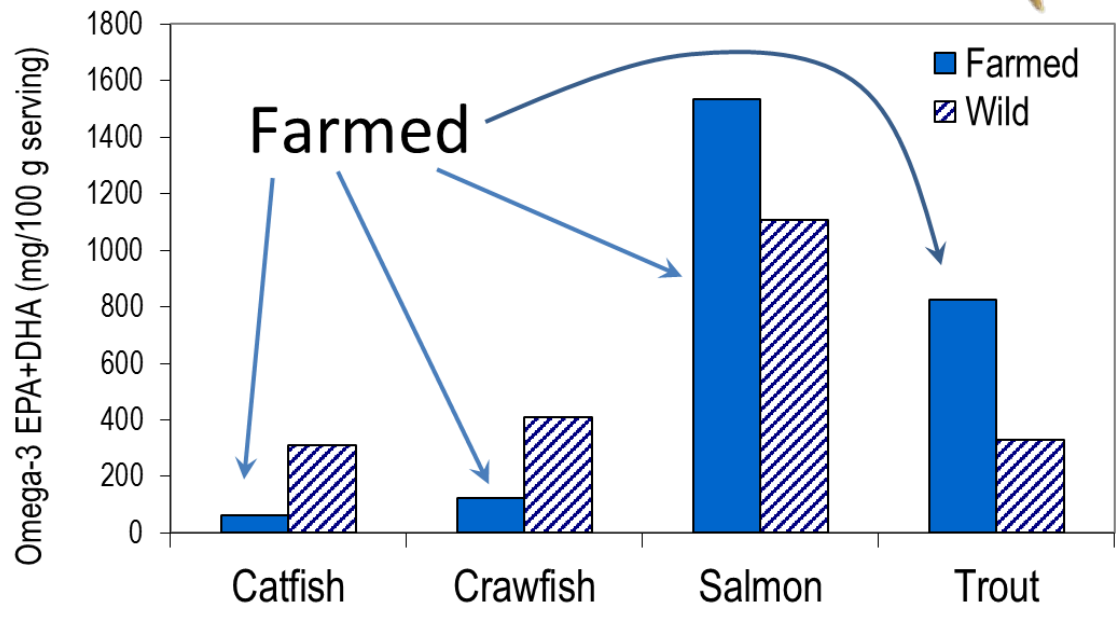
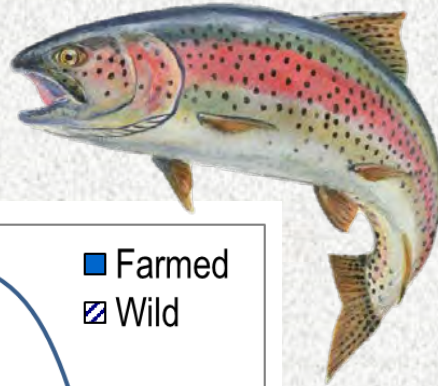


- Omega 3 Index (O3I) increased significantly at 4 months
  - O3I is a long term measure of exposure (like HbA1c for diabetics)
  - Shows they started buying and preparing seafood up to at least 4 months and then trailed off – let’s give them a booster at 4 months?

# Farm vs. Wild Seafood: Omega-3 EPA and DHA



Scientific Report of the  
2015 Dietary Guidelines Advisory Committee



- Some farmed seafood is much lower in omega-3 than wild
  - Even catfish and crawfish (fresh water) with relatively low omega-3 can deliver significant amounts because they are consumed frequently
- Trout & salmon
  - Farmed is higher in DHA+EPA



**Figure 1.** Comparison of EPA and DHA in Seafood from USDA-ARS National Nutrient Database, Release 26 (\*) and from 2014 survey (Cladis *et al.*, 2014)



Scientific Report of the  
2015 Dietary Guidelines Advisory Committee

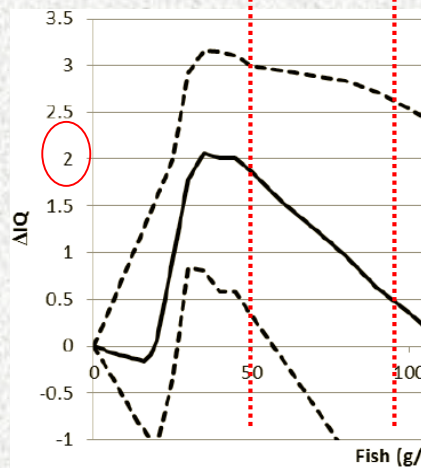
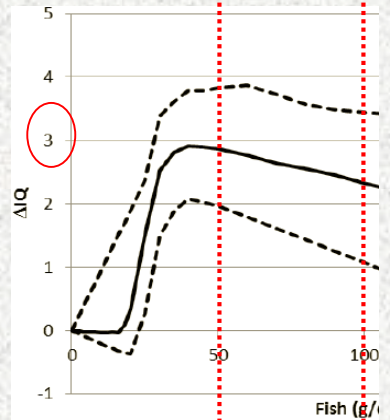
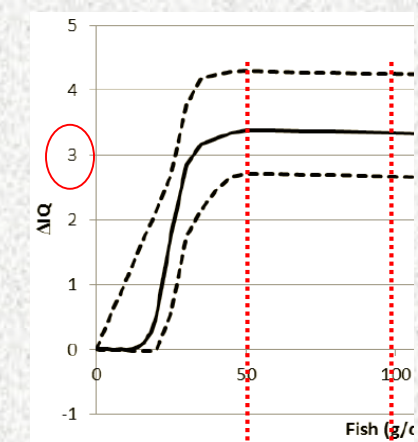
*“The U.S. population should be encouraged to eat a wide variety of seafood that can be wild caught or farmed, as they are nutrient-dense foods that are uniquely rich sources of healthy fatty acids. It should be noted that low-trophic farm-raised seafood, such as catfish and crayfish, have lower EPA and DHA levels than do wild-caught. **Nutrient profiles in ... farmed species should ... preserve nutrients similar to those of wild-caught seafood of the same species.**”*



# Net Effects on IQ

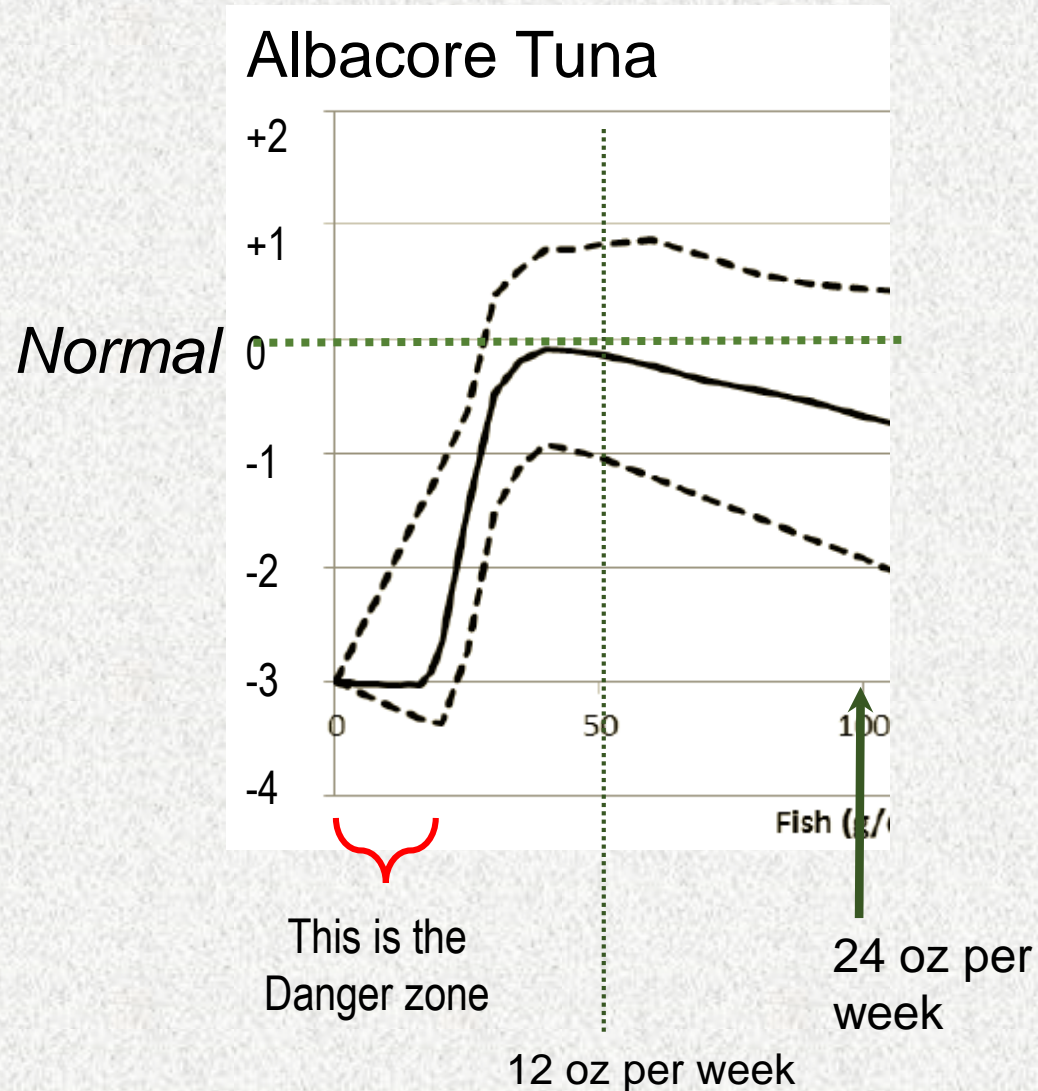
Should albacore tuna be singled out as being limited to 6 oz per week when the recommendation is for 12 oz per week of a variety of fish?

- Assumes consumption of all one fish (no variety)
- Fig D-4, Salmon (mean and 95% CI); Max benefit +3.3 IQ points
- Fig D-6, Albacore Tuna; Max benefit about +3 IQ points
- Fig D-7, Shark; Max benefit +2 IQ points
- Mean increase in 6-9 year old child IQ points from maternal intake during pregnancy.
- Dotted vertical lines
  - 12 oz per week = 2x 6 oz cans; ~50 g/d (48.6 g/d)
  - 24 oz per week = 4x 6 oz cans; ~100 g/d



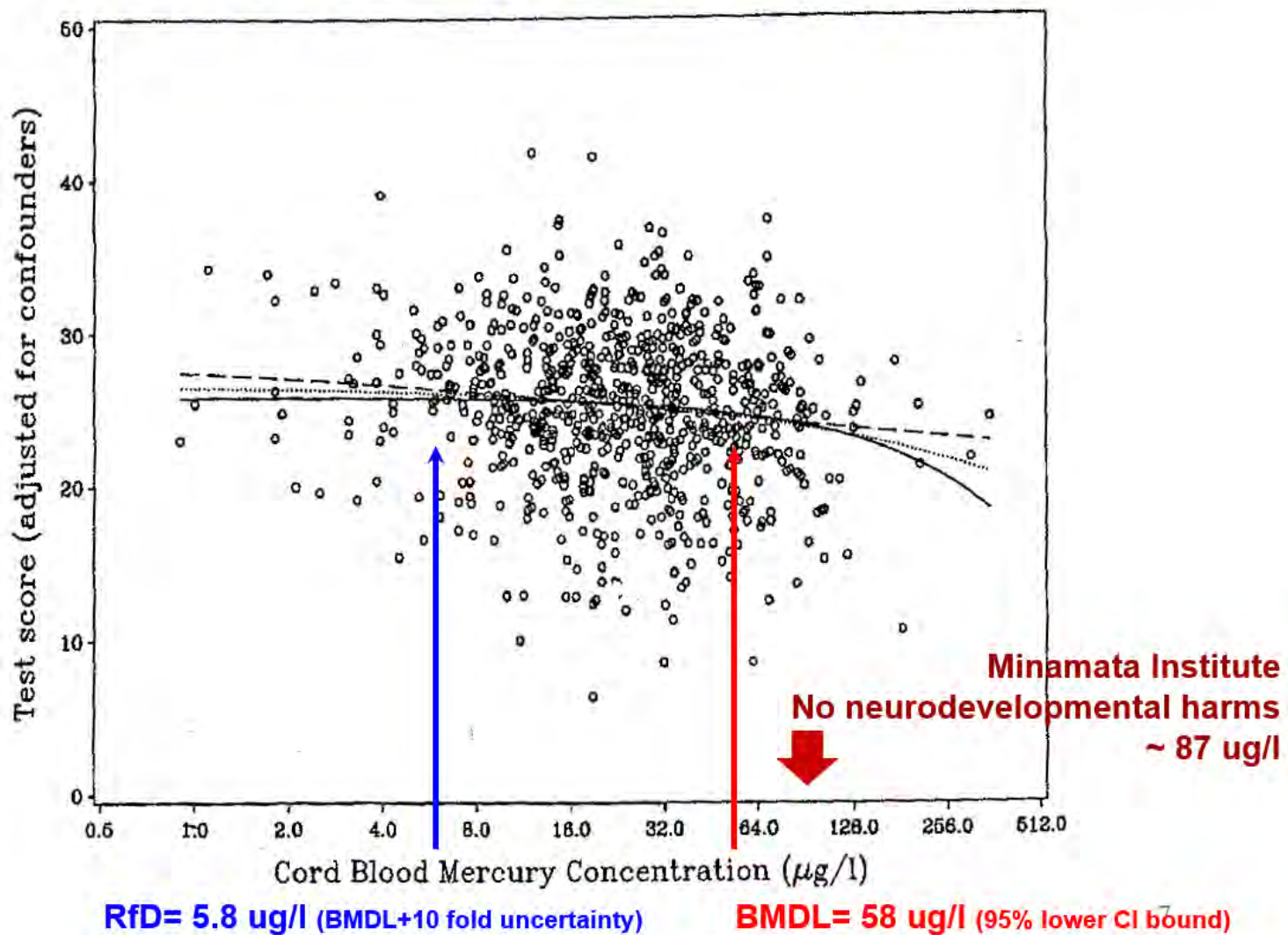
12 24 ounces per week

# Another View of Net Effects on IQ



- Normal should be defined as reaching maximal potential under normal nutritional conditions
- Normal is achieved, in this modeling, at about 10-11 oz of albacore tuna per day
- Anything less than normal is abnormal.
- In this scenario, the highly protective position is to recommend more 12 ounces or more of fish, not “up to 12 oz”.
  - *6 oz is near the upper bound of the danger zone.*

## Relationship between cord blood mercury and verbal development Faroe Islands study – the basis of the RfD



Toxicological Effects of Methyl Mercury, National Research Council 2000, page 296

# Key Points: Takeaways

- Dietary Guidelines for Americans 2015-2020 recommend more seafood consumption
- Brains are omega-3 organs and must be fed the right balance of PUFA to support optimal development
  - Kids who have omega-3 DHA in prenatal or postnatal life see better, and think better, than those who do not
  - Excess omega-6 linoleic acid suppresses omega-3 and creates an enhanced demand that can double requirements. That enhanced demand can more than double requirements. High oleic oils (olive, avocado, U.S. sunflower, others) mitigate against high intake of high linoleic soy and other oils.
- High level evidence supports consumption of EPA for moderation of major diagnosed depression = MDD is, at least in part, an EPA deficiency condition.
- Eat a variety of seafood, it is safe and good for you.

