Omega-3 Fatty Acid Deficiencies in Psychiatric Disorders

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Hierarchy for Clinical Efficacy in Evidence Based Medicine

- Hypothesis
- Epidemiological association (Ecological)
- Direct case based observational associations
- Plausible biological mechanism
- Open (non-blinded) intervention trials
- Randomized masked placebo controlled trials
- Large scale, multi-center placebo controlled trials
- Meta-analysis, weighted analysis of efficacy

- Treatment recommendations

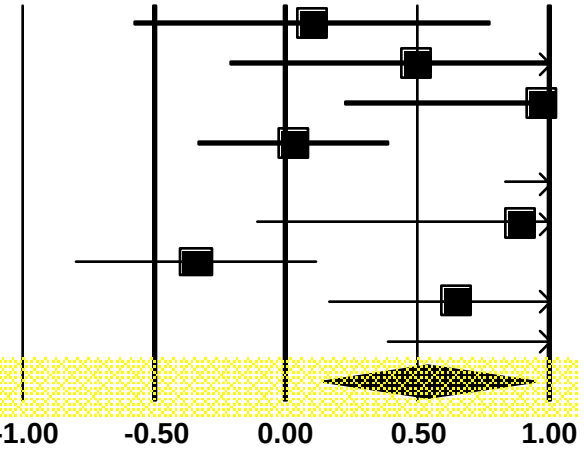
Meta-analysis of omega-3's on depressive symptoms, randomized placebo controlled trials, effect size = 0.54, p<0.008

Omega-3 EFA in Affective Disorders

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Marangell	0.096	0.346	0.120	-0.582	0.774	0.277	0.782
Peet	0.496	0.362	0.131	-0.214	1.205	1.370	0.171
stoll	0.974	0.386	0.149	0.217	1.730	2.523	0.012
Keck	0.030	0.187	0.035	-0.337	0.396	0.159	0.873
Su	1.887	0.542	0.293	0.826	2.949	3.485	0.000
Nemets	0.892	0.512	0.263	-0.113	1.896	1.740	0.082
Silvers	-0.342	0.234	0.055	-0.799	0.116	-1.462	0.144
Frangou	0.645	0.245	0.060	0.165	1.126	2.630	0.009
Hallahan	1.020	0.327	0.107	0.379	1.660	3.120	0.002
	0.538	0.203	0.041	0.140	0.936	2.646	0.008

Statistics for each study

Hedges's g and 95% CI



Eff ect Size g, SE, Variance 95% CI Z and P (Best Case)

Freeman M, Hibbeln JR, Davis JM et al.
American Psychiatric Associations treatment recommendations for omega-3 fatty acids in psychiatric disorders. J Clin Psychiatry 2006

How much EPA and DHA should I eat each day?

Calculation of daily intakes based on RDA criteria to prevent deficiencies.

Use of RDA criteria for estimating LC-omega-3's

Recommended Dietary Allowance (RDA): the average daily dietary nutrient intake level sufficient to meet the nutrient requirement of nearly all (97 to 98 %) healthy individuals in a particular life stage and gender group.

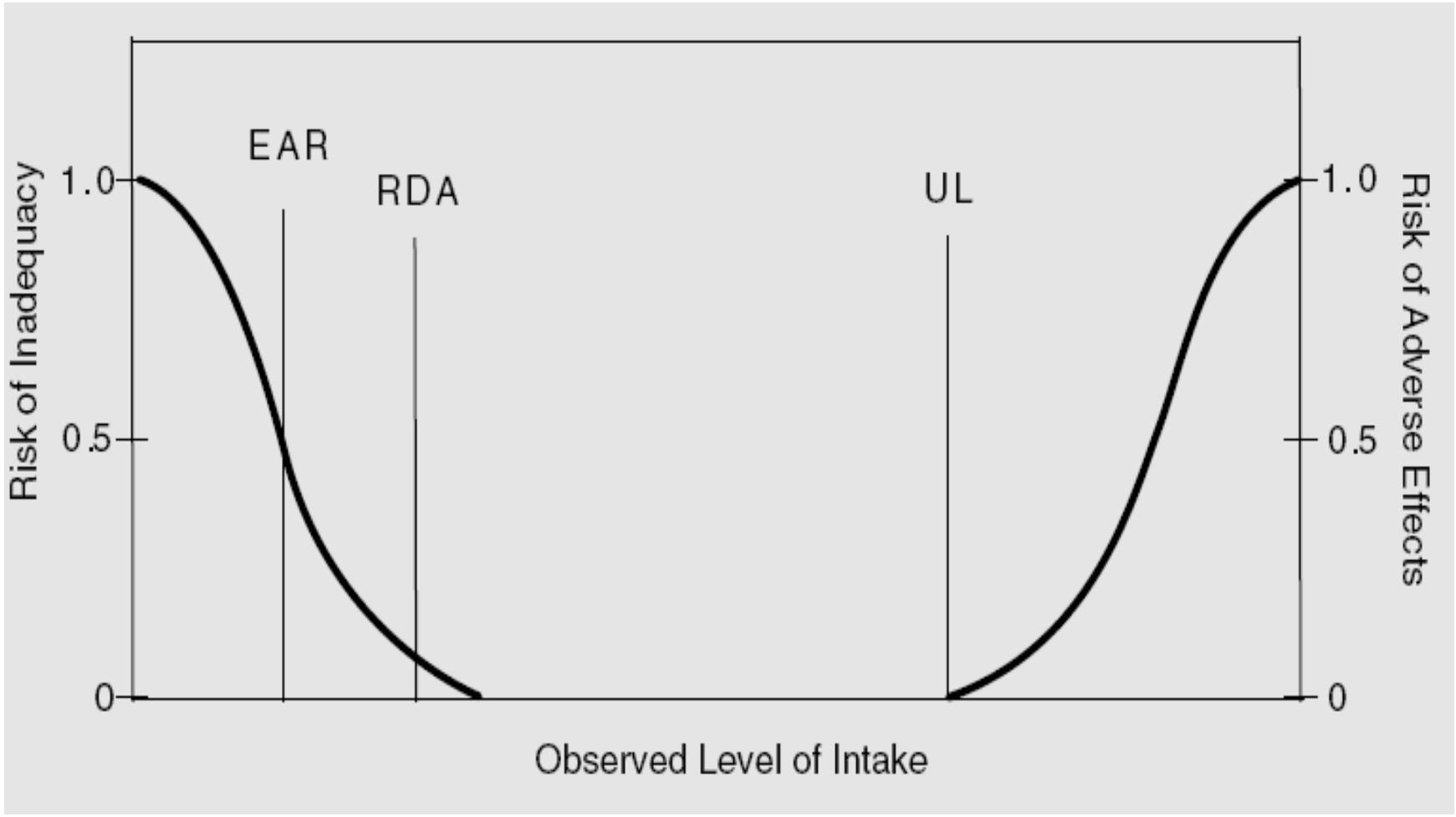
1. Requires a pathological condition resulting from nutrient deficiency.
(Here chronic, cardiovascular psychiatric illnesses)

2. Requires population based dose response data.
(Here cross-national ecological data)

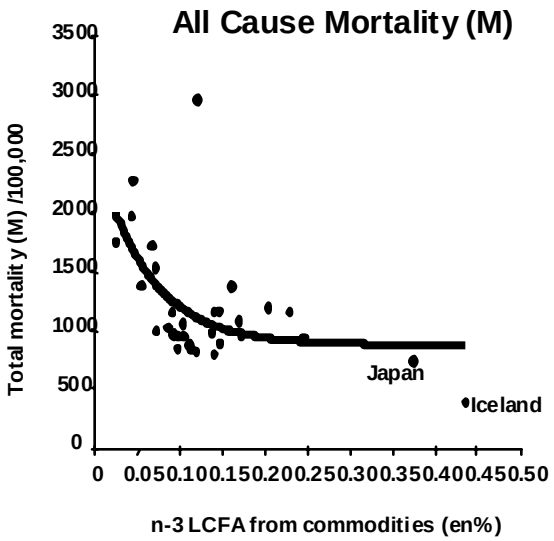
3. Tissue compositions considered.

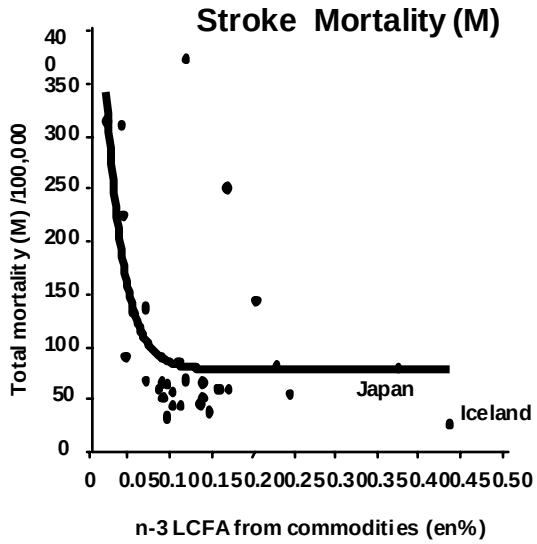
4. Requires estimation of upper level of benefit.
(Here we do not know if the absence of depression or aggression is the upper level of benefit or if further improvements of happiness are possible)

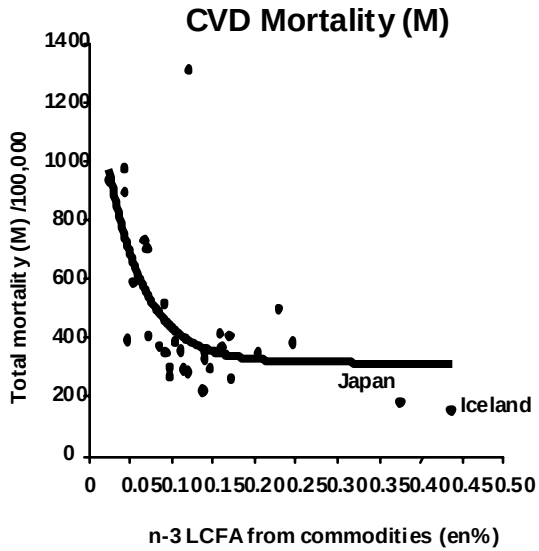
Dietary Reference Intakes: Guiding Principles for Nutrition Labeling and Fortification Committee on Use of Dietary Reference Intakes in Nutrition Labeling. National Academies Press, 2003

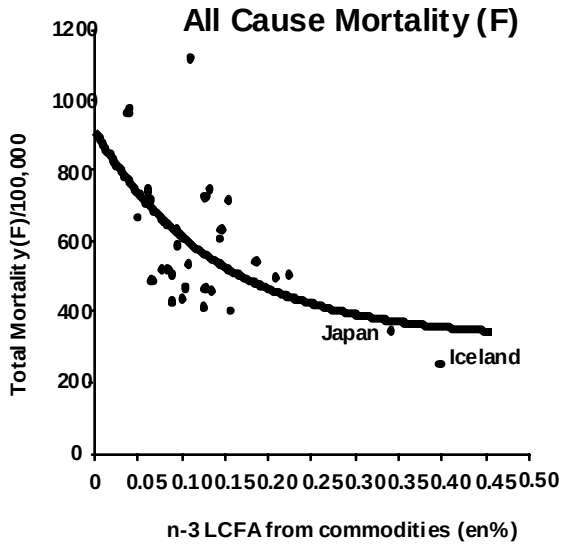


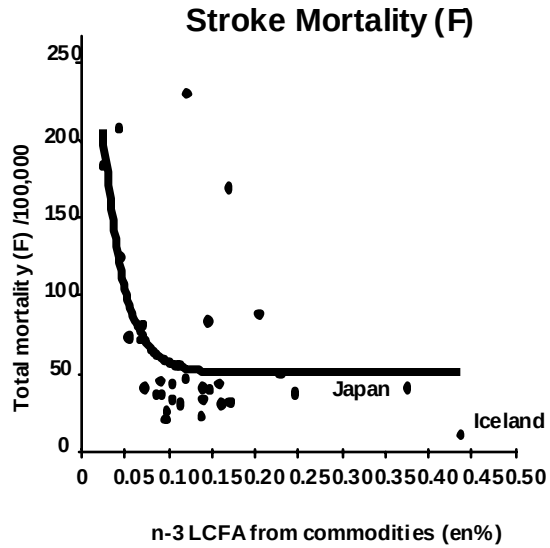
Dietary Reference Intakes: Guiding Principles for Nutrition Labeling and Fortification Committee on Use of Dietary Reference Intakes in Nutrition Labeling. National Academies Press, 2003

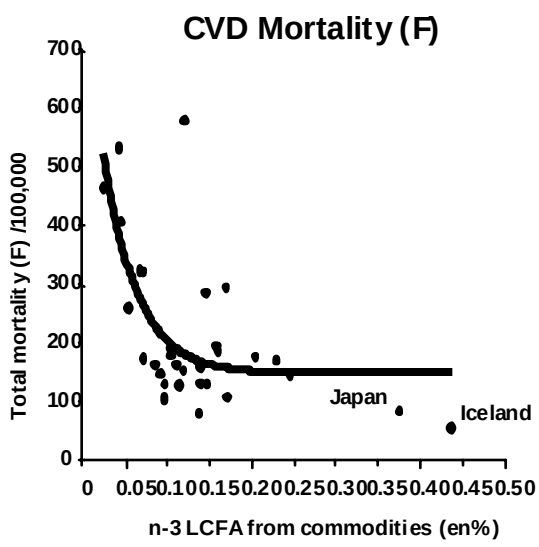




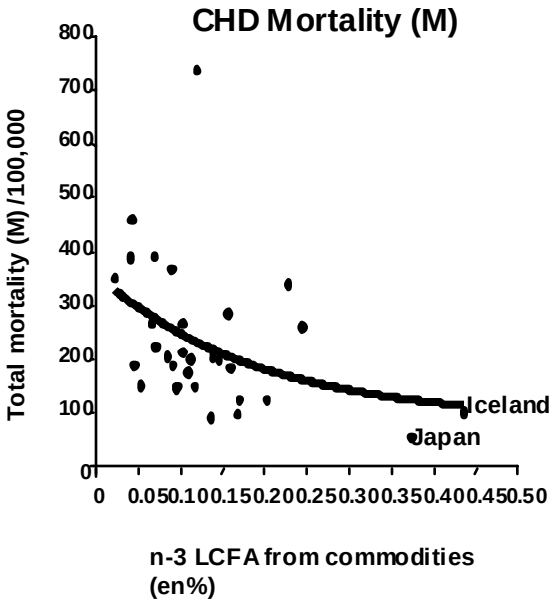


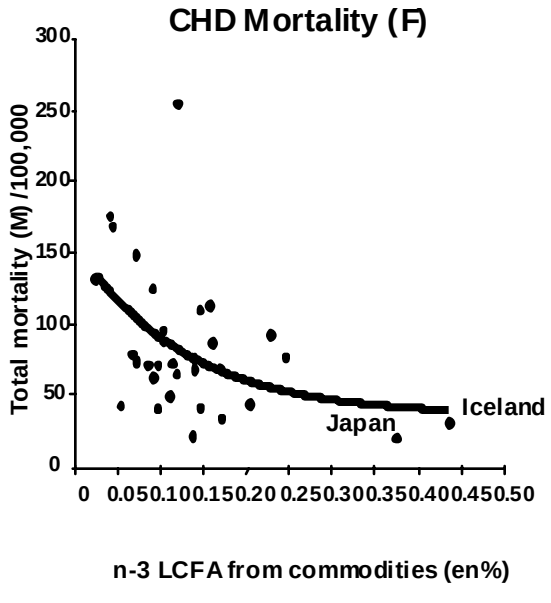


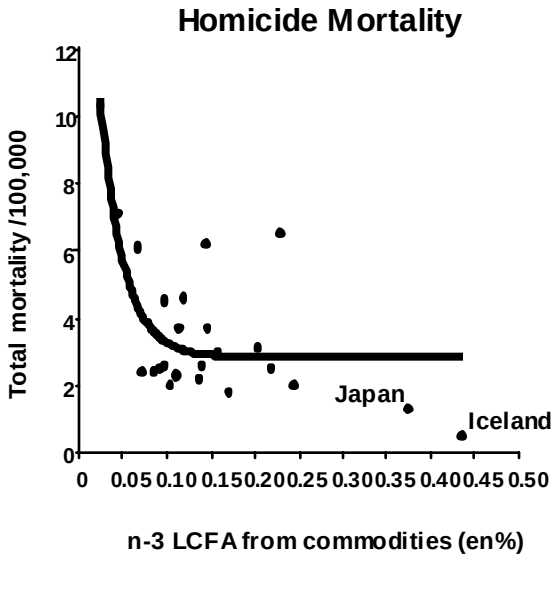


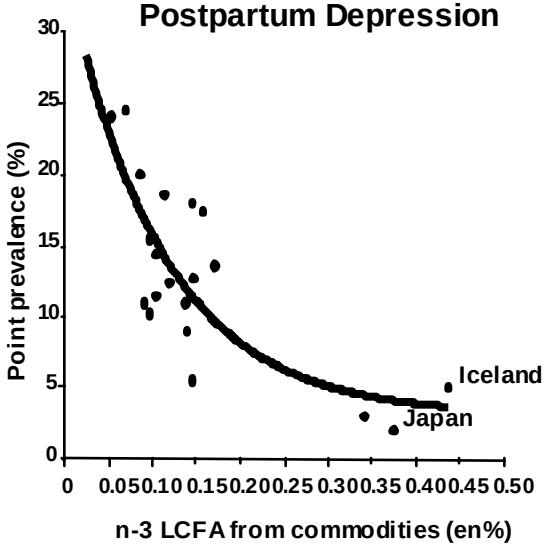


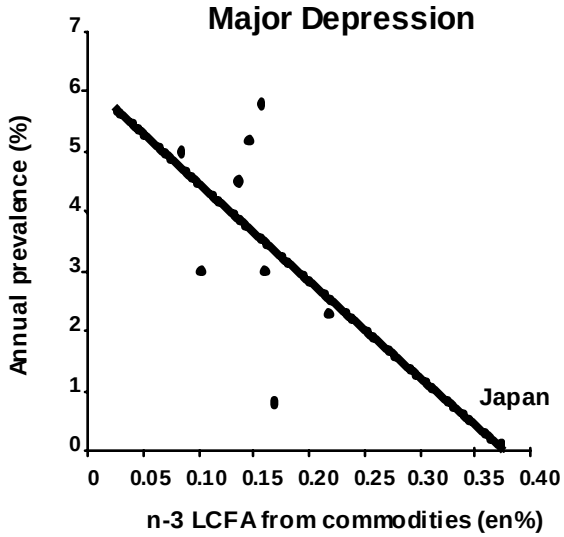
Hibbeln et al Am J Clin Nutr 2006; 83; 1483S-93S

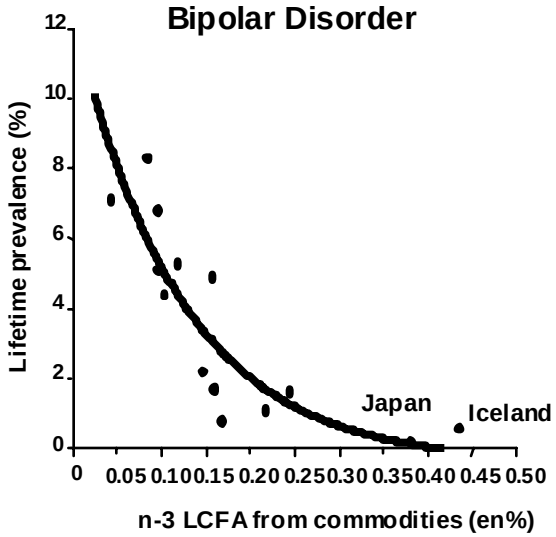






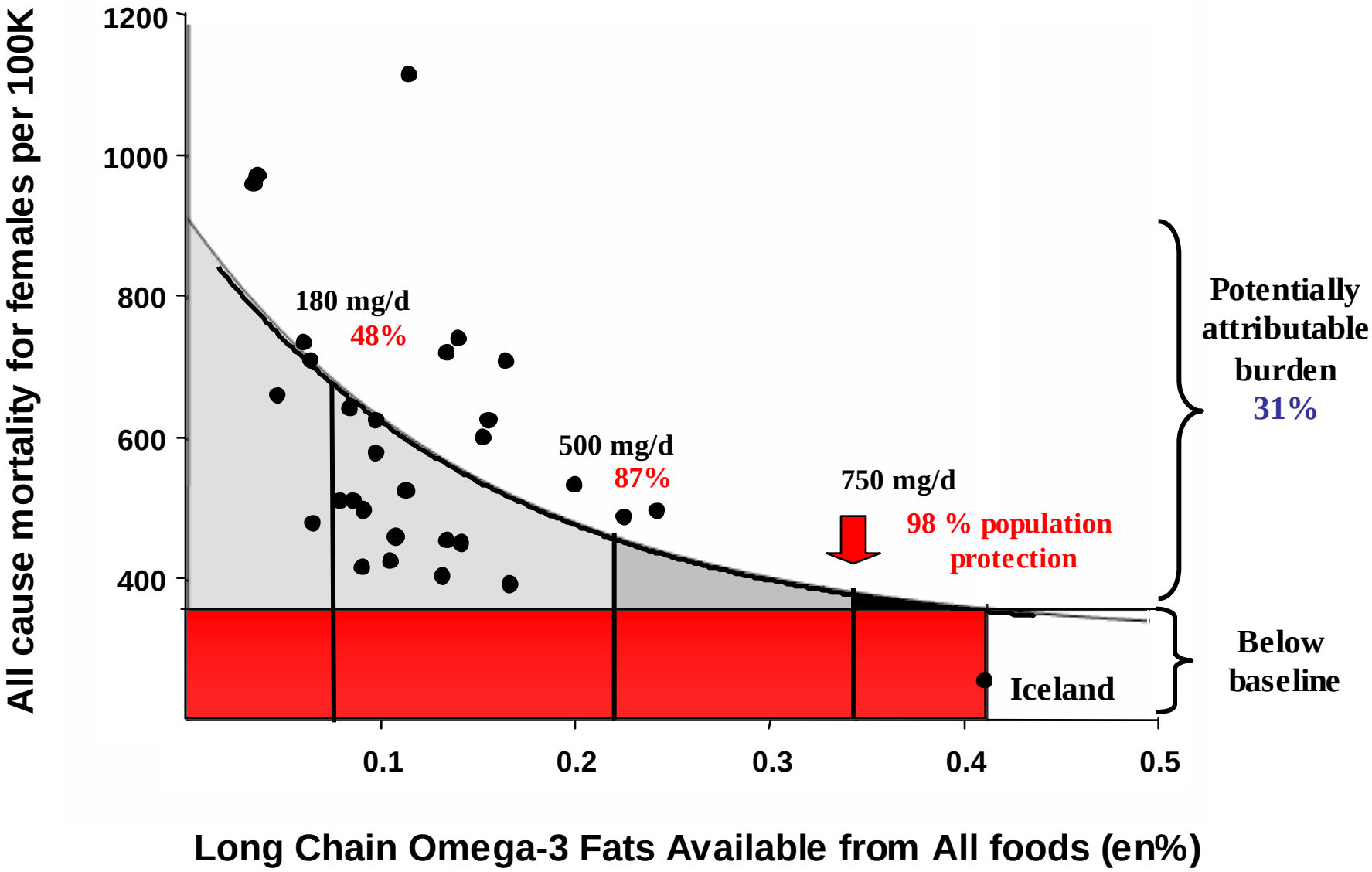






Hibbeln et al Am J Clin Nutr 2006; 83; 1483S-93S

All cause mortality for females

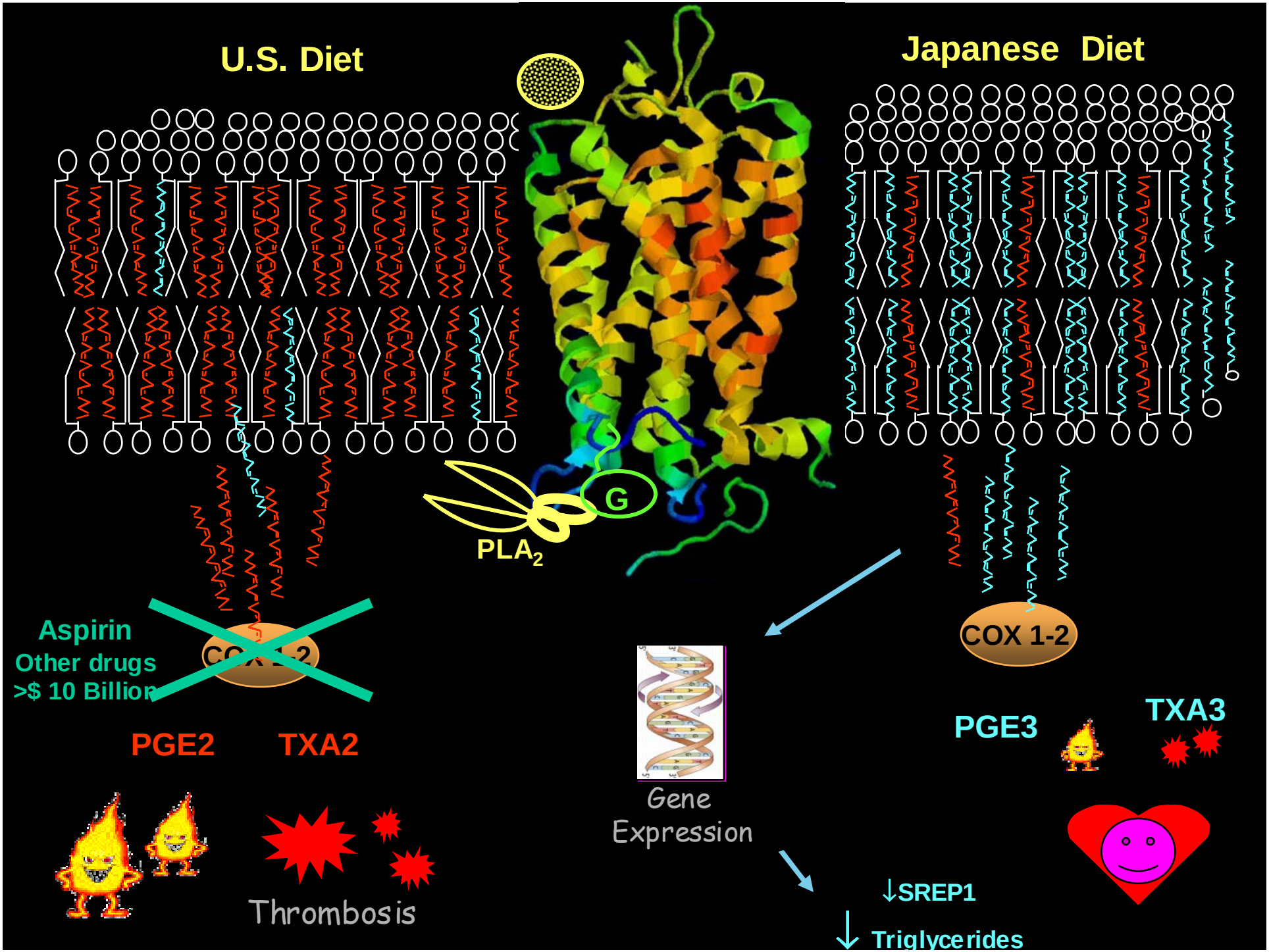


Hibbeln et al Am J Clin Nutr 2006; 83; 1483S-93S

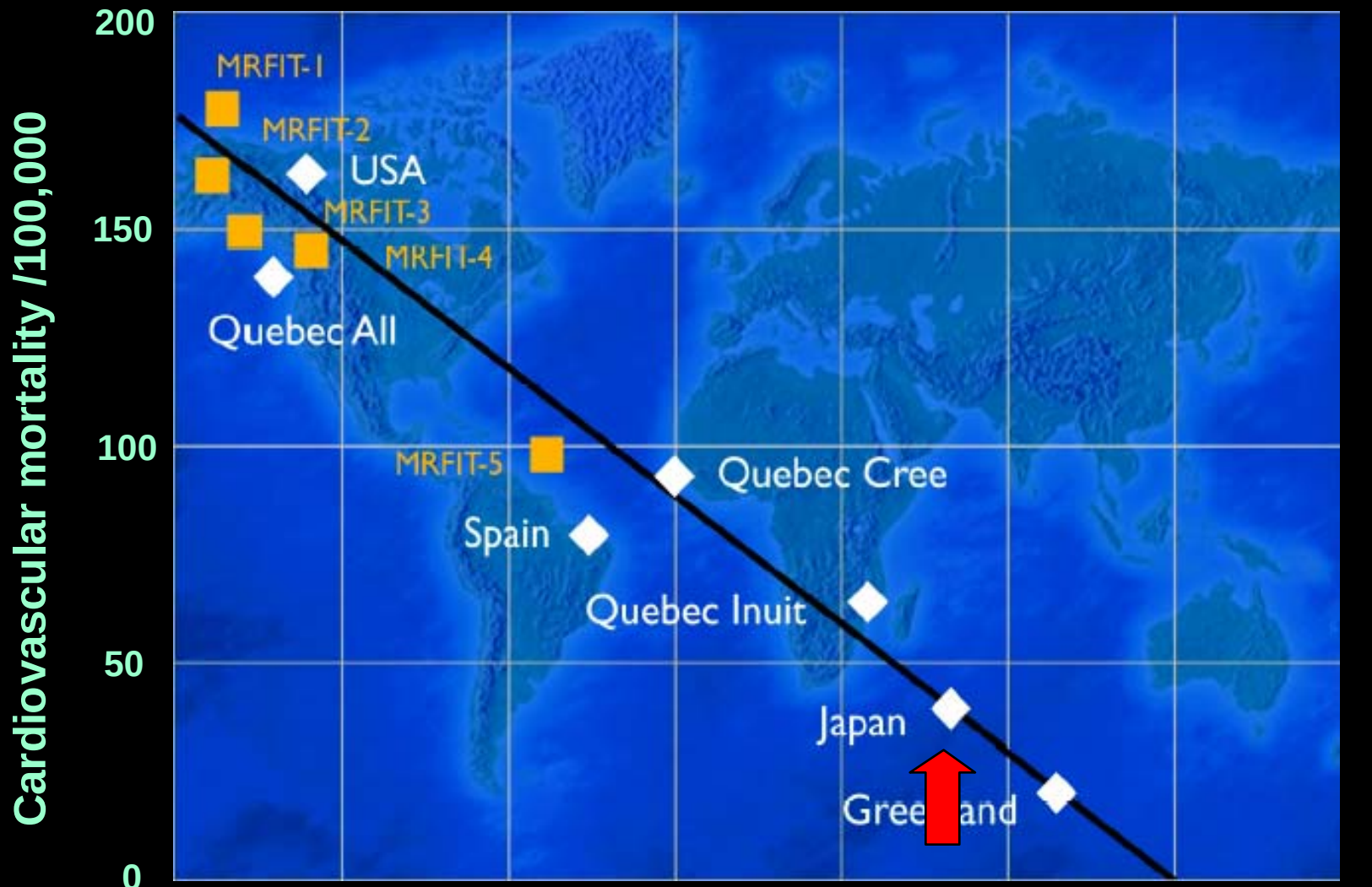
Disease/Disorder Model	Disease burden potentially modifiable by n-3 HUFAs	Percent vulnerable population protected from illness (%)		
		Model Advice for n-3 HUFA Intake		
		0.08 en% (180 mg/d)	0.22 en% (500 mg/d)	0.34 en% (750 mg/d)
CHD mortality M	41.2%	45.2	85.4	97.9
CHD mortality F	42.5%	52.4	89.7	98.6
Stroke mortality M	32.9%	97.7	99.9	>99.9
Stroke mortality F	31.1%	96.4	99.9	>99.9
CVD mortality M	26.1%	83.4	99.3	>99.9
CVD mortality F	29.1%	86.9	99.6	>99.9
All Cause mortality M	20.8%	73.6	97.7	99.8
All Cause mortality F	31.5%	48.3	87.3	98.2
Homicide mortality	28.4%	95.6	>99.9	>99.9
Postpartum depression	65.5%	55.7	91.3	98.9
Major depression	98.5%	38.5	83.2	99.2
Bipolar disorder	99.9%	56.1	92.3	99.5

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

Tissue is the Issue



Cardiovascular deaths and Omega-3 in tissues



Essential Fats: Metabolism and Dietary Sources

Omega-6

18:2n-6 linoleic acid, LA

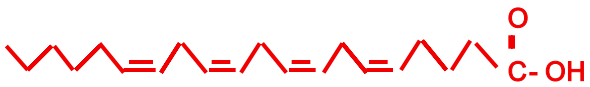
Soy bean oil
Safflower oil
Corn oil

Omega-3

18:3n-3 linolenic acid, LNA

Canola oil
Flax seed
Leaf plants

competition for
Δ6 and Δ5 desaturase
and elongation
enzymes



20:4n-6, arachidonic acid
AA

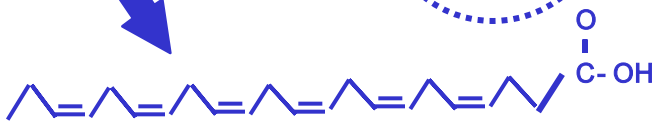
Meat,
Organs

20:5n-3,eicosapentaenoic acid,
EPA

Fish
Seafood
Seaweed

Series 2
Prostaglandins
Thromboxanes
Series 4
Leukotrienes

Series 3
Prostaglandins
Thromboxanes
Series 5
Leukotrienes

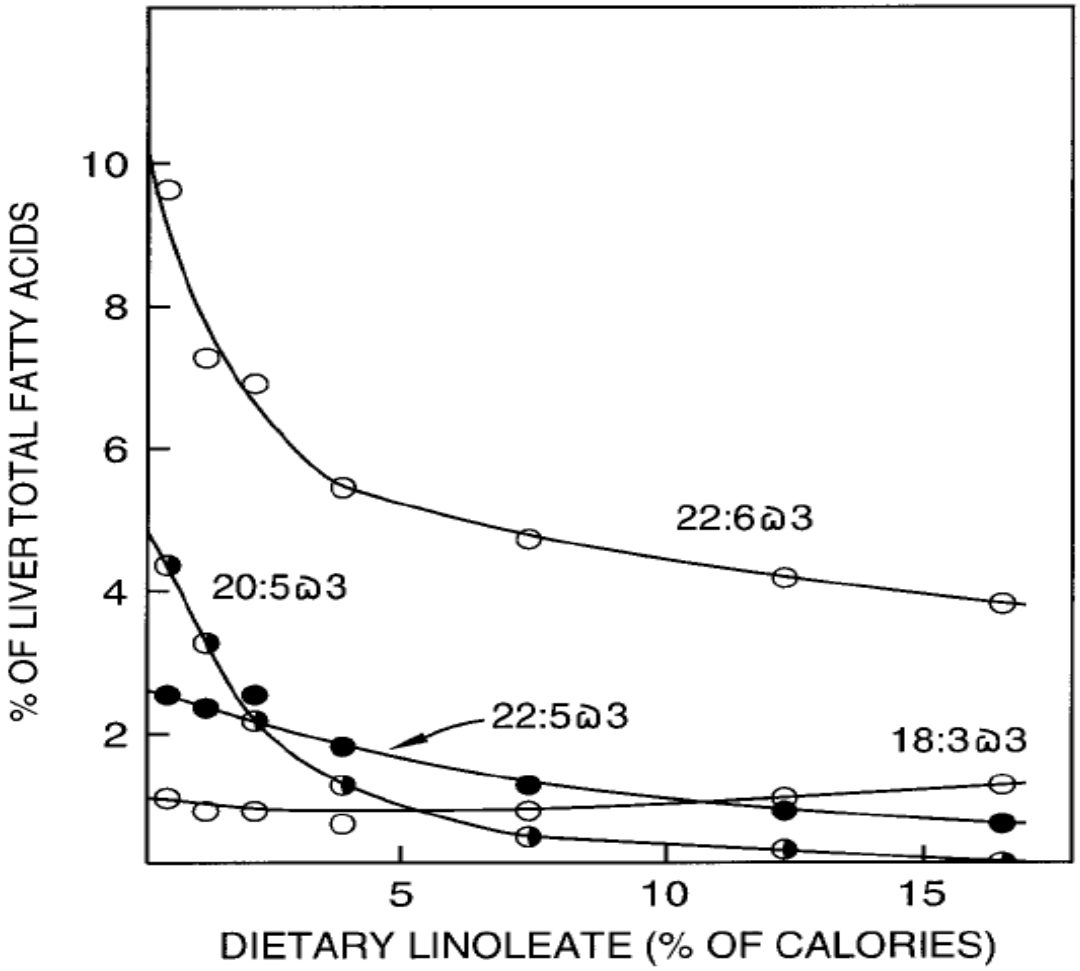


22:6n-3, docosahexaenoic acid,
DHA
(brain, retina, testis)

platelet activity
immune responses
smooth muscle
Bone health

Dietary LA (18:2n-6) reduces tissue DHA and EPA

Molhauer and Holman, 1963



Ralph T. Holman J. Nutr. 128: 427S–433S, 1998.
The Slow Discovery of the Importance of ω-3 Essential Fatty Acids in Human Health

	Tissue target	Concurrent dietary intake (en%)			n-3 HUFA required to meet tissue target in each country	
COUNTRY	% n-3 in LCFA	LA	α-LNA	AA	(en%)[2]	(mg/d)[3]
Philippines	60%	0.80	0.08	0.06	0.125	**278**
Denmark	60%	2.23	0.33	0.09	0.45	**1000**
Iceland	60%	2.48	0.33	0.10	0.54	**1200**
Colombia	60%	3.21	0.24	0.04	0.51	**1133**
Ireland	60%	3.57	0.42	0.06	0.62	**1378**
UK	60%	3.91	0.77	0.07	0.72	**1600**
Netherlands	60%	4.23	0.28	0.08	0.88	**1956**
Australia	60%	4.71	0.49	0.07	0.90	**2000**
Italy	60%	5.40	0.51	0.06	0.95	**2111**
Germany	60%	5.57	0.62	0.06	1.00	**2222**
Bulgaria	60%	7.02	0.06	0.05	1.25	**2778**
Israel	60%	7.79	0.67	0.07	1.45	**3222**
USA	60%	8.91	1.06	0.08	1.65	**3667**

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

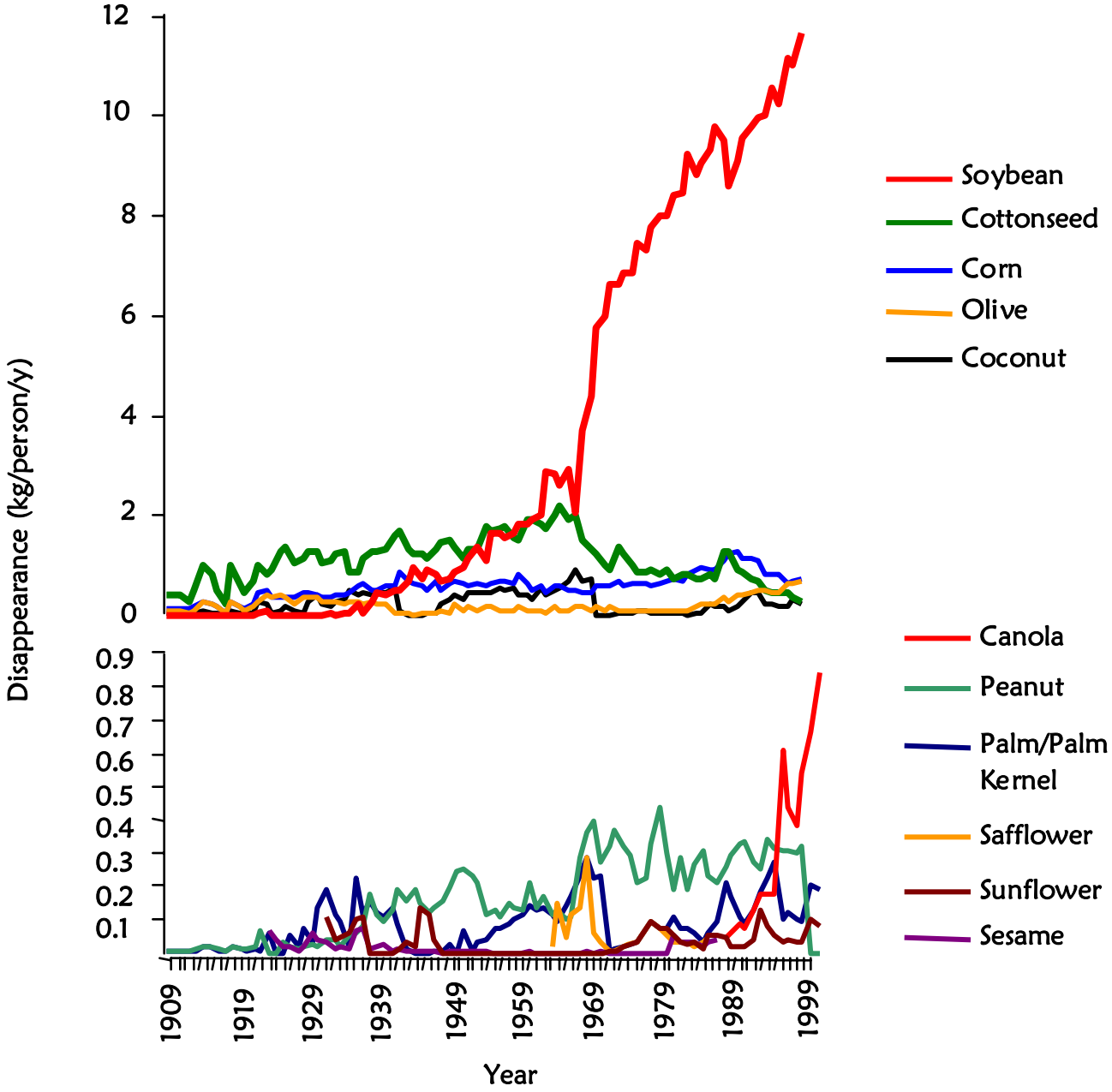
Dietary intakes of long chain omega-3 fats vary more than 10-fold necessary to achieve Japanese tissue levels (98% protection) of long chain omega-3 fatty acids

This variation is due to greater background intakes of linoleic acid (omega-6).

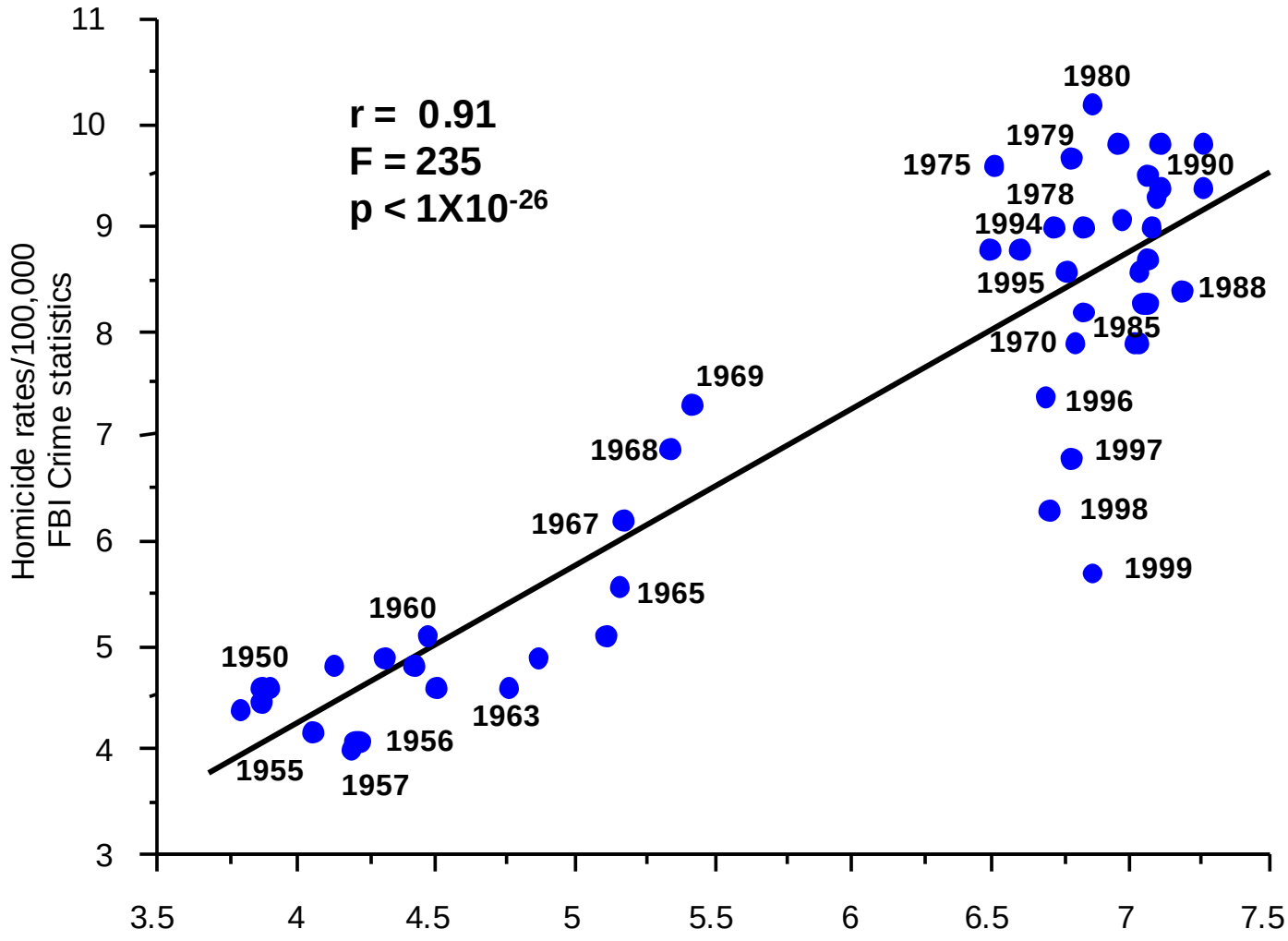
Lowering linoleic acid intakes from seed oils can reduce the burden on fisheries.

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

Oilseeds in the US Food Supply in the 20th Century

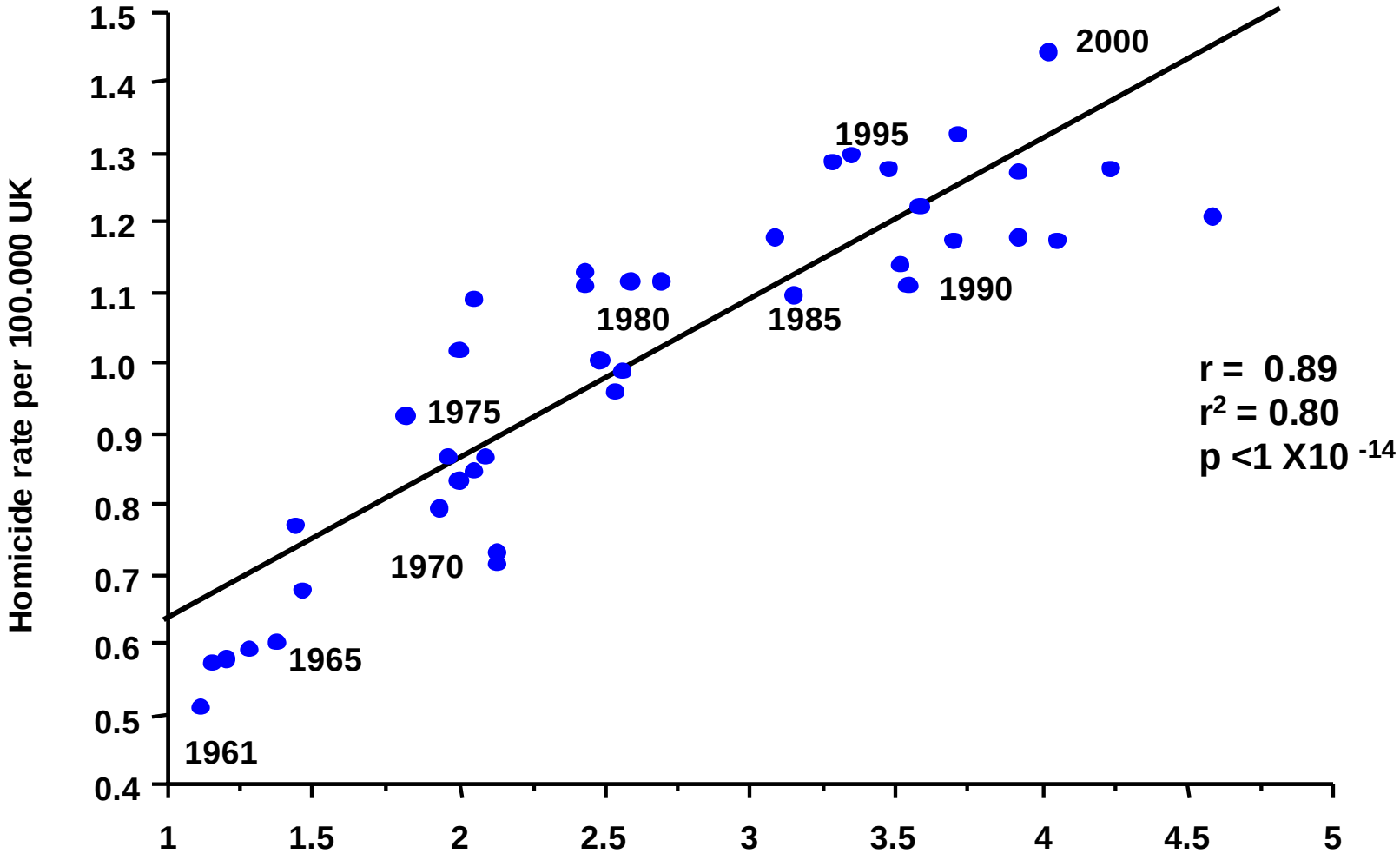


Homicide mortality in the United States from 1950 to 1999 and availability of omega-6 fatty acids (18:2n-6) in the food supply



Hibbeln and Lands unpublished

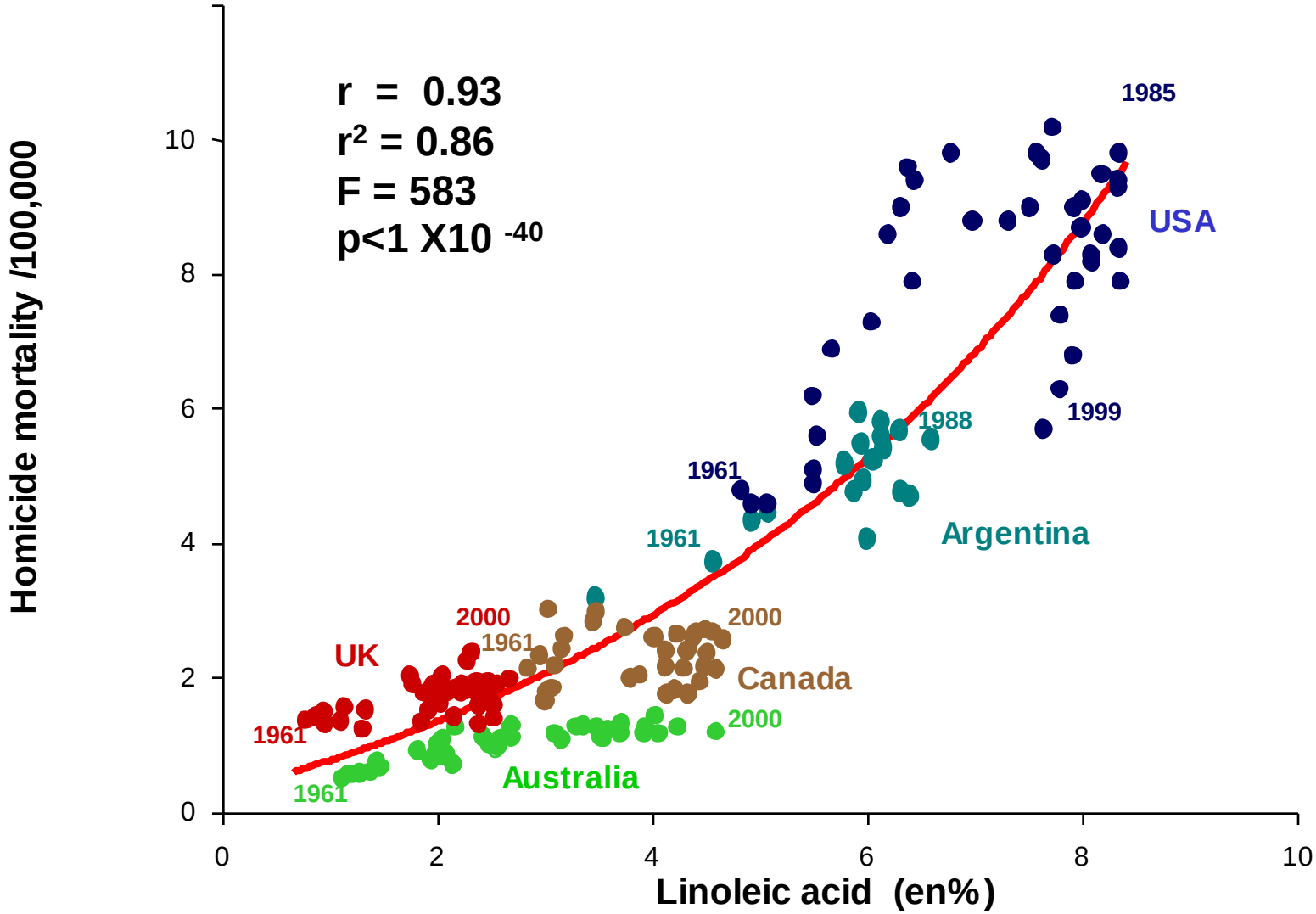
Homicide mortality in the United Kingdom and availability of Omega-6 fats (18:2n-6) in the food supply 1961-2000



Y = 0.4 + 0.23 * X

Hibbeln et al 2004

Homicide mortality and availability of linoleic acid (en%)
Combined Australia, United Kingdom, Canada
Argentina and USA data from 1961-2000

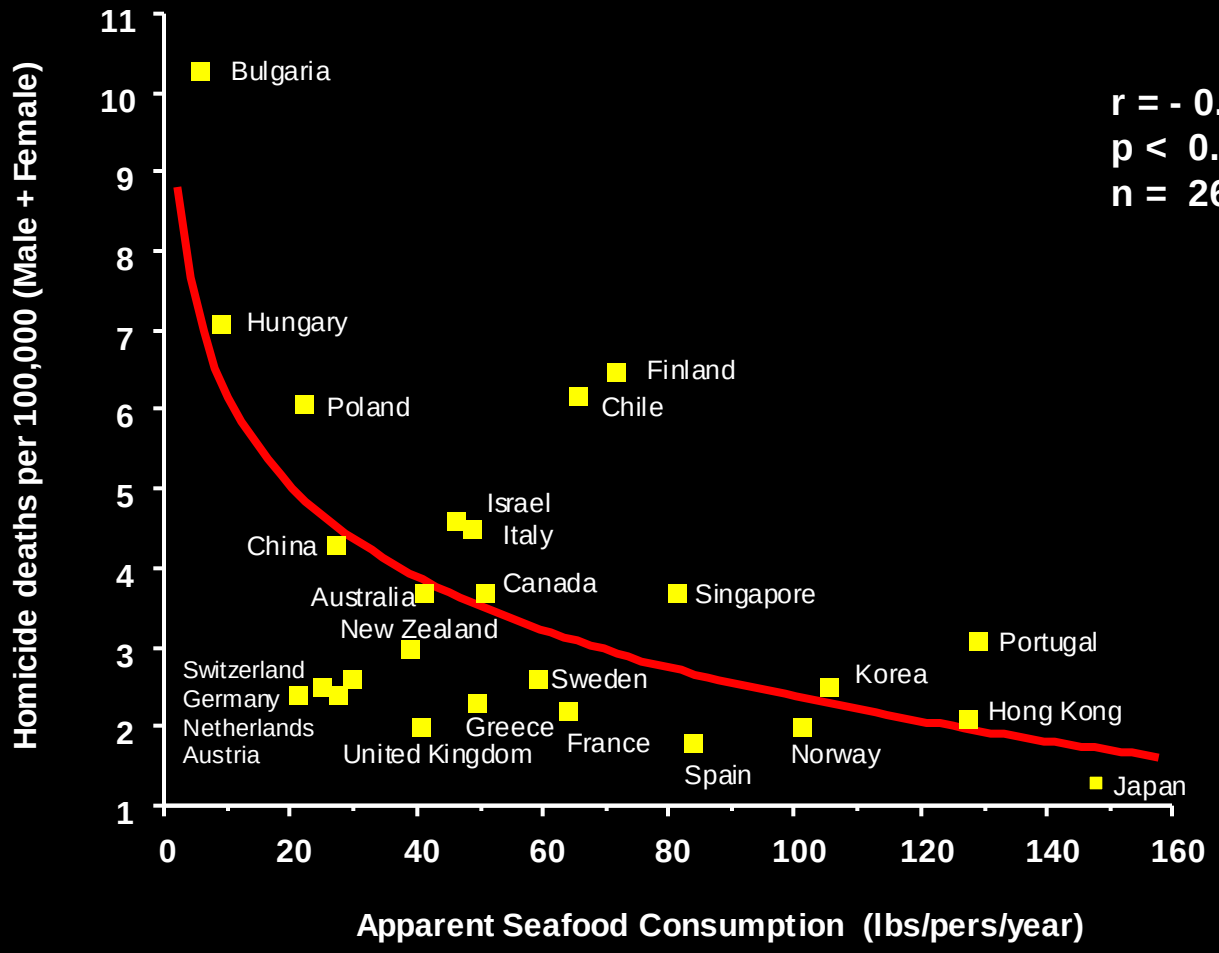


[from 12 seed oils as en% of all commodities available for food consumption]

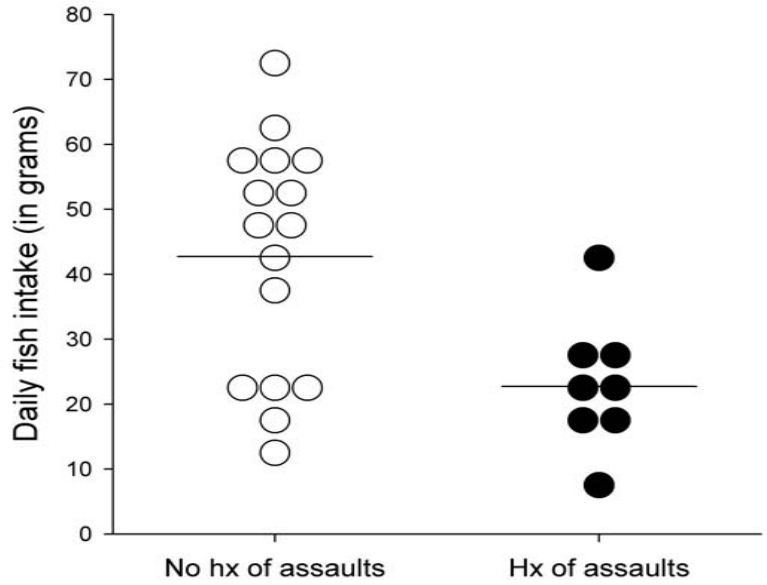
f=y0+a*exp(b*x) y0 = -1.98207a = 2.14258 b = 0.203595

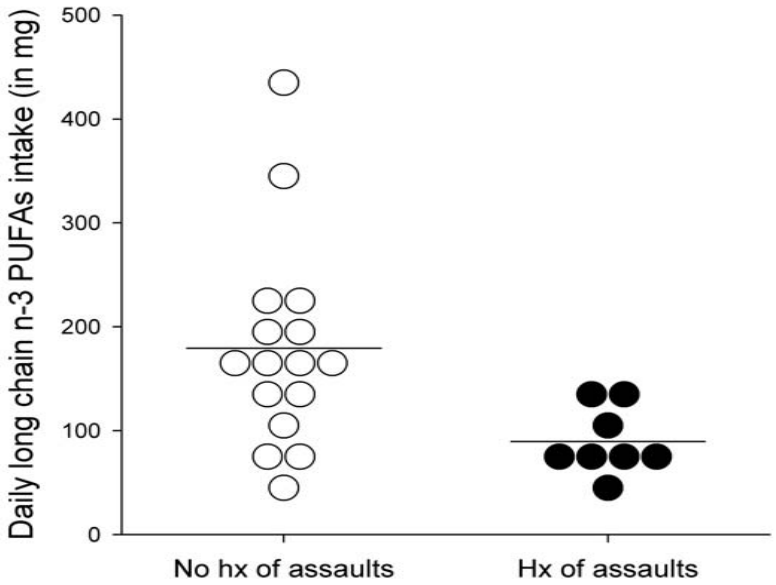
Hibbeln et al 2004

Homicide Mortality Rates[1] and Seafood Consumption



[1]World Health Statistics Annual 1995, WHO, Geneva Switzerland **Hibbeln, JR World Rev Nutr Diet, 2001; 88; 41-46**

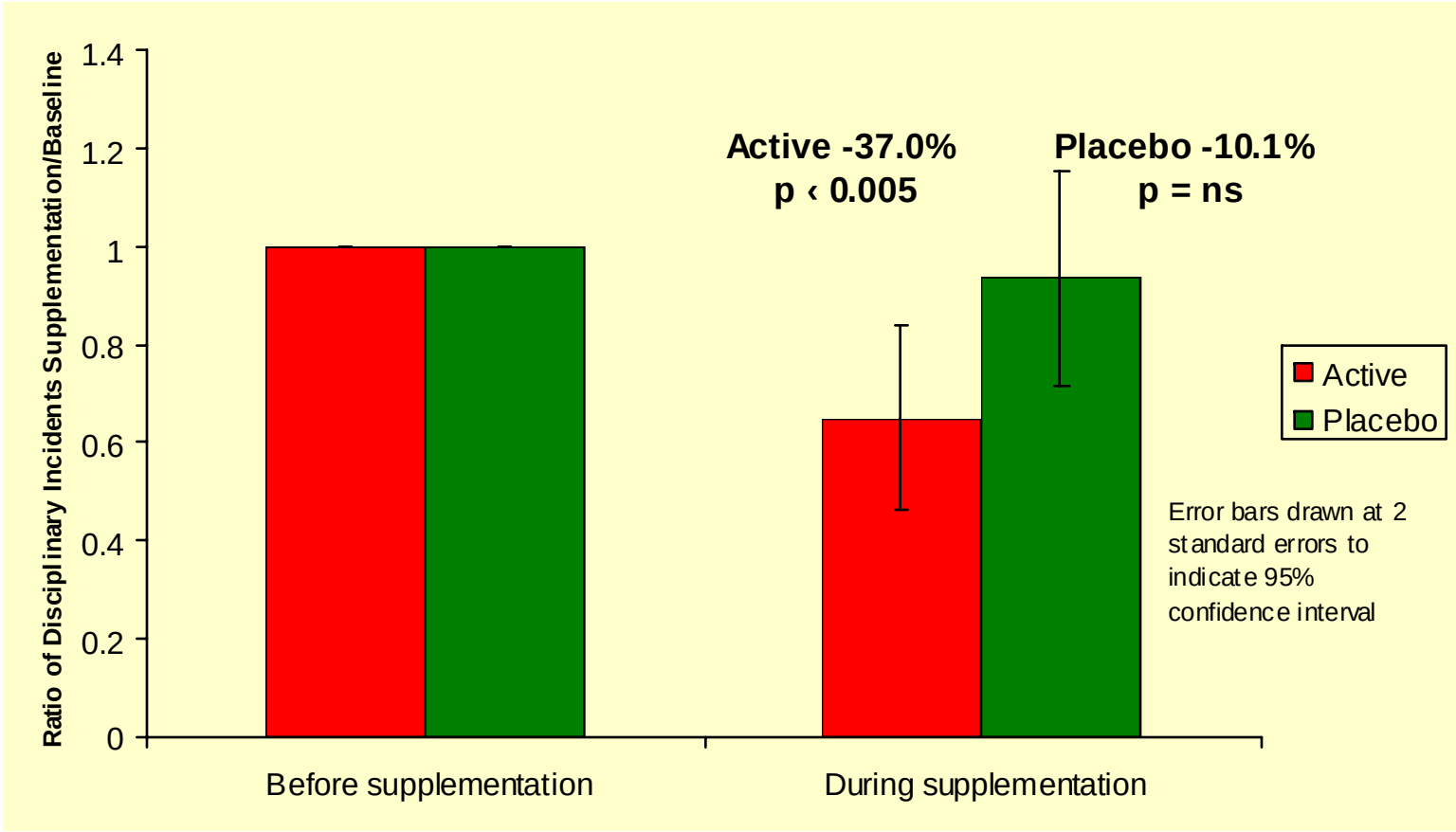




Low seafood consumption and greater lifetime history of assaults among polysubstance abusers

Branchey, Hibbeln et al in press 2007

Reductions in felony level violent offences among prisoners in placebo controlled trial of recommended daily amounts of vitamins, minerals and essential fatty acids



338 offences among 172 prisoners over 9 months treatment in a UK maximum security prison compared to 9 months baseline.
Analysis: Negative binomial mixed Poisson regression analysis

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

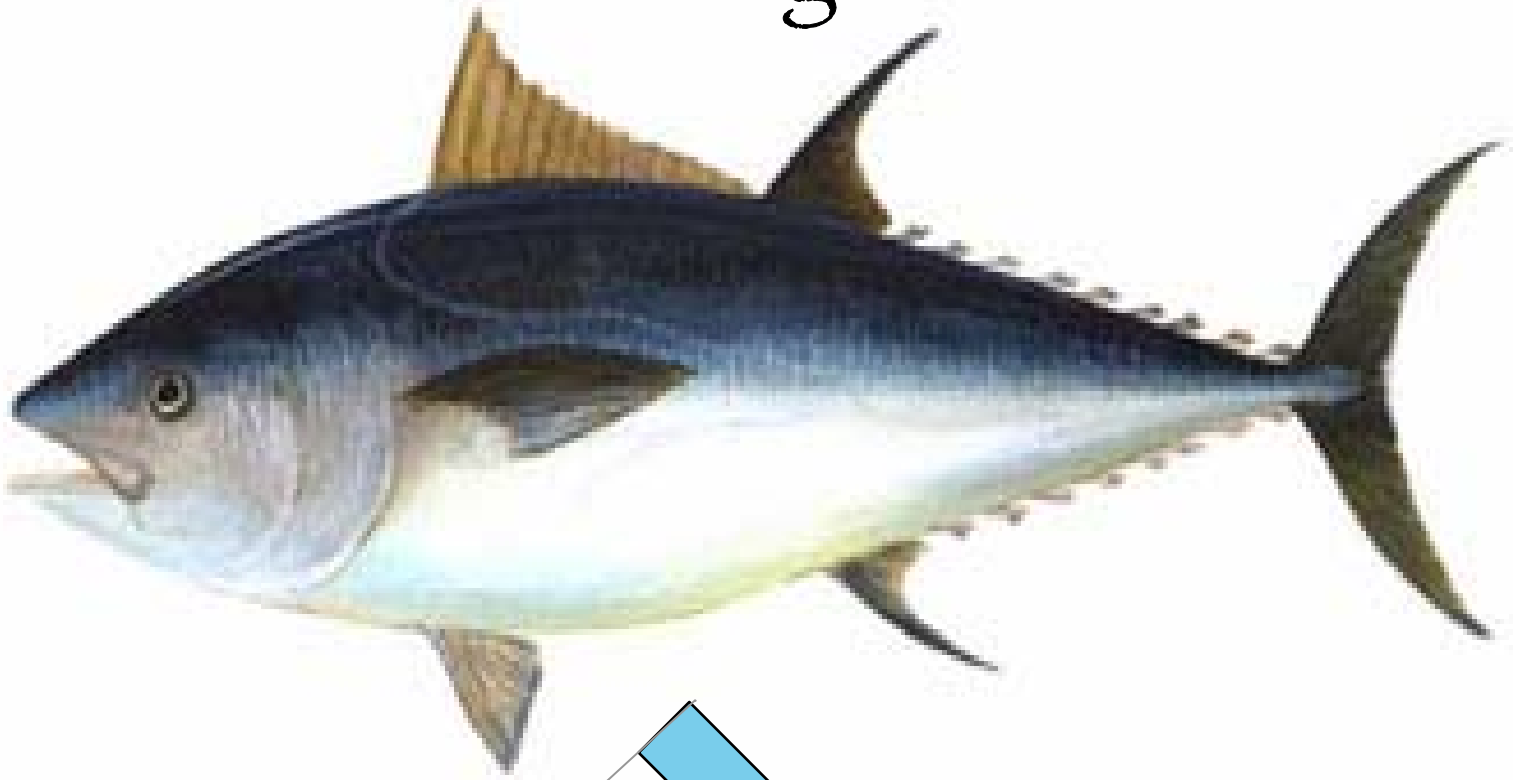
Thank you

	Tissue target	Concurrent dietary intake(en%)[1]			n-3 HUFA required to meet tissue target	
COUNTRY	% n-3 in HUFA	LA	LNA	AA	(en%)[2]	(mg/d)[3]
Philippines	50%	0.80	0.08	0.06	0.06	**133**
Denmark	50%	2.23	0.33	0.09	0.26	**578**
Iceland	50%	2.48	0.33	0.10	0.31	**689**
Colombia	50%	3.21	0.24	0.04	0.30	**667**
Ireland	50%	3.57	0.42	0.06	0.36	**800**
UK	50%	3.91	0.77	0.07	0.39	**867**
Netherlands	50%	4.23	0.28	0.08	0.50	**1111**
Australia	50%	4.71	0.49	0.07	0.51	**1133**
Italy	50%	5.40	0.51	0.06	0.56	**1244**
Germany	50%	5.57	0.62	0.06	0.57	**1267**
Bulgaria	50%	7.02	0.06	0.05	0.73	**1622**
Israel	50%	7.79	0.67	0.07	0.85	**1889**
USA	50%	8.91	1.06	0.08	0.98	**2178**

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

Bluefin Tuna (Thunnus Thynnus)

200 kg



~ 0.01 gm
methyl mercury

~ 2,500 gm
long chain omega-3's

U.S. Department of Health and Human Services
and
U.S. Environmental Protection Agency

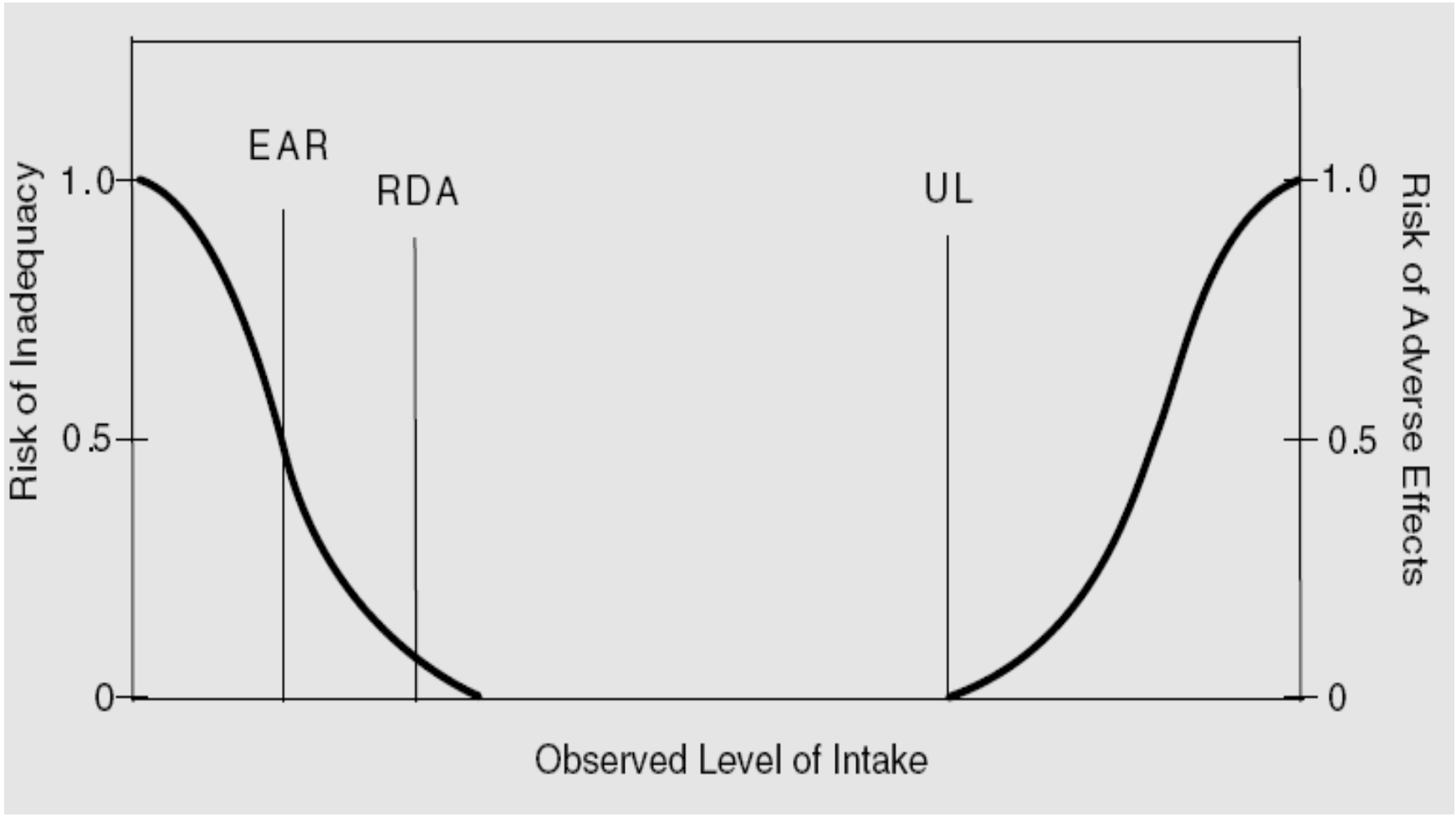
What You Need to Know About Mercury in Fish and Shellfish

2004 EPA and FDA Advice For:
Women Who Might Become Pregnant, Women Who are Pregnant
Nursing Mothers and Young Children

Fish and shellfish are an important part of a healthy diet. Fish and shellfish contain high-quality protein and other essential nutrients, are low in saturated fat, and contain omega-3 fatty acids. A well-balanced diet that includes a variety of fish and shellfish can contribute to heart health and children's proper growth and development. So, women and young children in particular should include fish or shellfish in their diets due to the many **nutritional benefits**.

However, nearly all fish and shellfish contain traces of mercury. For most people, the risk from mercury by eating fish and shellfish is not a health concern. Yet, some fish and shellfish contain higher levels of mercury that may harm an unborn baby or young child's developing nervous system. The **risks from mercury** in fish and shellfish depend on the amount of fish and shellfish eaten and the levels of mercury in the fish and shellfish.

March 2004 EPA-823-R-04-005



Dietary Reference Intakes: Guiding Principles for Nutrition Labeling and Fortification Committee on Use of Dietary Reference Intakes in Nutrition Labeling. National Academies Press, 2003

Toxicological risk of methyl-mercury: benchmark equation (exposure from pilot whale)

Equation used for the 2004 EPA/FDA Seafood Advisory

$$P(x) = Pr(Y > C|x) = 1 - Pr(Y \leq C|x) = 1 - \Phi\left(\frac{C - \mu(x)}{\sigma}\right).$$

+ 10-fold uncertainty factor added to minimize exposure risk

Personal communication Louise Ryan, Ph.D. 05 OCT 2004
for the NAS committee on the Toxicology of Methyl-Mercury

Nutritional benefits of seafood:
Equation used for the 2004 EPA/FDA Seafood Advisory

None

Is the 2004 EPA and FDA advisory effective in preventing risk of poor verbal development?

Avon Longitudinal Study of Parents and Children (ALSPAC)

Recruited 14,541 pregnant mothers, the largest and most complete longitudinal study in the world.

- **Enrollment included every pregnancy between April 1st 1991 and December 31st 1992 in Avon (Southwest of London, UK)**
- **Children are now between 11.5 and 15 years of age**
- **Participants mail in questionnaires every 6 months**
- **1,500 children have been seen in clinics every year since birth**
- **85% of children have been seen in clinics every year starting at age 7**

- **Collaboration with John M. Davis, M.D. Univ. of Illinois**
- **Jean Golding, Ph.D., Pauline Emmett, Ph.D.- ALSPAC study group**

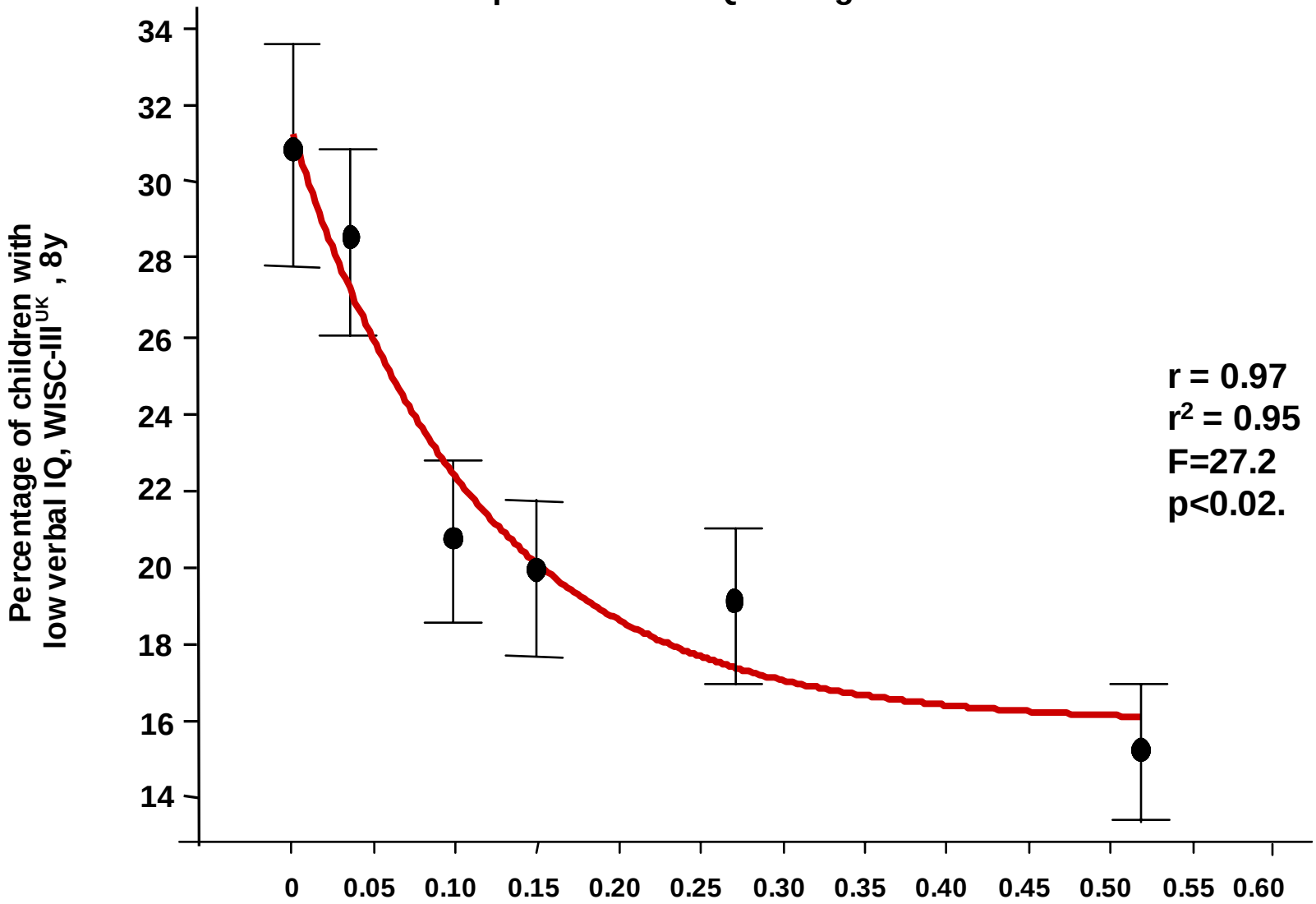
Maternal seafood consumption at 32 wk gestation

How often nowadays do you eat?	White fish (cod, haddock, plaice, fish fingers, etc.)	Dark or Oily fish (tuna, sardines, pilchards, mackerel, herring, kippers, trout, salmon, etc.)	Shellfish (prawns, crabs, cockles, mussels ect.).
One portion Composition of based on typical consumption patterns of women in England	+50g of fried plaice in batter +30g of baked cod fillets +30g of fried haddock in crumbs +20g of grilled fish fingers	+60g of tuna canned in brine +12g of homemade salmon fish cakes +10g of canned pink salmon +8g of brown trout +5g of steamed salmon +5g of sardines canned in oil +5g of pilchards canned in tomato sauce +3g of sardines canned in tomato sauce	+43g of scampi, bread-crumbed and fried +21g of canned crab +10g of boiled mussels +15g of boiled prawns
Omega-3	**0.32 g**	**0.89 g**	**0.34 g**

Never / rarely	once in 2 wk	1–3 times per wk	4–7 times per wk	more than once a day
0 portions/wk	0.5 portions/wk	2 portions/wk	5.5 portions/wk	10 portions/wk
0 gm/w	86 g/wk	347 g/wk	951 g/wk	1730 gm/wk

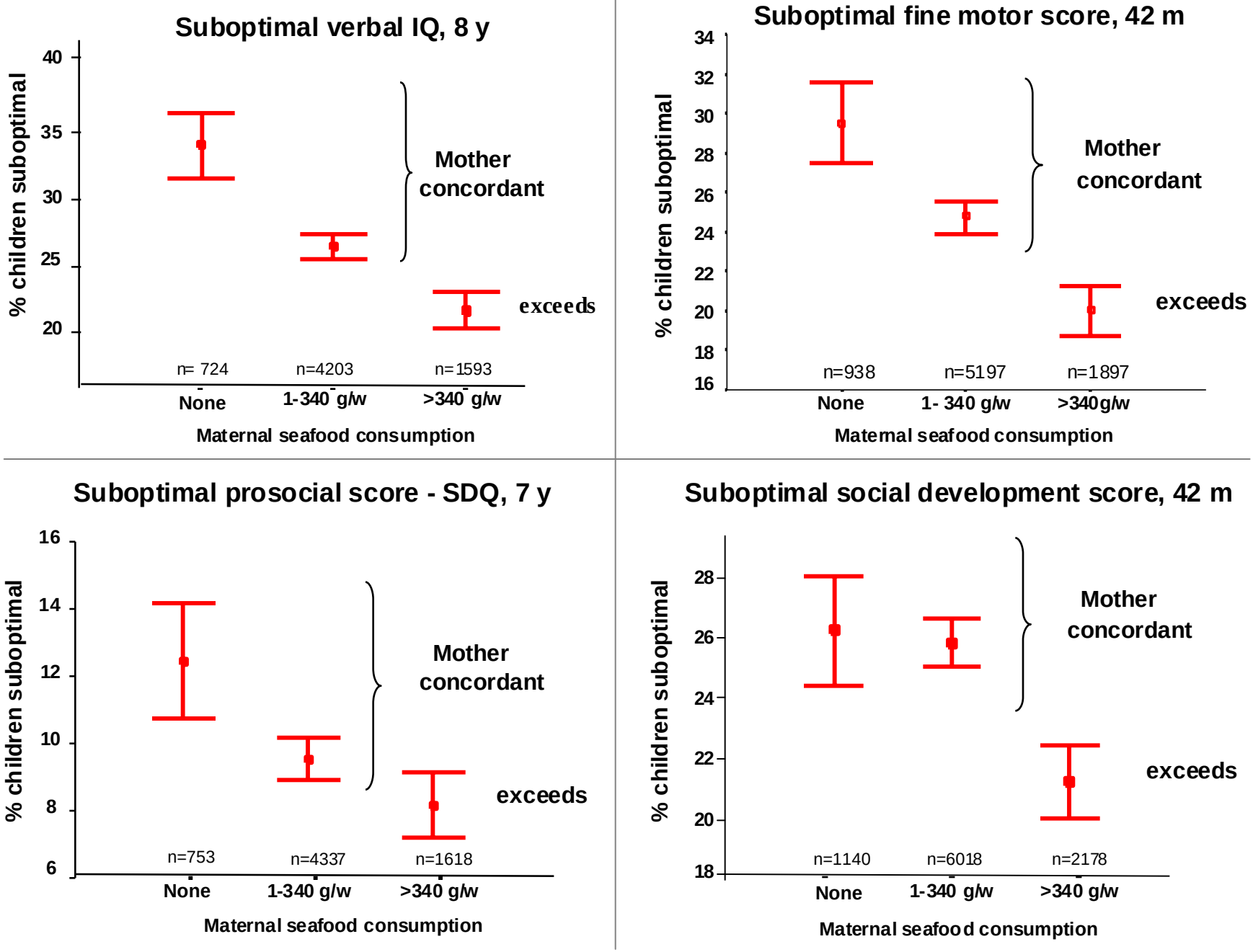
Hibbeln et al the Lancet Feb 17, 2007

Low maternal omega-3 consumption from seafood and suboptimal verbal IQ among their children



Hibbeln et al, The Lancet, 17 Feb 2007

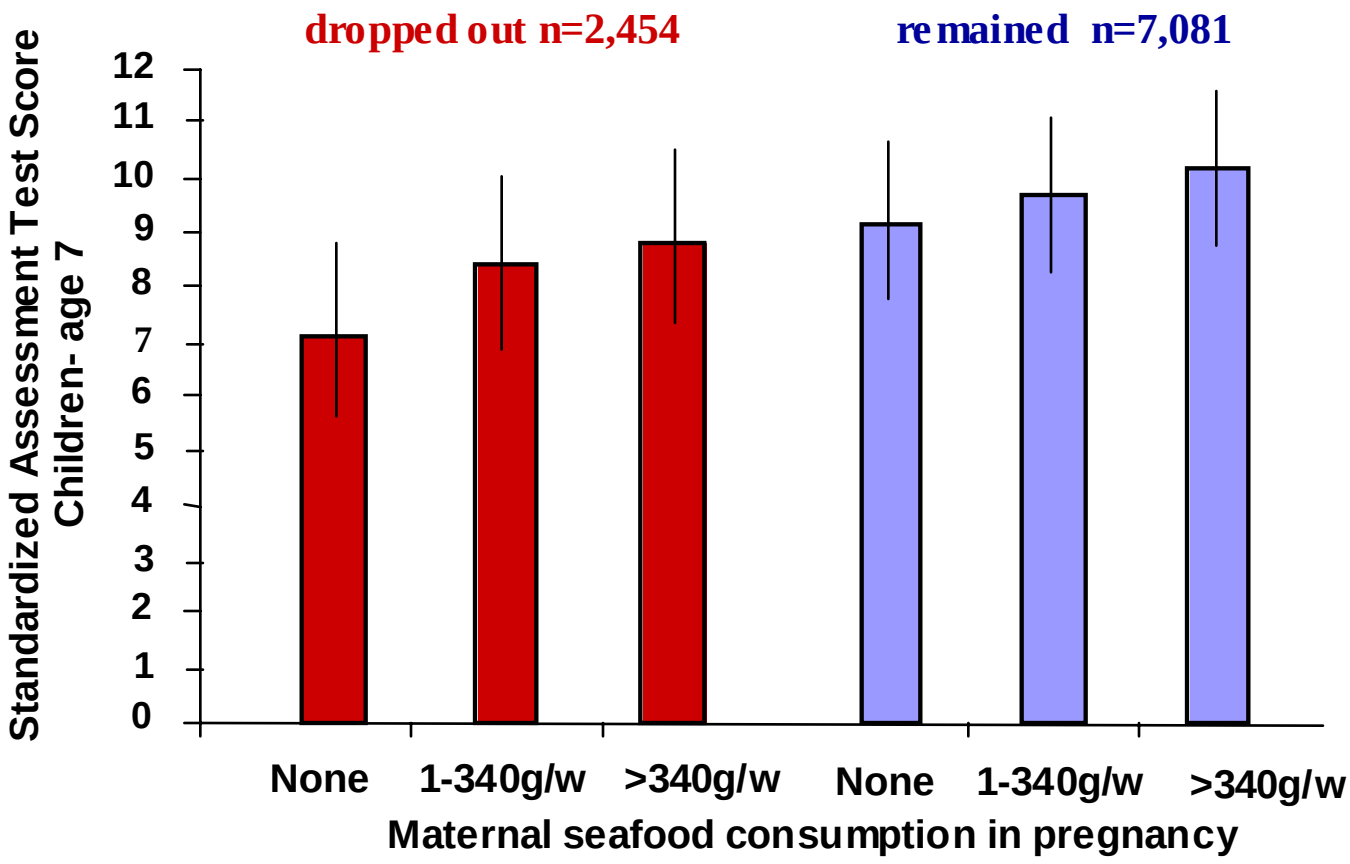
Figure 1



Hibbeln et al, The Lancet, Feb 17 2007

Attrition bias?

Disproportionate attrition of low seafood/disadvantaged families
SATs tests for all British public schools students, regardless of cohort dropout



Mean (SD)
p<0.0009
ANOVA-intake and retention

Attrition <u>underestimates</u> the effects of low seafood consumption on cognition.

Hibbeln et al, The Lancet 17 Feb 2007

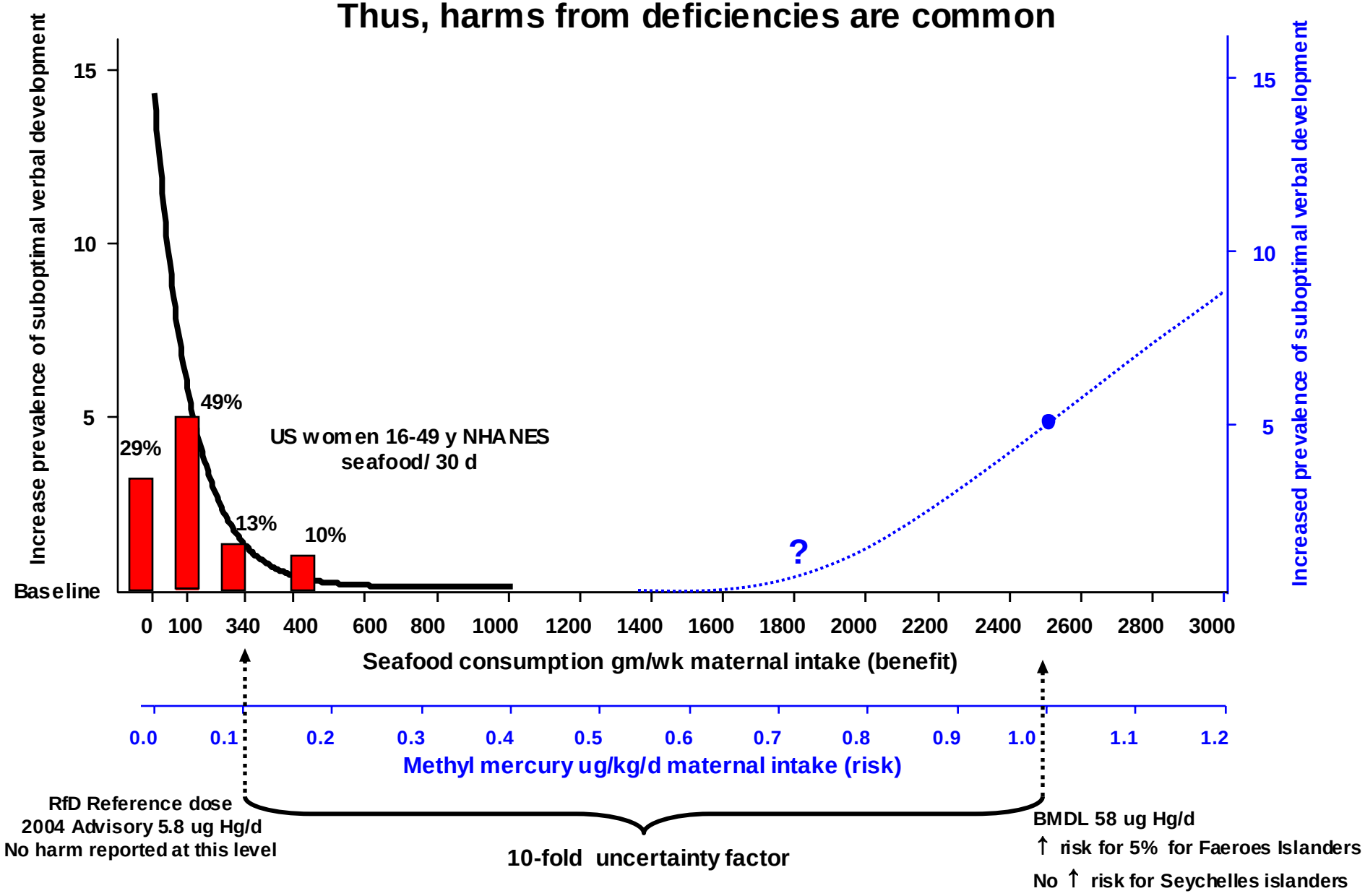
Verbal IQ by WISC-III ^{UK} at age 8 and concordance or excess of the advisory limit (>340 g/w) Effect of multivariate adjustment

		None vs. Exceeds (df=1)			Low vs. Exceeds (df=1)			3 group trend
WISC	n	OR	95% CI	p	OR	95% CI	p	p
unadjusted	5,407	2.16	1.72-2.71	0.001	1.43	1.21-1.68	0.001	0.0001
28 cofactors	5,407	1.48	1.16-1.90	0.002	1.09	0.92-1.29	0.06	0.004
28+ MeHg	5,407	1.90	1.16-1.90	0.001	1.34	1.05-1.72	0.01	0.0001

Risk of being in the lowest quartile of the cohort.

Hibbeln et al, The Lancet 17 Feb 2007

Harms from methyl-mercury in seafood are rare (no attributable risk at the RfD). In contrast most women consume insufficient amounts of seafood Thus, harms from deficiencies are common



ALSPAC Summary

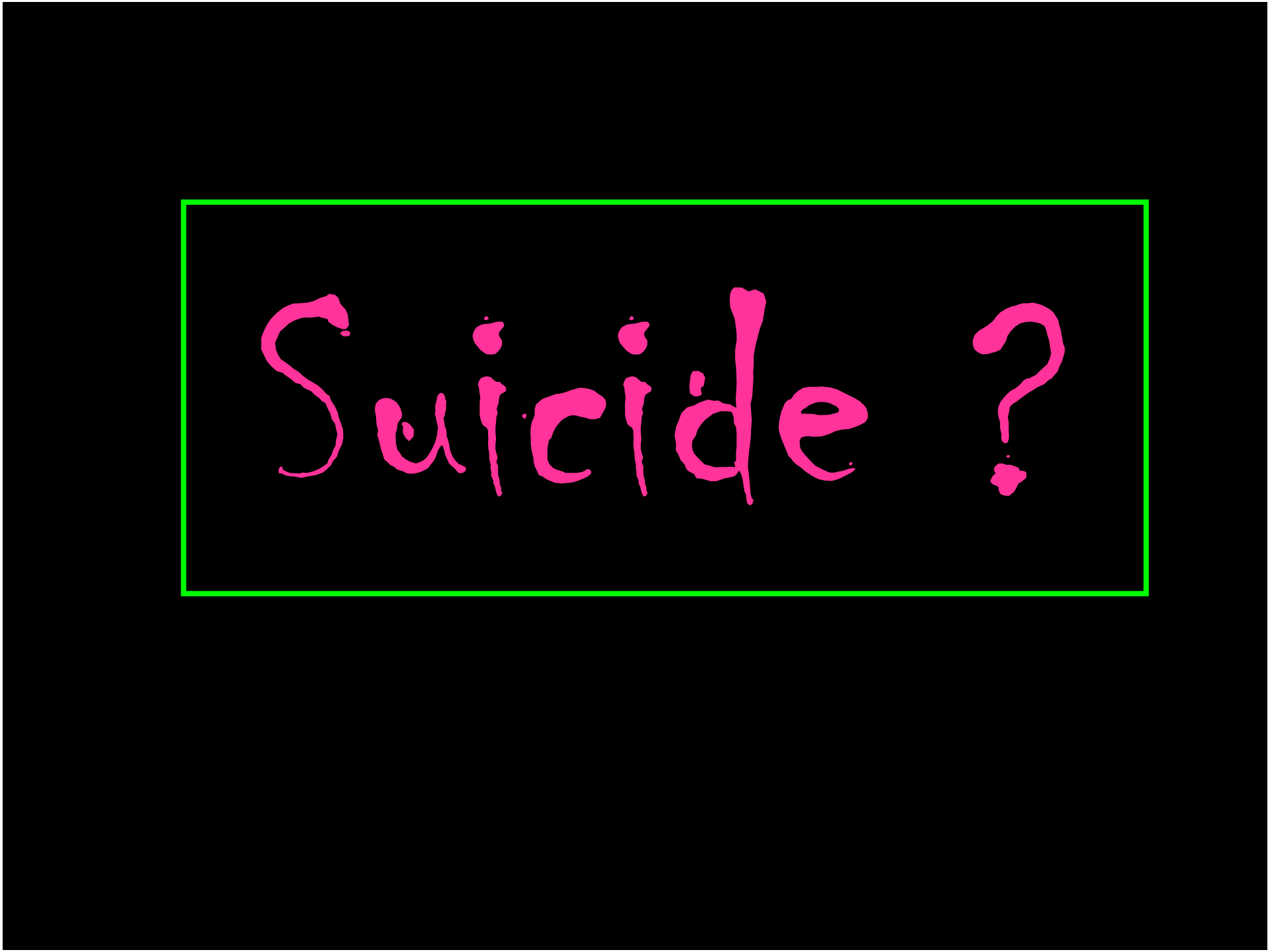
1. Maternal limitation of seafood consumption to <340g/w during pregnancy did not protect children from adverse outcomes.

2. In contrast, this observational study showed beneficial effects on child development when maternal seafood intakes exceeded 340 g/w, with no upper limit of benefit.

3. These findings were robust after adjustment for multiple potential confounders.

4. These data indicate that advice for mothers to limit seafood intake during pregnancy is detrimental.

Hibbeln et al, The Lancet 17 Feb 2007



Deliberate Self-Harm

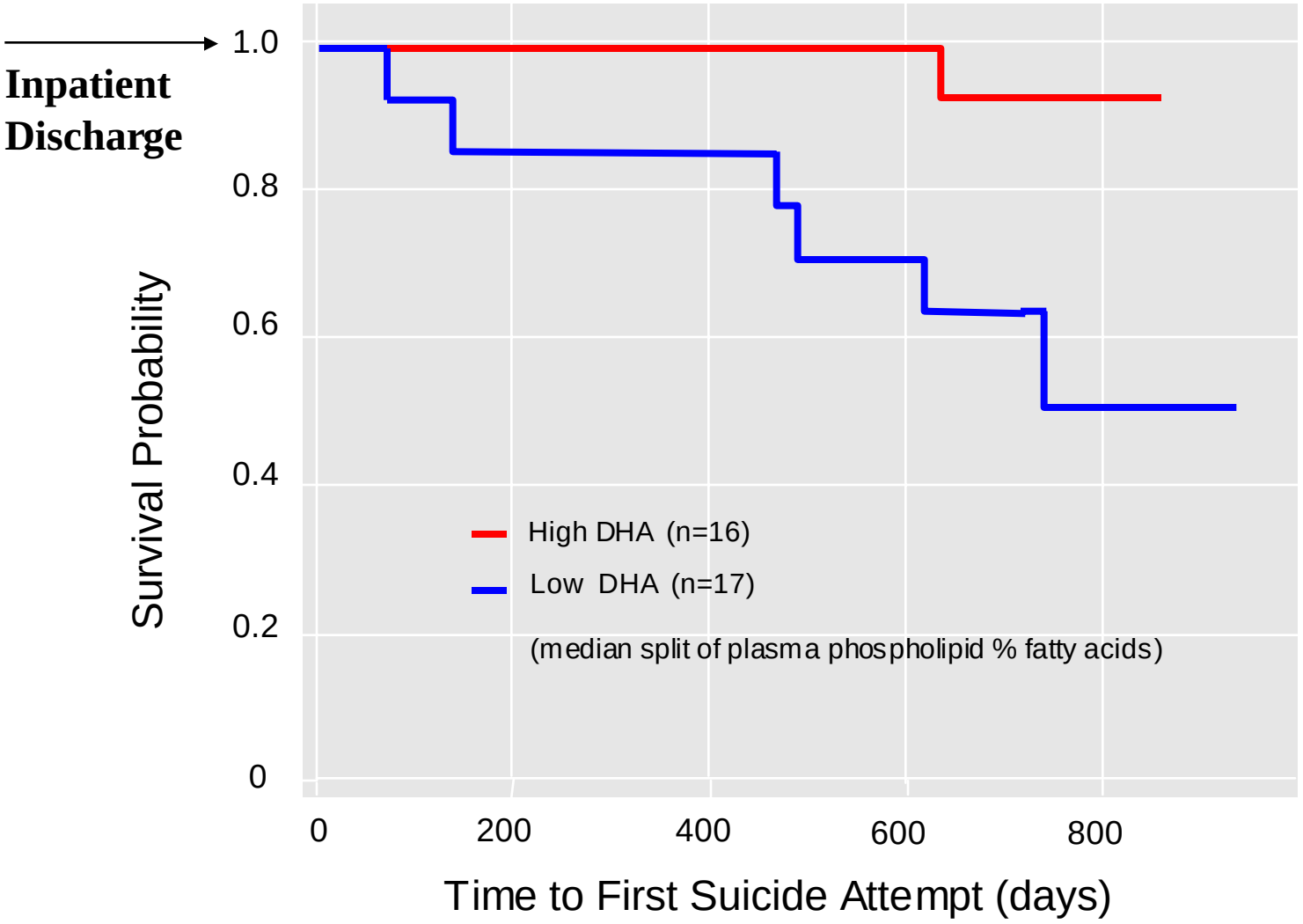
- Subjects n= 49
- Recruited from a Dublin emergency room
- 12 week, double-blind, placebo-controlled trial
- 2.1 g/d, (1.2 g/d EPA, 0.9 g/d DHA)
- (EPAX 5500, Pronova Biocare, Norway)

Results

- 50% reduction in depression (Beck)
- 35% reduction in suicidal thinking (OAS)
- 33% reduction in perception of stress (PSS)
- 30% improvement in "happiness" (DHUS)
- (perception of daily events as uplifting)

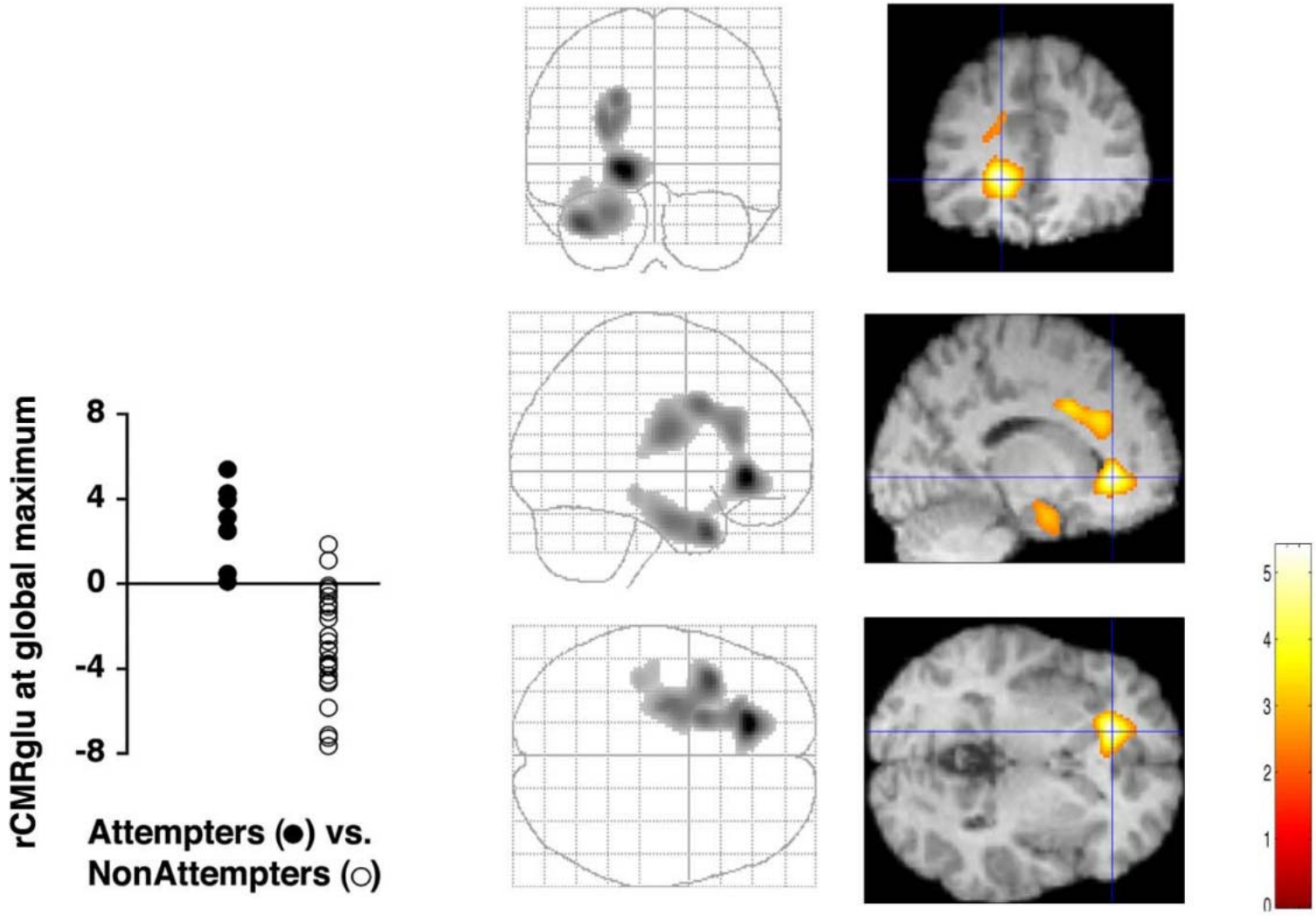
Hallahan, Hibbeln, Davis, Garland, Br J Psychiatry in press, 2006

Low Plasma DHA at Baseline Predicts Greater Risk of Future Suicide Attempts
Cox proportional hazard ratio=0.29, p<0.002



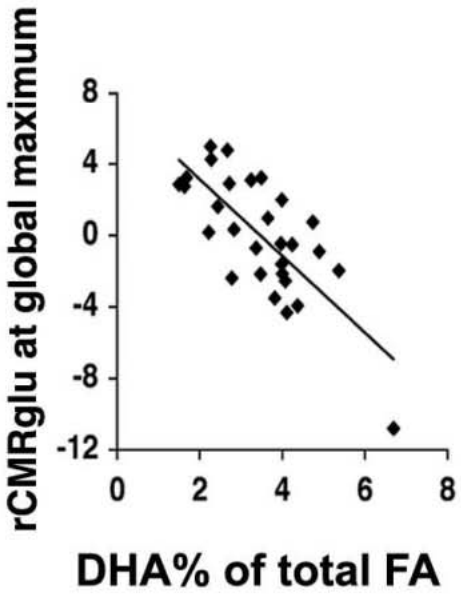
Sublette, Hibbeln et al Am J Psychiatry 2006;163: 1100-1102

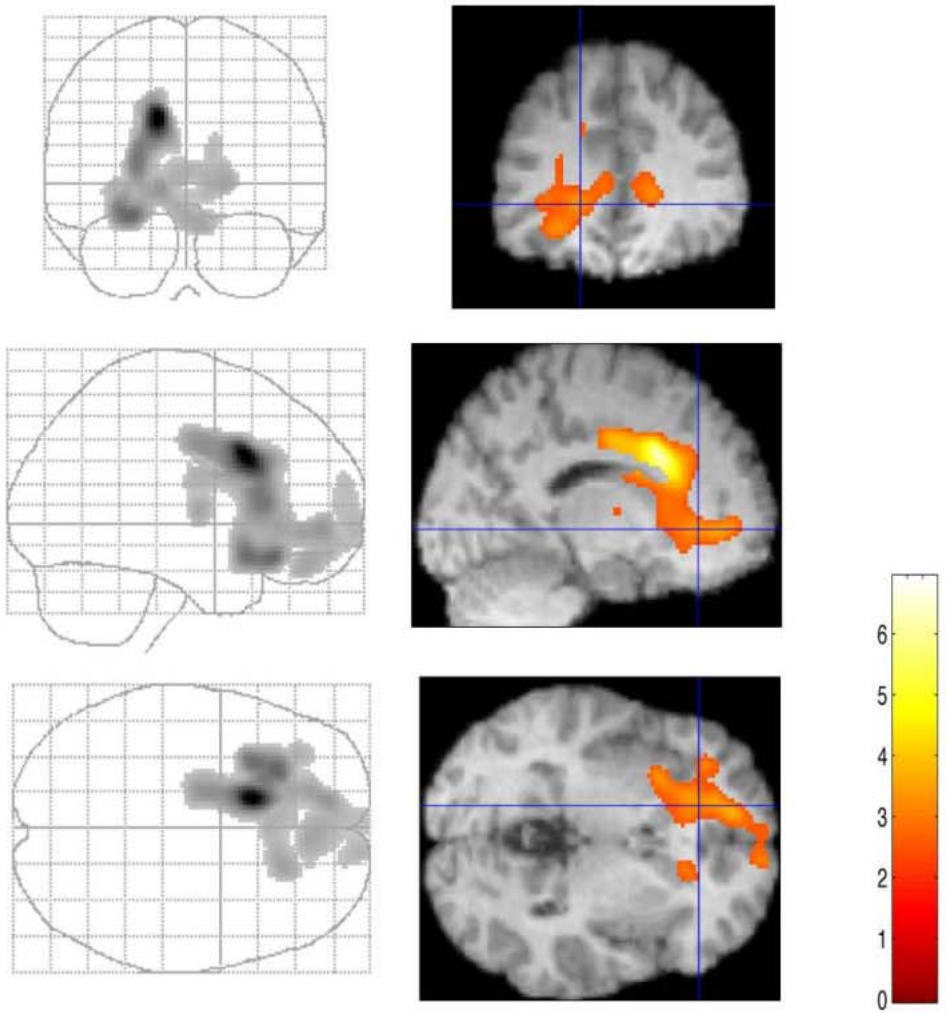
Amygdala and Ant. Cingulate hyperactivity predicts future suicide attempts



Sublette, Hibbeln, Mann, et al, unpublished 2006

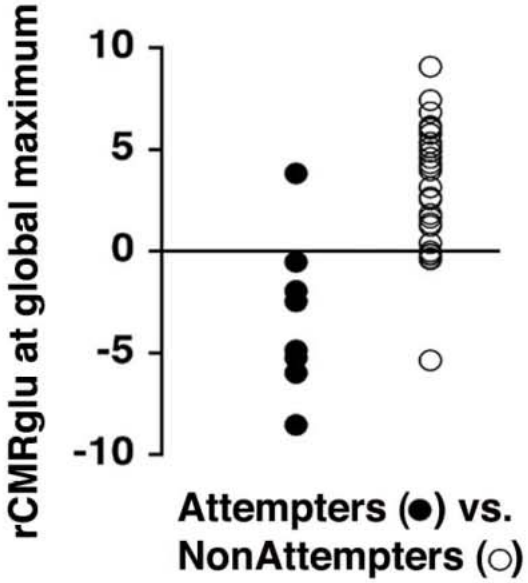
Lower DHA in plasma predicts amygdala and ant cingulate hyperactivity

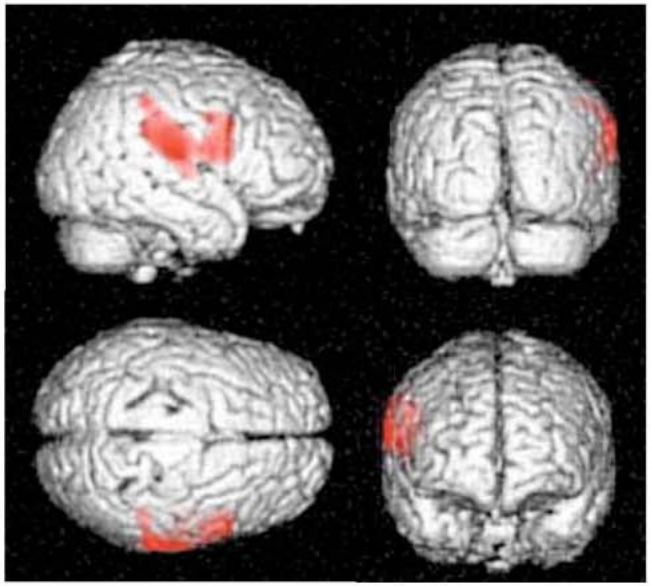


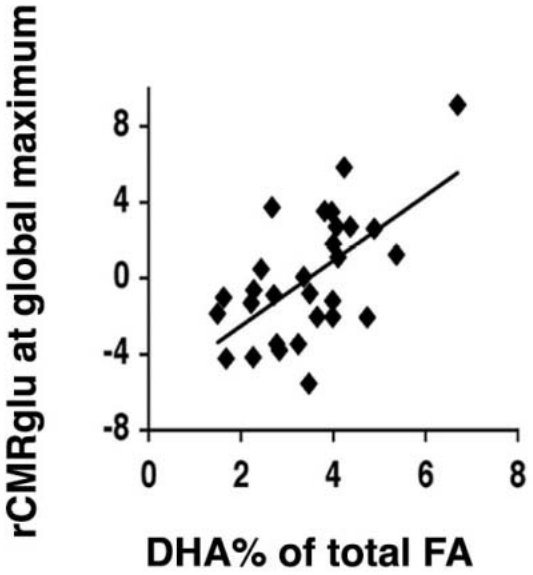


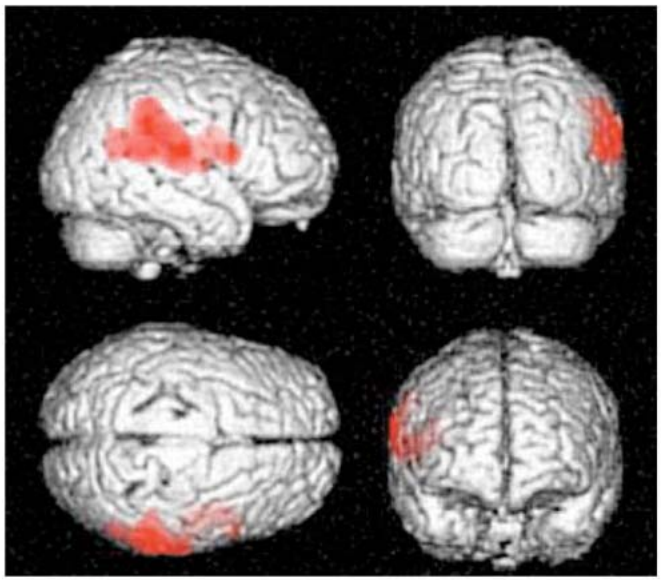
Sublette, Hibbeln, Mann, et al, unpublished 2006

Hypometabolism of parietal/temporal cortex predicts suicide attempts



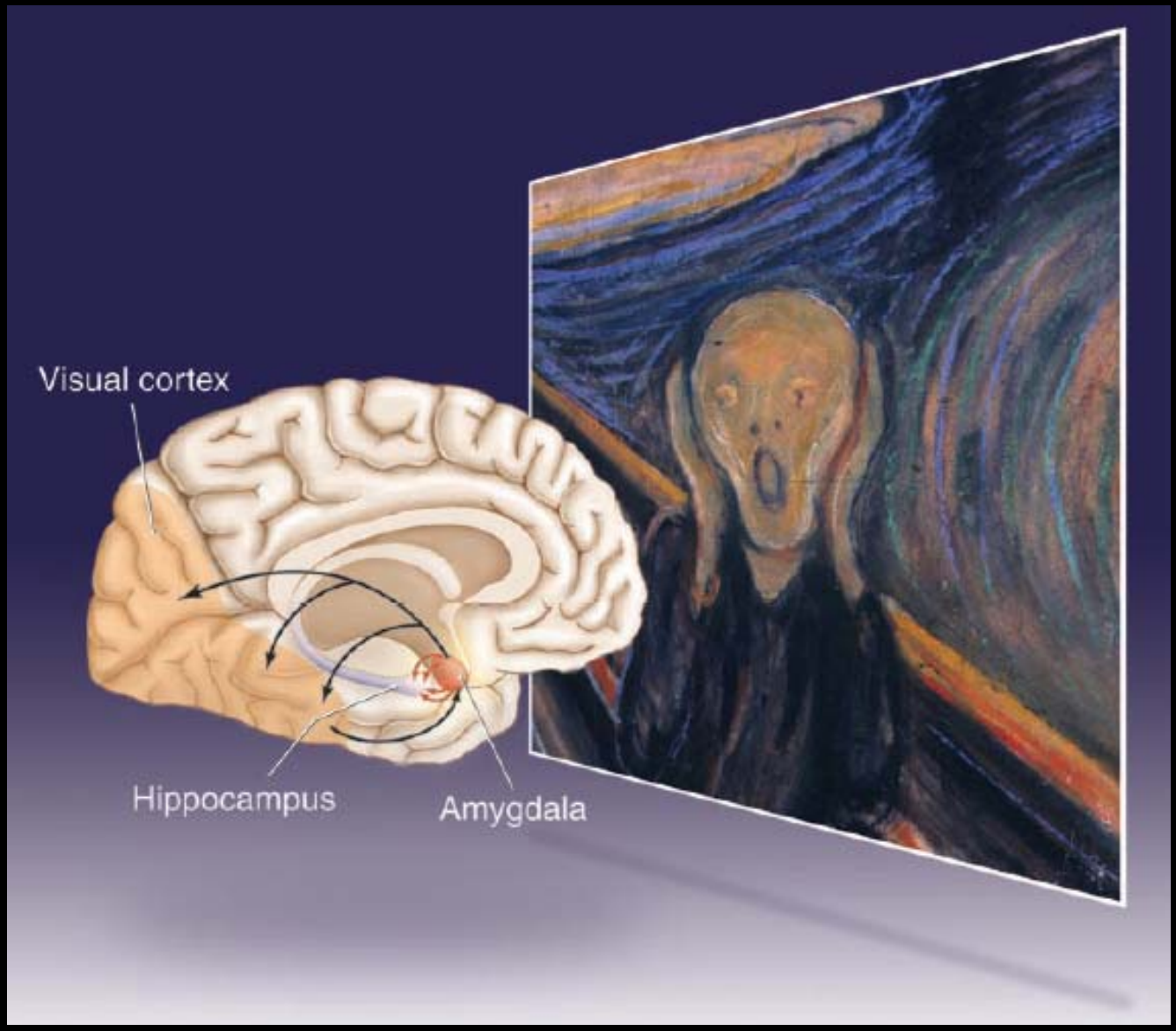






Low DHA predicts hypometabolism of parietal/temporal cortex

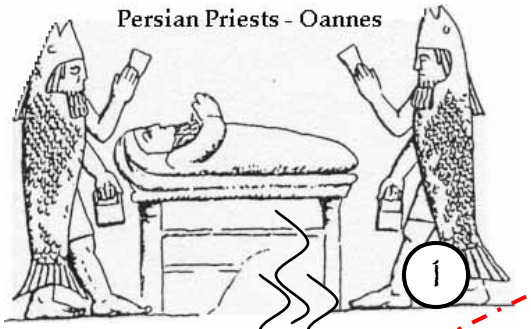
An emotional-perceptual-memory circuit in the human brain.

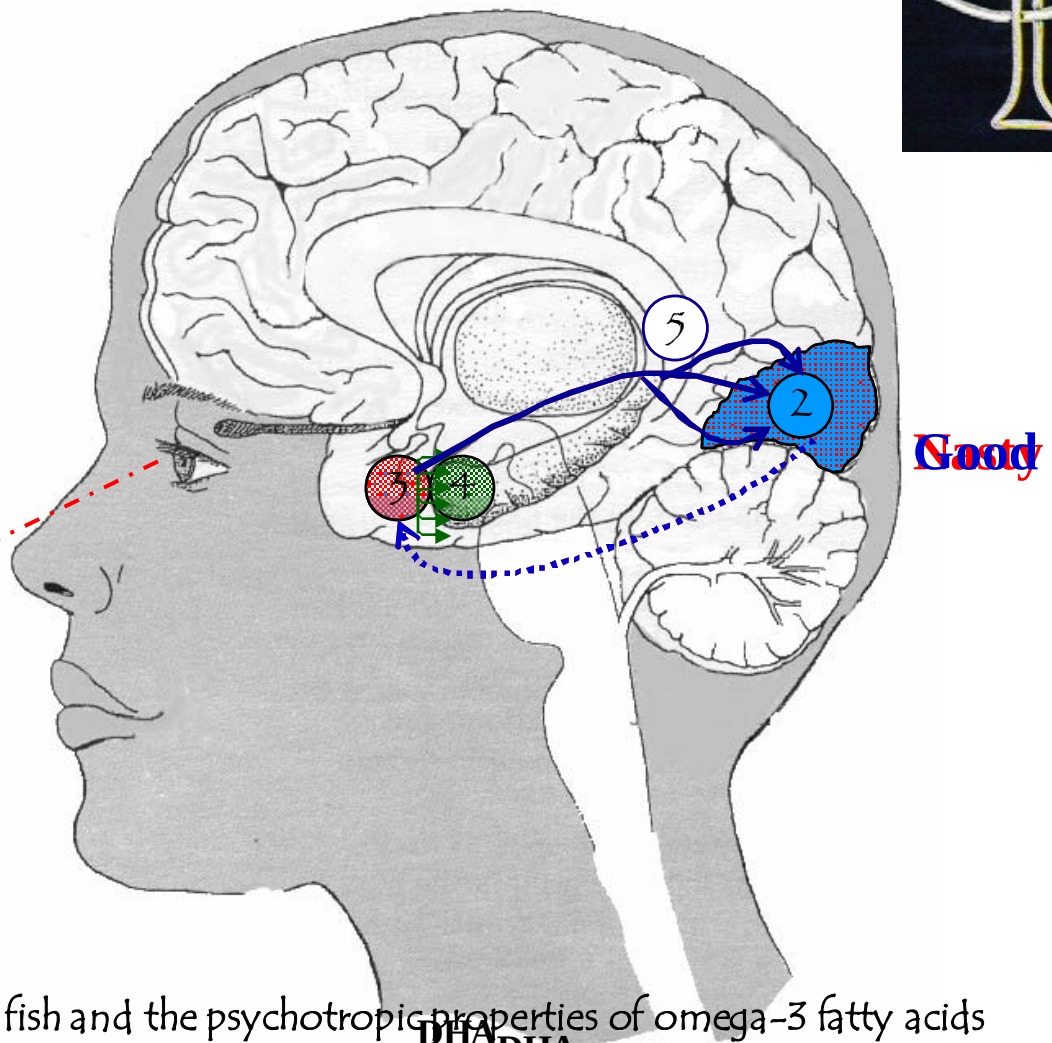


The amygdala (red), an anterior medial temporal lobe structure, is a crucial structure in registering emotional occurrences. Extensive connection (arrows) to visual cortex (orange) and hippocampus (blue) allows amygdala to modulate their function and facilitate perceptual and memory functions in those regions. R.J. Dolan, Science '02

Friday

6





Cultural symbolism of fish and the psychotropic properties of omega-3 fatty acids
Reis and Hibbeln Prost Leucot Essent Fatty Acids (2006), 75, 227-236

Taoism

Yin/Yang - The fish symbol, represents a central philosophy
Chinese medicine is based in part on balancing the
energies of the body with Yin or Yang foods

Yang foods:

Meats, fried foods, spicy foods, hot

Yin foods:

Grown underground, calming, mild, cold
Seafood, from cold water, is the archetypal yin food

Medicine for Hot Temper
Early 20th Century

Courtesy Natasha Louder- Science Correspondent The Economist

Shinto

Ebisu is the deity of prosperity in one's occupation. In agricultural villages he is considered a deity of the rice paddies, and in fishing villages he is believed to ensure a good catch. He is also venerated as a deity of the kitchen. Ebisu is usually depicted carrying a sea bream (a symbol of good luck) under his left arm and a fishing rod in his right hand.

1,000 Ebisu having fun

28 Potential Confounding Variables were Uniformly Included in all Logistic Regression Analyses

Individual (categorical) variables

1. Sex of the child (m,f),
2. Age of the mother (<, ≥ 20 y),
3. Parity (primiparous, multiparous),
4. Maternal education (<completed O level, rest),
5. Housing status (subsidized public housing, rented, owned/mortgaged),
6. Crowding (≤, > 1 per/room),
7. Stressful life events at 18 w gestation (upper 10%, lower 90% of cohort), had partner at time of birth (no, yes),
8. Smoking status (never, smoked before but not at 18 w gestation, or still smoking at 18 w gestation),
9. Alcohol use during pregnancy (non-drinker, drank before mid-pregnancy, still drinking mid-pregnancy) and
10. Breastfeeding (none, some) and
11. Ethnicity (White, Black, Asian).
12. Obstetric variables: prematurity (<, > 3 w early) and birth weight (<,> 5 Lbs, 3 oz).

Composite (continuous) variables

13. HOME Score at 6 mo
14. ALSPAC Family Adversity Index (during pregnancy)

Nutritional variables 12 food groups

Hibbeln et al, The Lancet, Feb 17, 2007

Factors Comprising the ALSPAC Family Adversity Index (ALSPAC - FAI) in Pregnancy

Demographic variables

1. Mother <20 at study delivery
2. Mother <17 at first birth

Housing

3. Became homeless
4. Persons/room >1
5. No sole use of bath or shower
6. No running hot water
7. No indoor toilet
8. No kitchen
9. Mold present
10. Roof leaks
11. Rodents or cockroaches present

Poor financial circumstances

12.-16. Derived from 5 questions

Partner relationship

17. No partner
18. No intimate bond
19. No affection
20. High aggression
21. Physically cruel
22. Emotionally cruel
23. No emotional support
24. No practical support
25. Afraid partner might leave

Education

26. Mother has no qualifications
27. Partner has no qualifications

Social network

28. Not able to share feelings
29. No one to discuss problems with
30. No friends to borrow money from in times of trouble
31. No relations to borrow money from in times of trouble
32. Maternal emotional status
33. High anxiety score
34. High depression score
35. Has attempted suicide

Substance abuse

36. Uses hard drugs
37. Has alcohol problem
38. Partner has alcohol problem
39. Drinks > 2 units /day
40. Partner drinks >2 units/day

Crime

42. In trouble with police
43. Convicted of an offence
44. Partner in trouble with police

FAI and HOME scores are composite scores included in multiple logistic regression analyses

Hibbeln et al, The Lancet, Feb 2007

IQ by WISC-III ^{UK} at age 8 and concordance or excess of the advisory limit (>340 g/w)

		None vs. Exceeds (df=1)			Low vs. Exceeds (df=1)			3 group trend
WISC	n	OR	95% CI	p	OR	95% CI	p	p
Full scale	5,262	1.29	0.99-1.69	0.06	1.19	0.99-1.42	0.06	0.04
Performance	5,402	0.98	0.76-1.27	ns	0.99	0.84-1.18	ns	ns
Verbal	5,407	1.48	1.16-1.90	0.002	1.09	0.92-1.29	0.06	0.004

Risk of being in the lowest quartile of the cohort.
Adjusted for 28 potential confounding variables in multivariate logistic regression analyses.

Hibbeln et al, The Lancet 17 Feb 2007

Motor/ Social/ Communications Development and concordance or excess of the advisory limit (>340 g/w)

		None vs. Exceeds (df=1)			Low vs. Exceeds (df=1)			3 group trend
	n	OR	95%CI	p	OR	95%CI	p	p
Fine motor								
6 m	8746	1.01	0.83-1.23	ns	1.12	0.99-1.28	0.08	ns
18 m	8228	1.25	1.04-1.51	0.02	1.09	0.96-1.23	ns	0.02
30 m	7728	1.04	0.85-1.27	ns	1.04	0.91-1.19	0.02	ns
42 m	7596	1.35	1.09-1.66	0.005	1.14	0.98-1.31	ns	0.005
Social Development								
6 m	8743	1.15	0.95-1.40	ns	1.01	0.89-1.16	ns	ns
18 m	8226	1.01	0.83-1.24	ns	1.01	0.88-1.15	ns	ns
30 m	7711	1.24	1.01-1.53	0.04	1.12	0.98-1.29	ns	0.03
42 m	7592	1.21	0.98-1.50	0.07	1.17	1.01-1.35	0.03	0.04
Communications Development								
6 m	8745	1.30	1.04-1.63	0.02	1.15	0.98-1.35	0.08	0.02
18 m	8237	1.26	1.03-1.53	0.02	1.02	0.90-1.17	ns	0.05

Risk of being in the lowest quartile of ALSPAC Early Developmental Index. Adjusted for 28 potential confounding variables in logistic regression analyses.

Hibbeln et al, The Lancet, 17 Feb 2007

Behavioral disorders at age 7 and concordance or excess of the advisory limit (>340 g/w)

		None vs. Exceeds (df=1)			Low vs. Exceeds (df=1)			3 group trend
	n	OR	95%CI	p	OR	95%CI	p	p
Total score	6570	1.17	0.86-1.60	ns	0.98	[0.79-1.22]	ns	ns
Peer problems	6581	1.25	0.96-1.62	ns	0.97	[0.80-1.16]	ns	ns
Conduct Disorders	6586	1.21	0.89-1.64	ns	1.01	[0.81-1.25]	ns	ns
Emotional	6582	1.09	0.83-1.44	ns	0.96	[0.80-1.17]	ns	ns
Hyperactivity	3179	1.13	0.84-1.53	ns	0.91	[0.73-1.12]	ns	ns
Prosocial	6582	1.44	1.05-1.97	0.02	1.16	[0.93-1.44]	ns	0.02

Risk of being in the lowest quartile of Strengths and Difficulties Questionnaire.
Adjusting for 28 potential confounding variables in logistic regression.

Hibbeln et al, The Lancet 17 Feb 2007