Seafood intake in pregnancy: neurodevelopmental benefits and hypothetical risks

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Committee on the Role of Seafood Consumption in Child Growth and Development of the National Academy of Sciences, Engineering and Medicine

Washington, DC

This presentation is solely the responsibility of the presenter, Joseph R. Hibbeln, MD

The charge of this NASEM committee is to examine associations between seafood intake (maternal and child) and child growth and development.

This talk will directly address this charge by examining data regarding **seafood consumption as a whole food by pregnant women** especially in long-term cohort studies.

I have been studying this subject for more than 20 years primarily at the National Institutes of Health, DHHS, and have authored numerous and foundational research papers in this field.

Outline

1. Importance of brain critical nutrients available predominantly in seafood, for human neurodevelopment, focus on omega-3 fatty acids

2. Current scientific evidence for determining safe and beneficial amounts of seafood consumption for human neurodevelopment

3. Scientific evidence of adverse child neurodevelopment from consuming seafood in pregnancy – no such evidence found in the scientific literature -

   Evidence of subtle diminishments in neurodevelopment from consuming Pilot Whale have been extrapolated to consuming seafood

1. Importance of brain critical nutrients

Seafood is the natural and primary source of omega-3 fatty acids and many other brain nutrients critical for optimal human neurodevelopment.

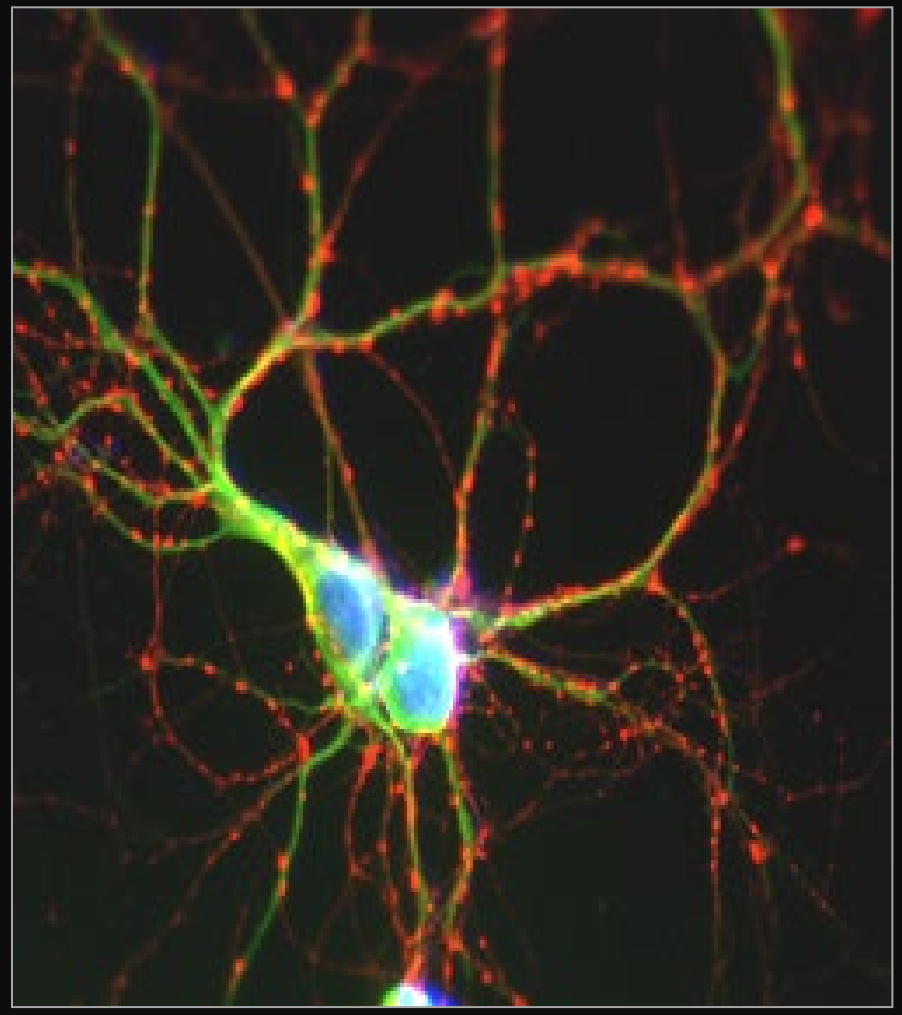
Docosahexaenoic acid (DHA) - an essential omega-3 fatty acid -

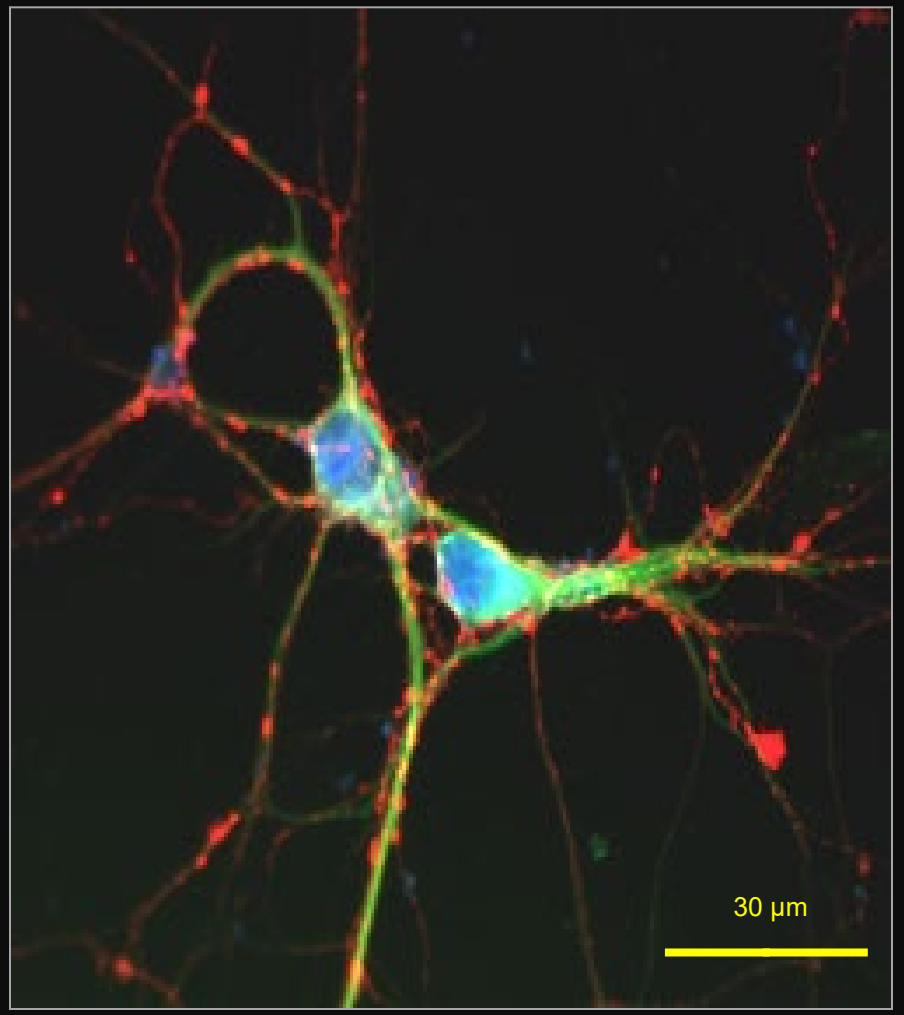
- **DHA comprises 10% - 20% dry weight of human brain**
- **DHA cannot be synthesized de novo in humans – *biochemically essential* –**
- **Must be consumed from dietary sources**
- **Seafood has been the primary dietary source of DHA throughout evolution access to seafood - disproportionate encephalization of *homo sapiens* brains -**
- **DHA is also – *functionally essential* –**
- **Hundreds of mechanisms have been identified impacting cellular, molecular metabolic and genetic expression pathways that are fundamental to human neurodevelopment**
- **DHA is crucial to the fundamental biophysics of synaptic neuronal membranes**
- **Adequate dietary access to DHA is essential for normal brain development**

Crawford MA et al Nutr Health 2012
Kim HY et al. Int J Mol Sci 2022

Adequate DHA (22:6 n-3)

Deficient (22:5 n-6)





Cao et al. *J. Neurochem.* 2009

2. Current scientific evidence for determining safe and beneficial amounts of seafood consumption for human neurodevelopment

A brief history of the advice to limit 12 oz/wk of seafood consumption in pregnancy

- **In 2000**, the FDA wanted to be prudent and an issue a upper limit for seafood consumption in pregnancy

  - Unfortunately- very few data on maternal consumption were available

- **In 2001, the FDA chose an amount that would not conflict with American Heart Association recommendations for heart health (2-3 meals/wk or 12 oz/wk)**

Thus, the 2001 FDA limit of (12 oz/wk) was not based on any calculation or evaluation of seafood consumption in pregnancy, nor even on the RfD

- **In 2004** FDA/EPA jointly reissued the 12 oz/wk limit (***same basis as 2001, no calculations, not based on RfD***)
- **In 2010** the DGA recommend 12 oz/wk limit because the 2001/2004, FDA/EPA had recommended it

  (***same basis as 2001, no calculations, not based on RfD***)

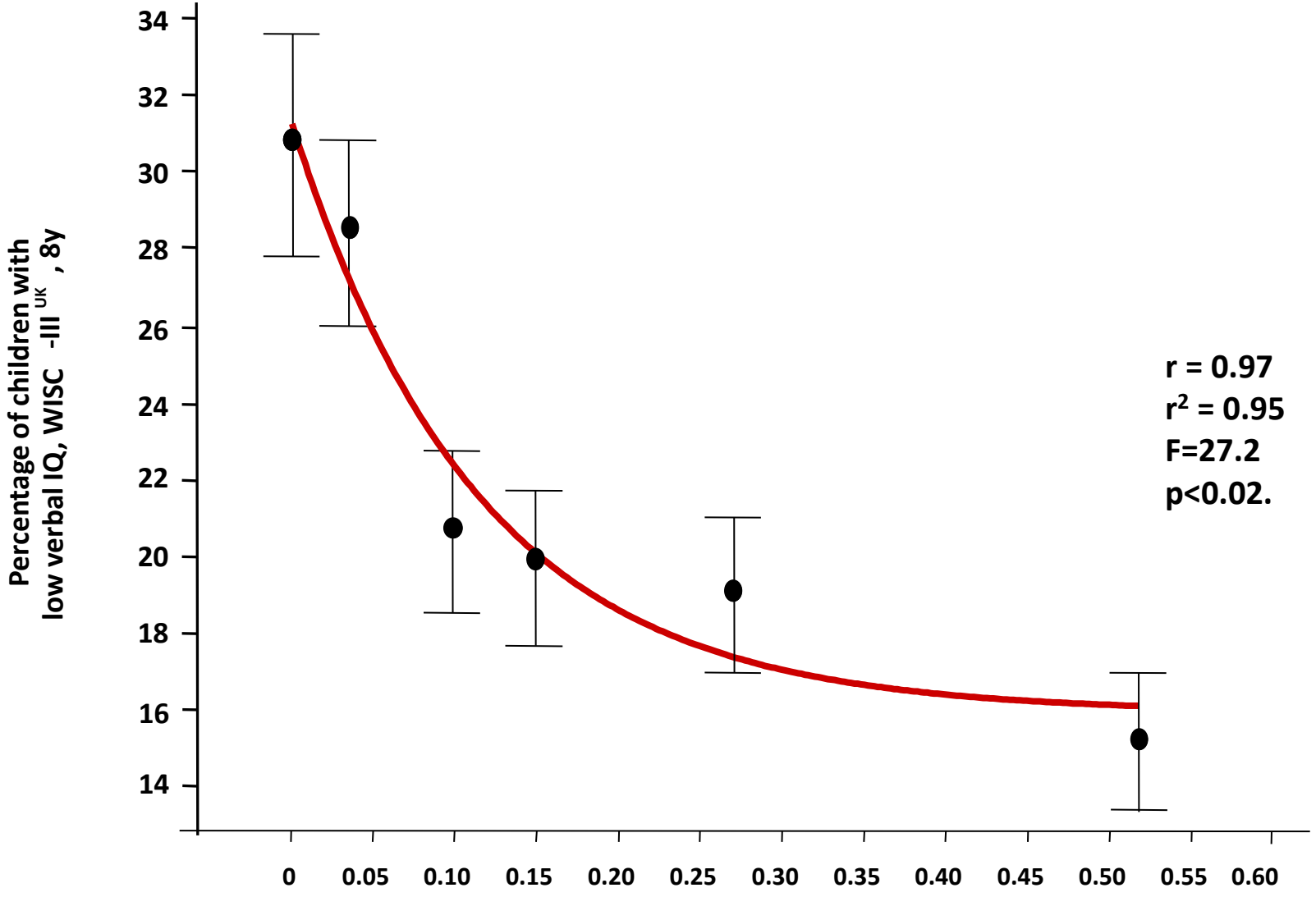
- **In 2020** DGA and FDA/EPA advice currently recommends a 12 oz/wk limit

  (***same basis as 2001, no calculations, no review of the data***)

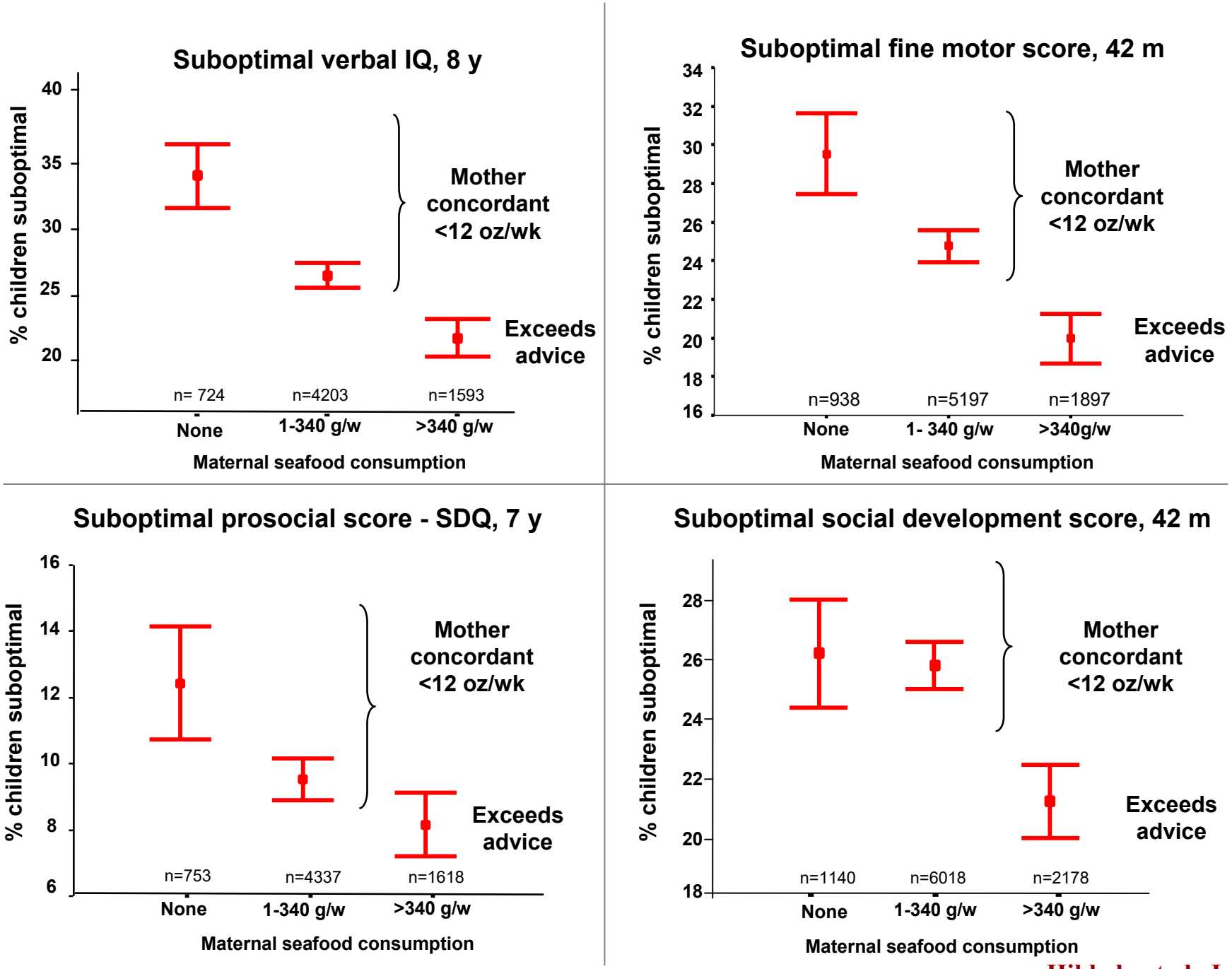
More scientific data are available now than in 2001

Thus, it is appropriate to re-evaluate efficacy of the advice to limit seafood consumption to 12 oz/wk in pregnancy

Low maternal omega-3 consumption from seafood and suboptimal verbal IQ among their children (n=8,916)

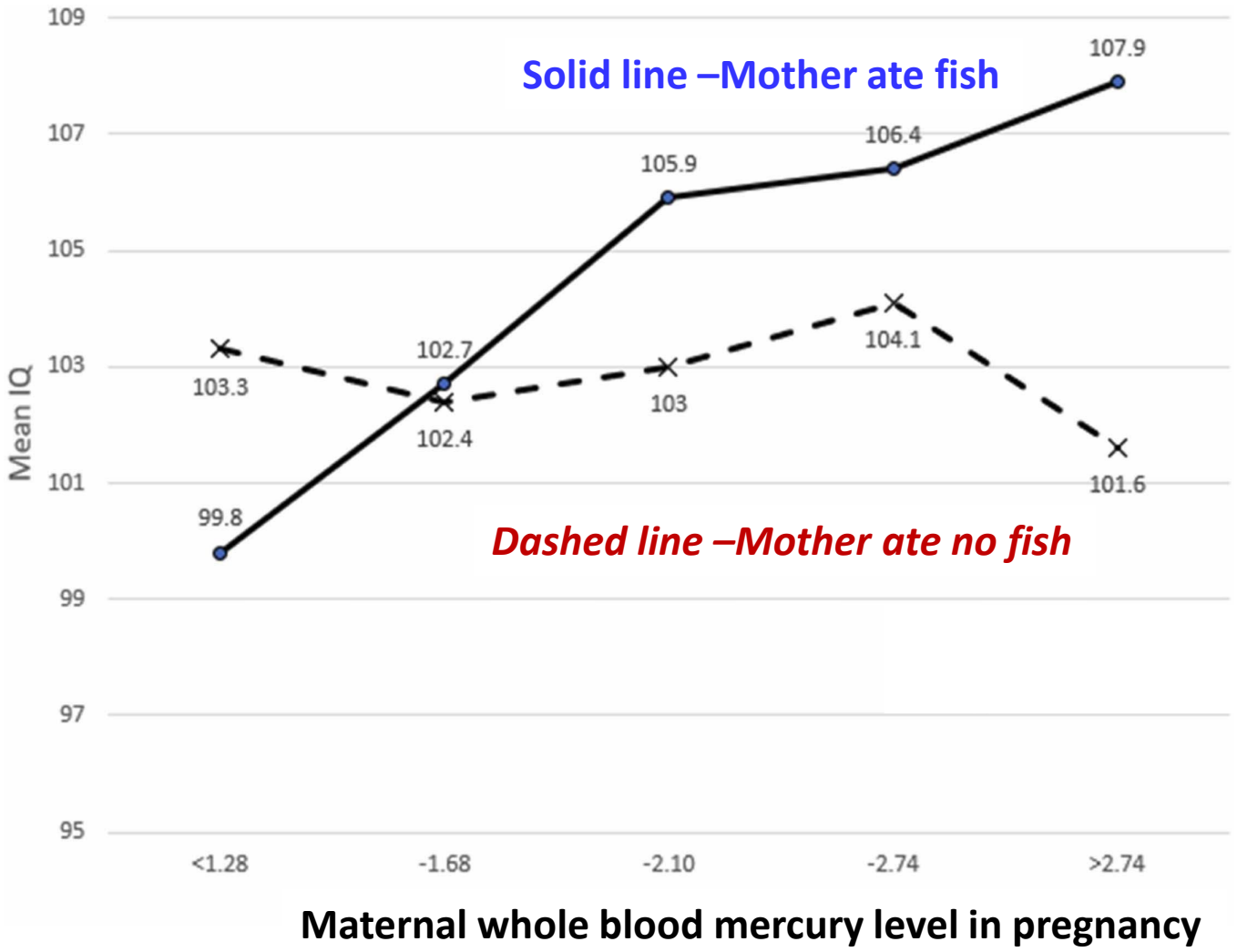


Hibbeln et al, Lancet 2007: 369: 578-585



Hibbeln et al, Lancet 2007: 369: 578-585

Children had 6.3 IQ points higher when mothers ate fish as compared to when mothers did not eat fish This despite both groups being exposed to the same levels of Hg



- **This interaction was true of five cognitive outcomes**
  - **full IQ**
  - **performance IQ**
  - **mathematical comprehension**
  - **science comprehension**
  - **social cognition.**

- Higher levels of maternal Hg were associated with better child outcomes
- Hg likely a biomarker of higher seafood consumption
- Does not support **'Closer to Zero'**

Golding et al Neurotox 2022 (91) p 22-30

Norwegian study of seafood consumption in pregnancy

Consumption of less than 14 oz/wk (<400 gm/wk) is associated with harm

n= 51,238 mother–child pairs

Table 1 Distribution of mean CBCL scores at children aged 3 and 5 years and by maternal reported weekly fish intake below and above 400 g

	All		<400 g fish weekly		≥400 g fish weekly	
CBCL outcome	**N***	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
3y Internalising	51 238	9.2 (8.3)	47 516	9.3 (8.3)	3722	8.7 (8.2)
3y Externalising	51 238	12.6 (7.2)	47 516	12.7 (7.2)	3722	12.2 (7.2)
5y Internalising	31 624	6.6 (7.8)	29 404	6.6 (7.8)	2220	6.2 (7.1)
5y Externalising	31 737	8.7 (7.0)	29 508	8.7 (7.1)	2229	8.3 (7.1)

Higher CBCL scores are indicating increased internalising and externalising behaviour problems.
*Participants that answered the 5-year questionnaire were included if they had also answered the 3-year questionary and the CBCL score. The number of participants that answered the CBCL externalising score at 5 years was n=31 737, while n=31 624 answered the CBCL internalising score.
CBCL, Child Behaviour Checklist.

Vejrup K *et al*. BMJ Nutrition Prevention & Health 2022

Higher mercury levels were associated with <u>better</u> neurodevelopmental outcomes

Current science on seafood consumption in pregnancy does not support the advice to limit to 12 oz/wk

- based on the 2001 AHA guidelines -

- Currently **16 cohort studies** have reported maternal seafood consumption >12 oz/wk and neurodevelopmental outcomes in offspring:

  - **10 reported benefits** to neurodevelopment >12 oz/wk
  - **6 reported no adverse effects on** neurodevelopment >12 oz/wk
  - **0 reported no adverse effects on** of neurodevelopment >12 oz/wk

- The amounts of seafood consumption >12 oz/wk in these studies:
  - 20's, 30's, 40's, 60's, >100 oz/wk

Current US advice to limit seafood consumption in pregnancy to <12 oz/wk (<340 gm/wk)

Likely causes the harms it intends to prevent

Limiting seafood in pregnancy likely results in deficiencies of critical brain nutrients and increase the risk of neurodevelopmental harms among the offspring

Is a higher upper limit associated with adverse neurodevelopment?

Systematic reviews using DGA methods report no evidence of adverse neurodevelopment from >100 oz/w seafood during pregnancy, only benefits

n=106,237 Mother-offspring pairs (total in 2019)

- **Hibbeln et al 2019 conducted two systematic reviews (Maternal and child consumption)**
- **Rigorously used methodologies detailed by the DGA Scientific Advisory Committee 2020**
- **NESR, Assessment of Bias, Grading of Evidence, Expert Panel with DGA training, double and triple checking**

- **44 publications on consumption of seafood among mother-infant pairs and children**
- **Maternal seafood consumption**
  - **"Overall, benefits to neurocognitive development began at the lowest amounts of seafood consumed (~4 oz/wk) and continued, above 12 oz/wk, some range up to >100 oz/wk."**
  - **Benefits of seafood consumption (higher IQ 7.7 pts) were found despite associated increases in me-Hg**
  - **Harm were only reported when inadequate amounts of seafood were consumed**

Hibbeln, JR et al PLEFA 2019

Additional publications since 2019 confirm that seafood consumption in pregnancy is safe >12 oz/wk - no evidence of adverse child development-

Current total n=209,391 mother-child pairs

N = 81,697 Hamazaki, et al 2022

n = 10,179 Wei et al 2023

n = 11,278 Lauzon-Guillain et al 2022

Harm were only reported when inadequate amounts of seafood were consumed

3. Scientific evidence of adverse human neurodevelopment from consuming seafood.
- none found -

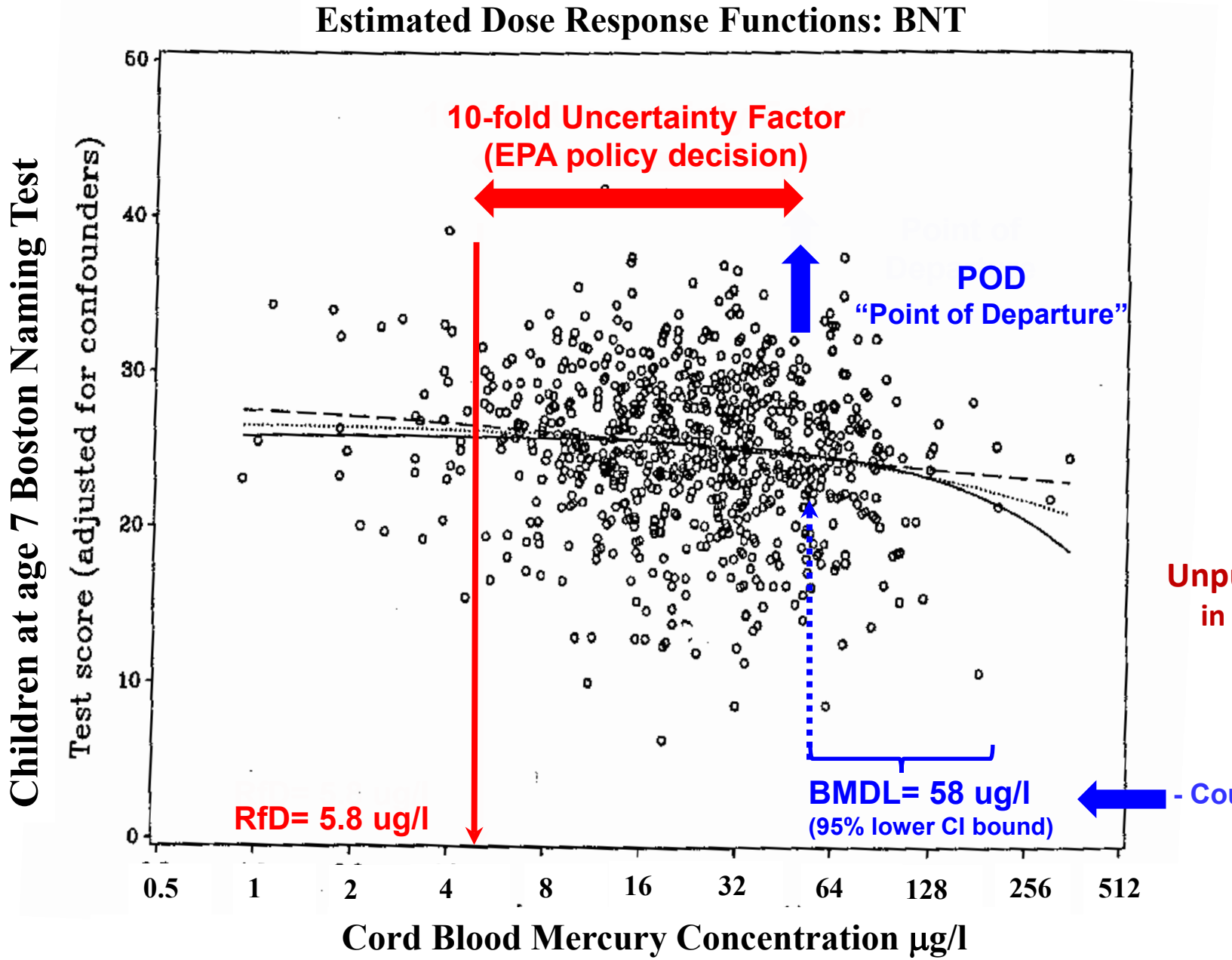
Evidence of a small diminishment in neurodevelopment from consuming Pilot Whale *has been extrapolated to seafood*

A small statistical association between higher mercury exposure from consumption of Pilot Whale during pregnancy and subtle evidence of neuropsychological deficits

Study complicated by co-exposures to PCBs and other toxicants

Pilot whales are sea mammals and not included in seafood by most countries

Faroe Islands study - the basis of the Reference Dose (RfD)



Unpublished Material
in NRC 2000, p. 296

NOEL
"No Observable Effects Level"
- Could not be calculated-

Note Log Scale

What is the magnitude of the theoretical harm avoided from me-Hg in Pilot Whale?

"Subtle evidence of neuropsychological deficits"
e.g. detectable abnormalities in the Boston Naming Test

Toxicological Effects of Methyl Mercury, National Research Council 2000

The number of pregnant women theoretically exposed to levels above the RfD from seafood consumption were estimated

“60,000 children are born each year at risk…”
(NRC 2000 soundbite p. 327)

They're being poisoned.

Your kids are being poisoned by deadly mercury from power plants.

President Bush: Protect America's Children, Not Power Company Profits!

Advertisement-USA Today March 17, 2004

The RfD is not a bright line between safety & harm

The EPA defines the RfD as "a safe dose that can be consumed daily for a lifetime"

"60,000 children are born each year at risk…" (NRC 2000, p. 327)

FDA was concerned that the public was interpreting this statement as meaning that any exposure over the RfD was inherently dangerous, a "bright line of harm"

FDA asked the chairman of the NRC committee to clarify what "at risk" meant (Levitt 2000).

The 2000 NAS committee chairman responded the term "at risk" actually referred to children born to mothers exposed over the RfD but that actual harm to these children had not been established. (Goyer 2000).

The Institute of Medicine National Academy of Sciences 2007 also clarified that:
"Reference levels for the intake of contaminants, such as for…methylmercury…can be misinterpreted as 'bright lines,' that intakes above the level are 'harmful' and intakes below the level are 'safe'

Current US Dietary Advice (2020) still treats the RfD as a bright line of harm

This chart can help you choose which fish to eat, and how often to eat them, based on their mercury levels.

What is a serving? As a guide, use the palm of your hand.

Pregnancy and breastfeeding:
1 serving is 4 ounces

Eat 2 to 3 servings a week from the "Best Choices" list
(OR 1 serving from the "Good Choices" list).

Childhood:
On average, a serving is about:

1 ounce at age 1 to 3
2 ounces at age 4 to 7
3 ounces at age 8 to 10
4 ounces at age 11

Eat 2 servings a week from the "Best Choices" list.

Best Choices

- Anchovy
- Atlantic croaker
- Atlantic mackerel
- Black sea bass
- Butterfish
- Catfish
- Clam
- Cod
- Crab
- Crawfish
- Flounder
- Haddock
- Hake
- Herring
- Lobster, American and spiny
- Mullet
- Oyster
- Pacific chub mackerel
- Perch, freshwater and ocean
- Pickerel
- Plaice
- Pollock
- Salmon
- Sardine
- Scallop
- Shad
- Shrimp
- Skate
- Smelt
- Sole
- Squid
- Tilapia
- Trout, freshwater
- Tuna, canned light (includes skipjack)
- Whitefish
- Whiting

Good Choices

- Bluefish
- Buffalofish
- Carp
- Chilean sea bass/ Patagonian toothfish
- Grouper
- Halibut
- Mahi mahi/dolphinfish
- Monkfish
- Rockfish
- Sablefish
- Sheepshead
- Snapper
- Spanish mackerel
- Striped bass (ocean)
- Tilefish (Atlantic Ocean)
- Tuna, albacore/ white tuna, canned and fresh/frozen
- Tuna, yellowfin
- Weakfish/seatrout
- White croaker/ Pacific croaker

Choices to Avoid HIGHEST MERCURY LEVELS

- King mackerel
- Marlin
- Orange roughy
- Shark
- Swordfish
- Tilefish (Gulf of Mexico)
- Tuna, bigeye

What about fish caught by family or friends? Check for fish and shellfish advisories to tell you how often you can safely eat those fish. If there is no advisory, eat only one serving and no other fish that week. Some fish caught by family and friends, such as larger carp, catfish, trout and perch, are more likely to have fish advisories due to mercury or other contaminants.

www.FDA.gov/fishadvice
www.EPA.gov/fishadvice

U.S. FOOD & DRUG ADMINISTRATION

EPA United States Environmental Protection Agency

This advice for fish species is based solely on Hg exposures assumed to stay below the RfD, treated as a bright line of harm

Nutritional benefits of seafood are promoted, but not quantitatively considered in this advice

SUMMARY

Substantial evidence of benefits vs. no evidence of adverse neurodevelopment *when seafood is eaten as whole food in pregnancy*

- **Substantial evidence for neurodevelopmental benefits**
  - **>40** beneficial outcomes in **29** studies **(n=209,391 mother-child pairs)**
    5 of the studies reported benefits when exposure **exceeded the RfD**
    10 of the studies reported benefits >12 oz/wk
    Important benefits (e.g. IQ, Mathematical and Science comprehension, Social envelopment, ect)

- **No evidence for harms (n=209,391 mother-child pairs)**
  - No outcomes where eating seafood was worse than eating no seafood.
    No adverse outcomes in **16** studies >12 oz/wk
    No adverse outcomes in **8** studies with exposures substantially exceeded the **RfD**

- **By contrast, only theoretical harms from Hg, of subtle magnitude**
  - The RfD was based on pilot whale consumption and extrapolated to seafood consumption as a whole food, without accounting for any of benefits from seafood.
  - **one study, n=866**, *2 subtle neurological outcomes,* Pilot whale is not seafood

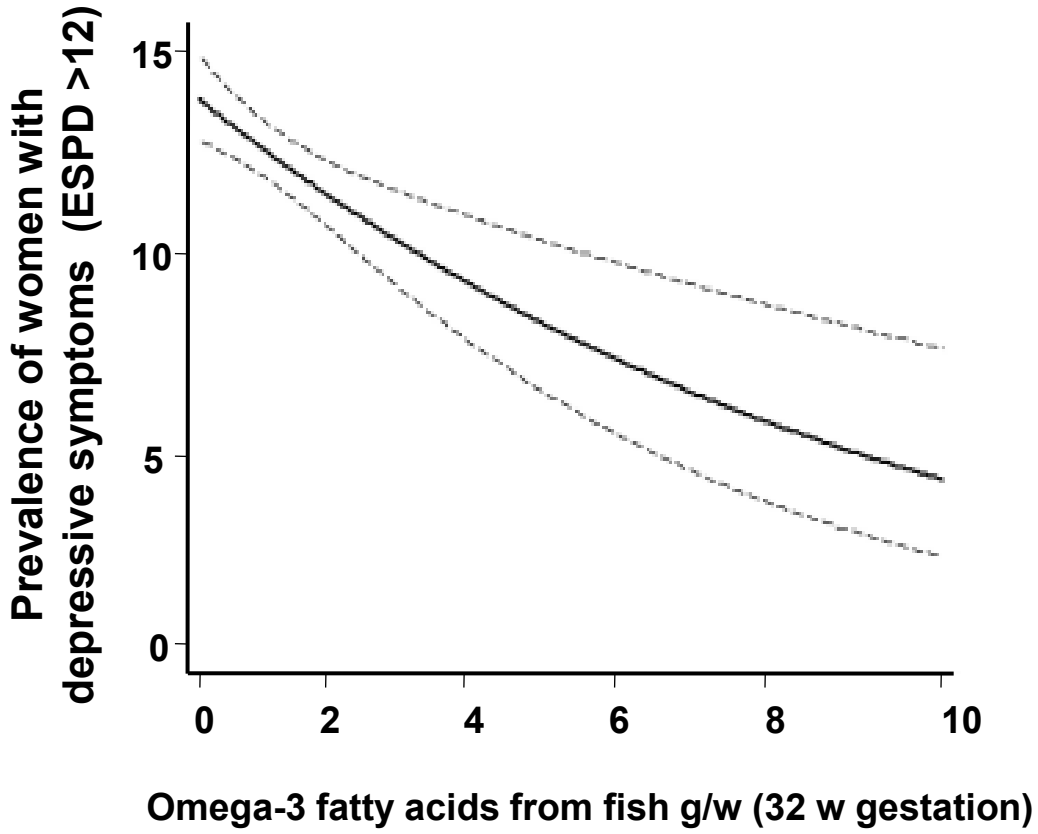
Current US advice for pregnancy likely causes the harms it intends to prevent

The public would be well served by updated dietary advice on seafood consumption in pregnancy that reflects current scientific findings

Depression during pregnancy
- Low maternal seafood consumption -

n=14,541 (UK)

Depression

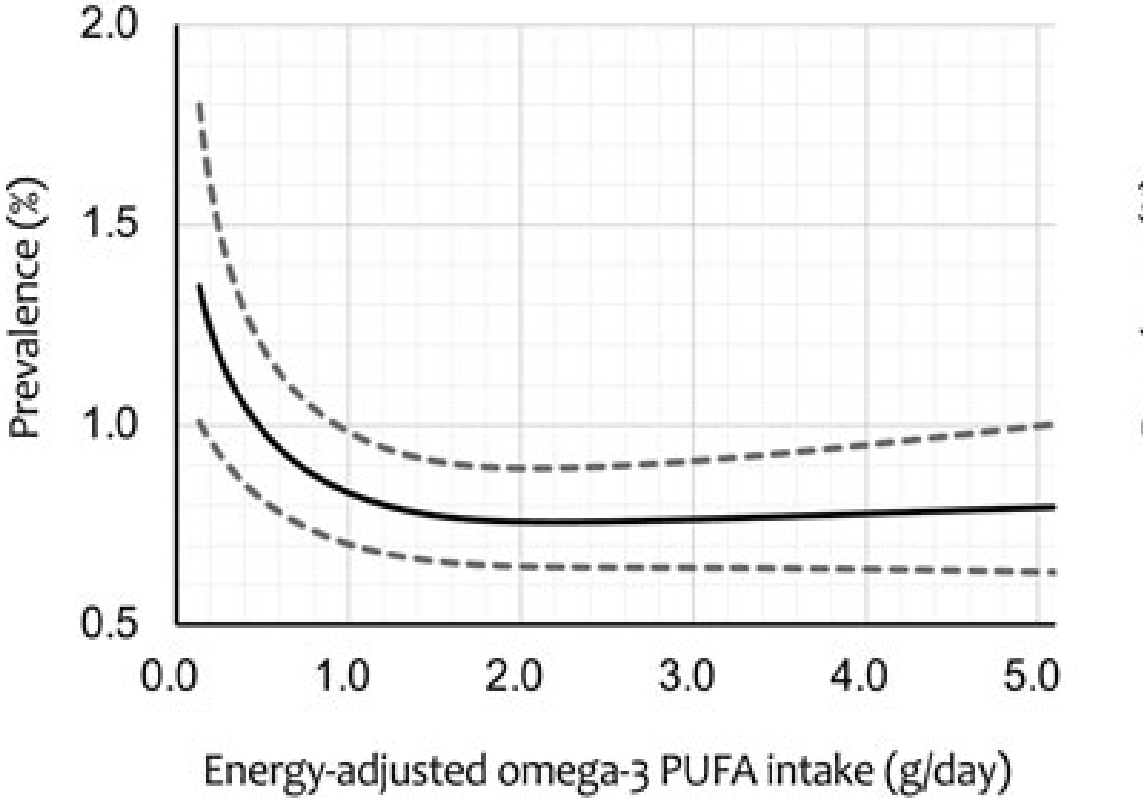


Golding, Hibbeln et al, Epidemiology 2009; 23:3: 1-6

Intimate partner violence during pregnancy
- Low male partner seafood consumption -

n=48,065 pairs (Japan)

Physical violence



Matsumura, Hamazaki, et al. *Epi Psych Sci* 31 (2022): e45.

Thank you

Estimated number of US children born each year at risk for harm from inadequate critical brain nutrients from maternal seafood <12 oz/wk

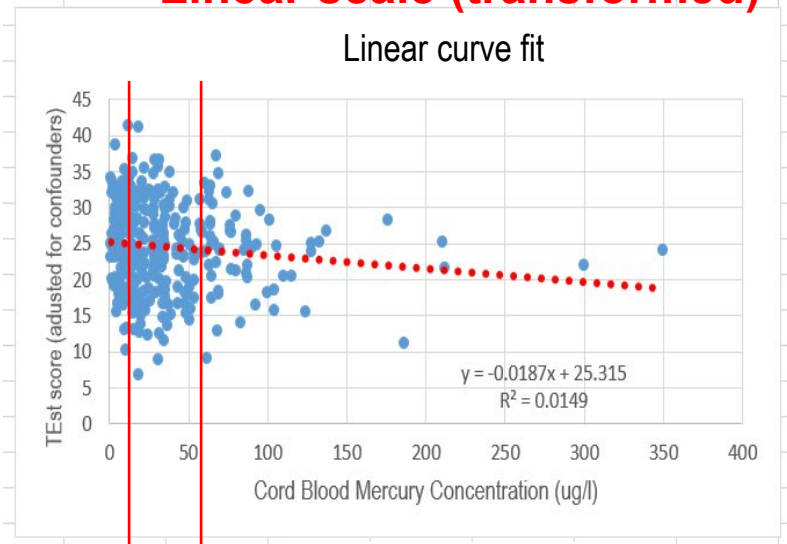
Characteristics*	Pregnant women	Postpartum women	Control group women
	n=1,286	n=522	n=1,349
Aware of mercury in food	73.3 %	74.0 %	58.9 %
Eat no fish	20.8 %	21.1 %	16.9 %
Eat >340.2 g/week (>12 oz/wk) of fish	2.2 %	3.4 %	5.3 %
Eat < 340.2 g/wk (< 12 oz/wk) of fish	**97.8 %**	**96.6 %**	**94.7 %**

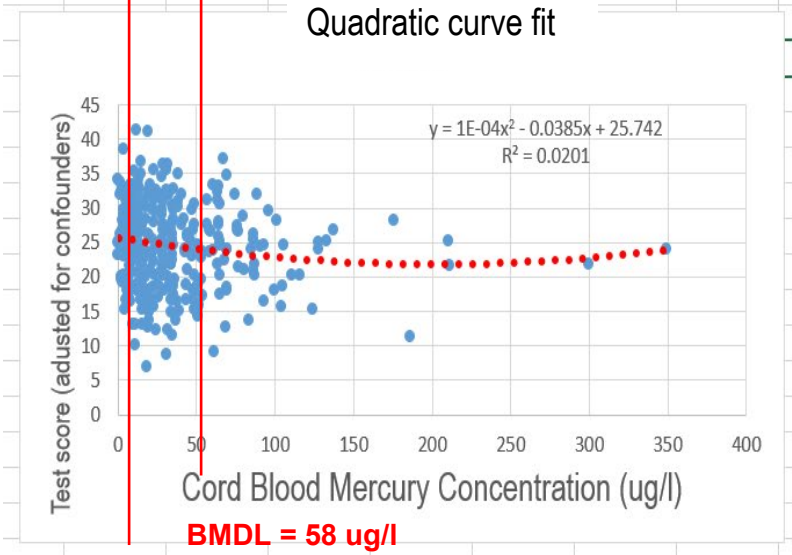
US Census data 2021			
Number of live births	3,664,292		
Number at risk of deficiency	**3,583,678**		
Number of women in US			167.5 million
Number at risk of deficiency			**158.3 million**

*2012 Lando et al Env Res 116 (2012) 85–92

Examination of NRC 2000 figure for the RfD on a linear scale as compared to the original log scale

Linear scale (transformed)





BMDL = 58 ug/l

RfD = 5.8 ug/l

Log scale (NRC 2000)