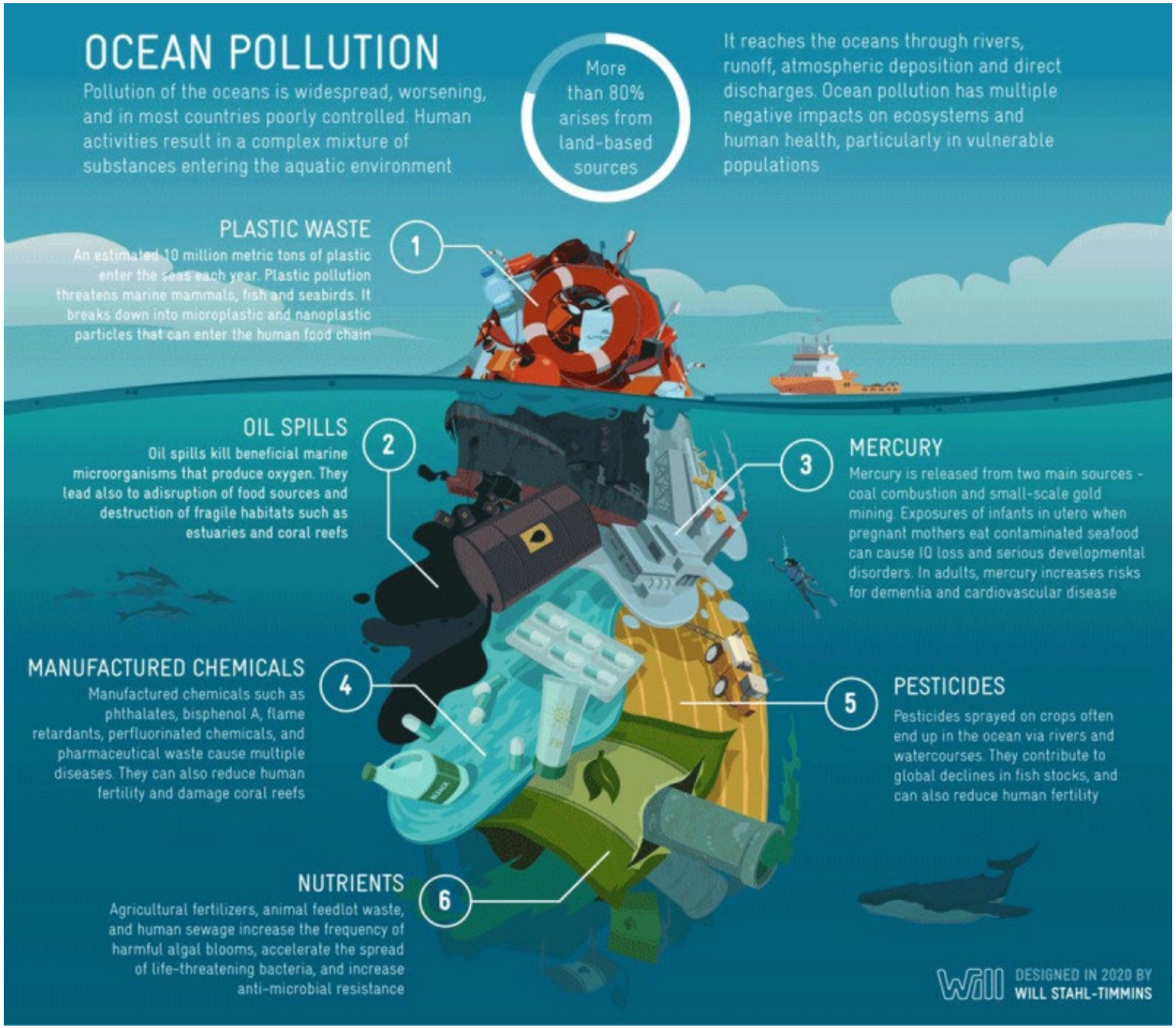
Contaminant mixture effects during pregnancy

Emily Oken, MD, MPH
Alice Hamilton Professor
Department of Population Medicine
Harvard Medical School and
Harvard Pilgrim Health Care Institute

Human Health and Ocean Pollution



Landrigan et al. Ann Glob Health. 2020 Dec 3;86(1):151. doi: 10.5334/aogh.2831

Dietary guidelines for fish consumption

DGA: USDA and HHS
https://www.dietaryguidelines.gov/

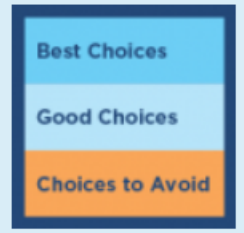
Pregnancy and childhood: FDA and EPA
https://www.fda.gov/food/consumers/advice-about-eating-fish

The *Dietary Guidelines for Americans* recommends eating fish as part of a healthy eating pattern.

The *Dietary Guidelines for Americans* recommends:

- At least 8 ounces of seafood (less for children§) per week based on a 2,000 calorie diet.
- Those who are pregnant or breastfeeding consume between **8 and 12 ounces per week** of a variety of seafood from choices that are **lower in mercury**.

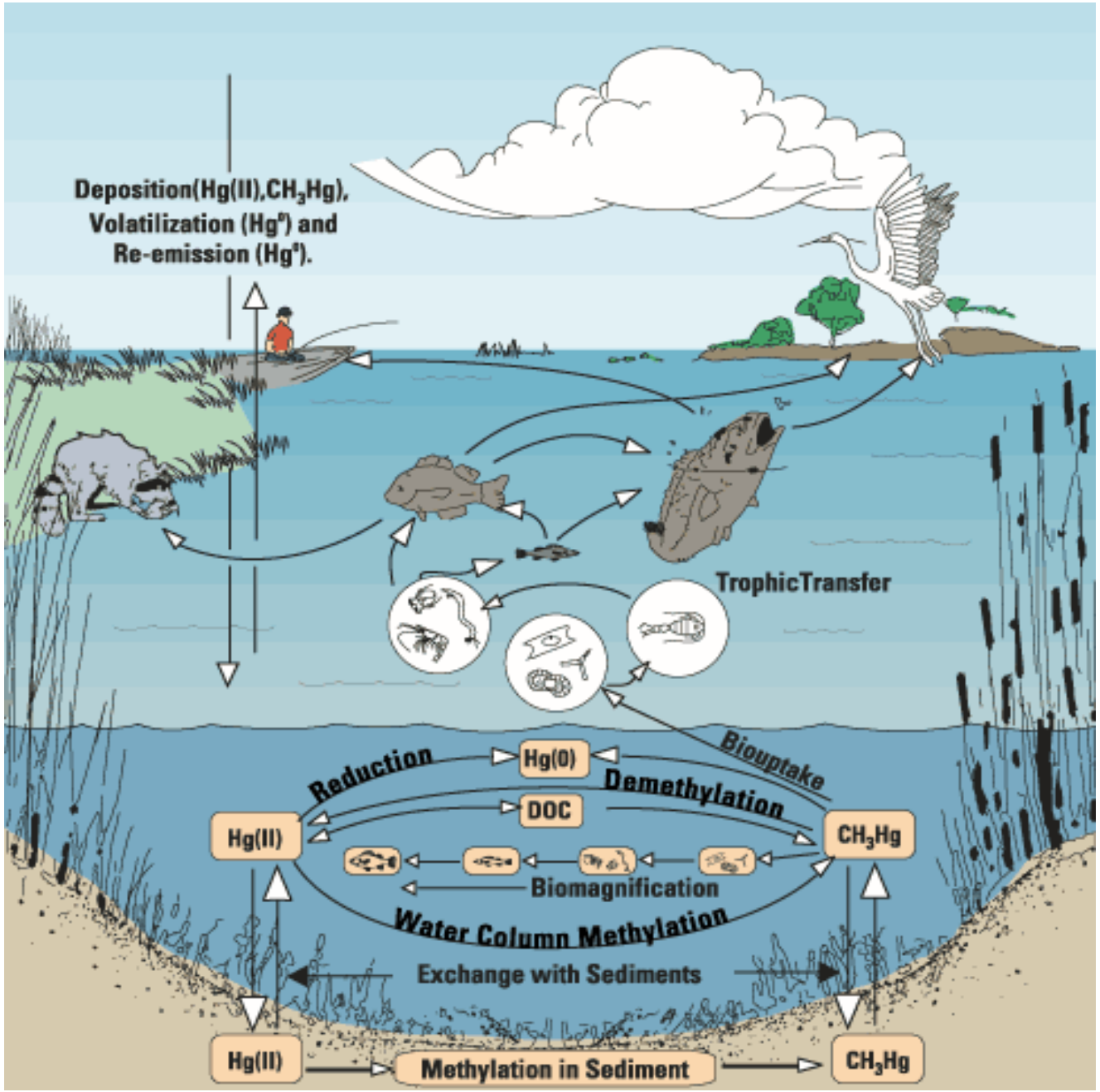
Choose a variety of fish that are lower in mercury.



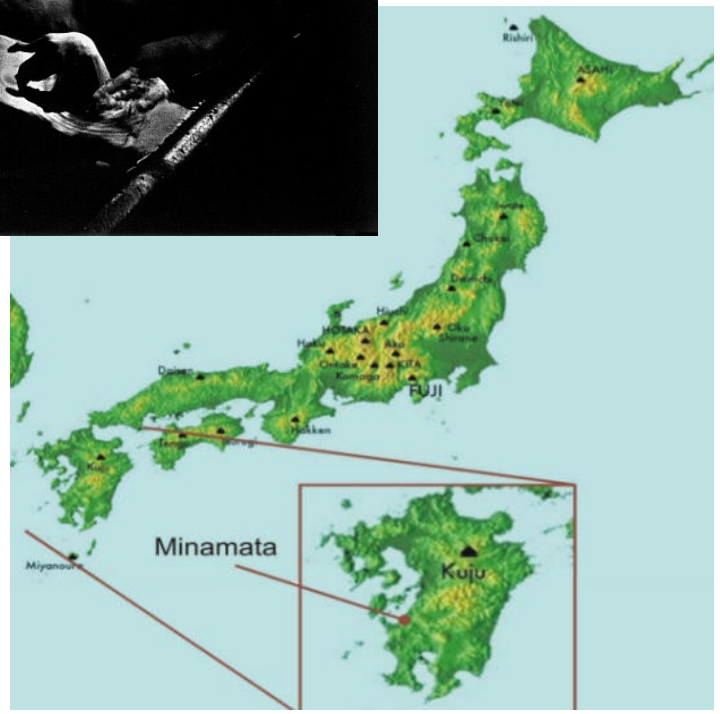
While it is important to limit mercury in the diets of those who are pregnant or breastfeeding and children, many types of fish are both nutritious and lower in mercury.

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

Why a federal advisory for mercury specifically?



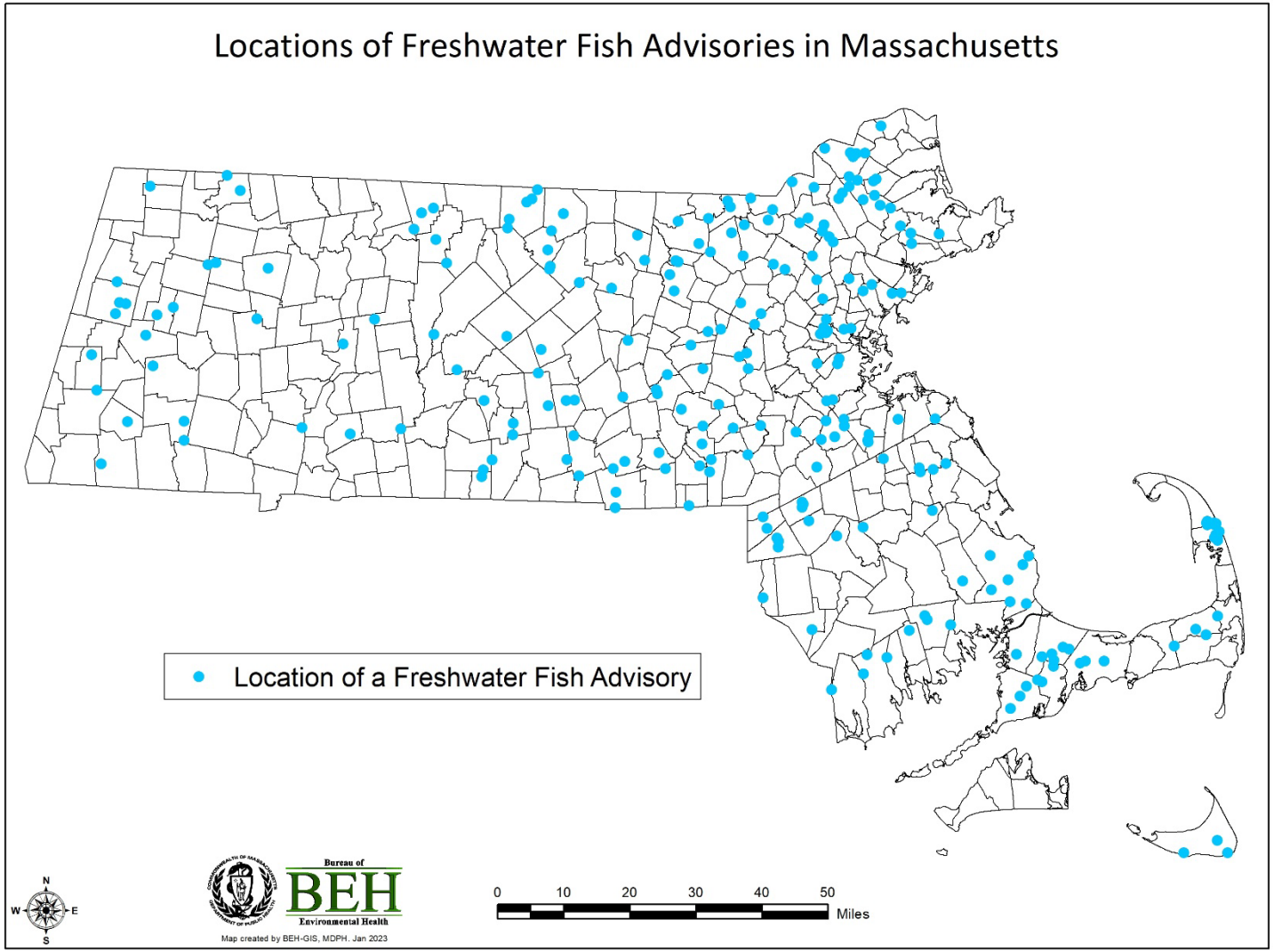
Why pregnancy and childhood?



It’s complicated!

- Water body characteristics: oceans vs. coastal waters vs. fresh water
- Fish characteristics: species, age, size, location, aquaculture vs. wild, feed
- Variable individual consumer susceptibility: age, sex, lifestage
- Fish is not just a bag of mercury!
  - Other contaminants

Territory, State, and Local Advisories



https://fishadvisoryonline.epa.gov/Contacts.aspx

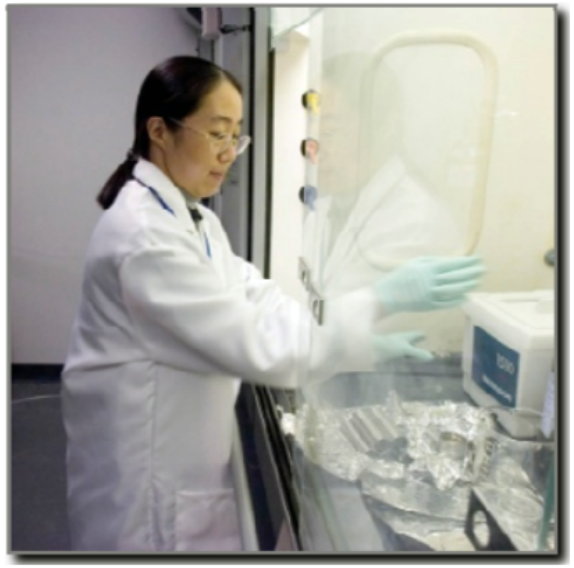
Territory, State, and Local Advisories

Contaminants: What is of Concern?

Chemical Contaminants

Most advisories are based on contamination from five toxins that persist for long periods of time in sediments at the bottom of certain water bodies:

- Mercury
- Polychlorinated Biphenyls (PCBs)
- Chlordane
- Dioxins
- Dichloro-Diphenyl-Trichloroethane (DDT)



Scientist working with contaminants in a laboratory fume hood

Nearly all fish and shellfish contain traces of mercury, no matter what body of water they come from. The risk from consuming mercury by eating fish and shellfish may include harm to an unborn baby or a young child's developing nervous system if the mercury levels are high enough.

https://fishadvisoryonline.epa.gov/Contacts.aspx

Territory, State, and Local Advisories

WATERBODY	MUNICIPALITY	HAZARD(S)*	MEAL ADVICE** Children under 12, pregnant women, nursing mothers, women of child-bearing age	MEAL ADVICE** General public
Boon, Lake	Hudson, Stow	Mercury	Do not eat Black Crappie, Largemouth Bass	Limit Black Crappie, Largemouth Bass to 2 meals/month
Box Pond	Bellingham, Mendon	DDT	Do not eat White Sucker	Do not eat White Sucker
Bracket Reservoir (Framingham Reservoir #2) – See Sudbury River				
Browning Pond	Oakham, Spencer	Mercury	Do not eat Largemouth Bass, Yellow Perch	Limit Largemouth Bass, Yellow Perch to 2 meals/month
Buckley Dunton Lake	Becket	Mercury	Do not eat any fish	Do not eat Largemouth Bass
Buffomville Lake	Charlton, Oxford	Mercury	Do not eat any fish	Limit all fish to 2 meals/month
Burr's Pond	Seekonk	Mercury	Do not eat Largemouth Bass	Limit Largemouth Bass to 2 meals/month
Cabot Pond – See Rumford River				
Canton River (between the Neponset River and Neponset Street dam)	Canton	PCBs, DDT	Do not eat any fish	Do not eat American Eel, White Sucker Limit other species to 2 meals/month
Cedar Swamp Pond	Milford	Mercury	Do not eat any fish	Limit all fish to 2 meals/month
Chadwicks Pond	Boxford, Haverhill	Mercury	Do not eat any fish	Do not eat any fish
Charles River (between the Medway Dam in Franklin and Medway and the South Natick Dam in Natick)	Dover, Franklin, Medfield, Medway, Millis, Natick, Norfolk, Sherborn	Mercury, Chlordane, DDT	Do not eat any fish	Limit all fish to 2 meals/month
Charles River (between the South Natick Dam in Natick and the Museum of Science Dam in Boston/Cambridge)	Boston, Cambridge, Dedham, Dover, Natick, Needham, Newton, Watertown, Wellesley, Weston, Waltham	PCBs, Pesticides	Do not eat Carp, Largemouth Bass	Do not eat Carp Limit Largemouth Bass to 2 meals/month
Chebacco Lake	Essex, Hamilton	Mercury	Do not eat Largemouth Bass	Limit Largemouth Bass to 2 meals/month
Chicopee Reservoir	Chicopee	PFAS	Do not eat any fish	Do not eat any fish
Clay Pit Pond	Belmont	Chlordane	Do not eat any fish	Do not eat any fish
Cleveland Pond	Abington	Mercury	Do not eat Black Crappie	Limit Black Crappie to 2 meals/month

Fish consumption advisories apply to the consumption of all native game fish but do not apply to stocked trout at a waterbody. Stocked fish are raised in fish hatcheries and then released. Therefore, they are unlikely to spend enough time in a waterbody to become contaminated.

* See page 15 for hazard codes.

** Uncooked serving sizes should be 8 to 12 oz. of fish for adults and children over 12, with smaller amounts for younger children.

***This waterbody has not been evaluated for mercury. Per DPH's statewide fish consumption advisory for mercury, sensitive populations should not eat fish from this waterbody until more information on mercury levels is available.

https://fishadvisoryon

Single vs. multi-contaminant advisories: more stringent when multiple contaminants considered

Table 3

Distribution (in percent) of the advisories (meals/month) simulated using the one-chem and multi-chem approaches.

		0	1	2	4	8	12	16	32	Total
General population	0	**100%**	59%	4%						10%
	1		**41%**	54%	3%					10%
	2			**42%**	56%	7%	2%			16%
	4				**42%**	71%	31%	2%		21%
	8					**23%**	49%	28%		14%
	12						**19%**	28%	1%	8%
	16							**42%**	12%	10%
	32								**87%**	11%
	Total	5%	7%	13%	16%	15%	10%	21%	13%	100%
Sensitive population	0	**100%**			59%	11%	2%			47%
	4				**41%**	63%	38%	5%		25%
	8					**26%**	33%	33%		12%
	12						**27%**	19%		5%
	16							**43%**	13%	6%
	32								**87%**	5%
	Total	30%			25%	17%	10%	13%	5%	100%

The same advisories from both approaches are presented in bold, and more stringent advisories from the multi-chem approach are highlighted with blue shading. The distributions in the number of advisories are presented in Table S3.

Are **Fish** Consumption Advisories for the Great Lakes Adequately Protective against Chemical **Mixtures**? Gandhi N, Drouillard KG, Arhonditsis GB, Gewurtz SB, Bhavsar SP.Environ Health Perspect. 2017 Apr;125(4):586-593. doi: 10.1289/EHP104. Epub 2016 Oct 4.PMID: 27697747

Other metals and seafood

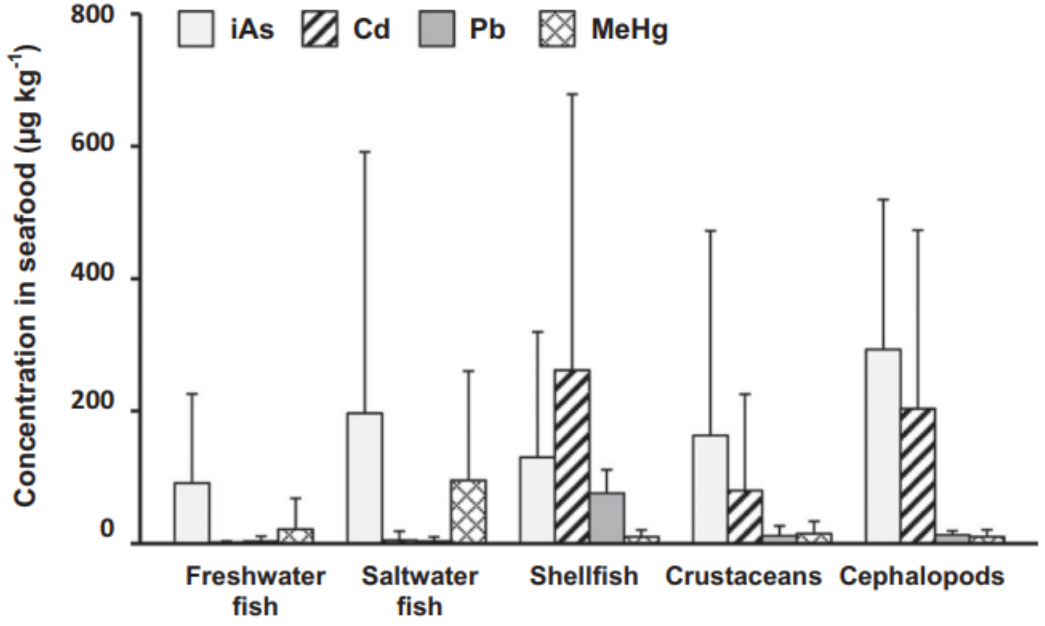


Fig. 1. Concentrations of iAs, Cd, Pb, and MeHg in five categories of seafood.

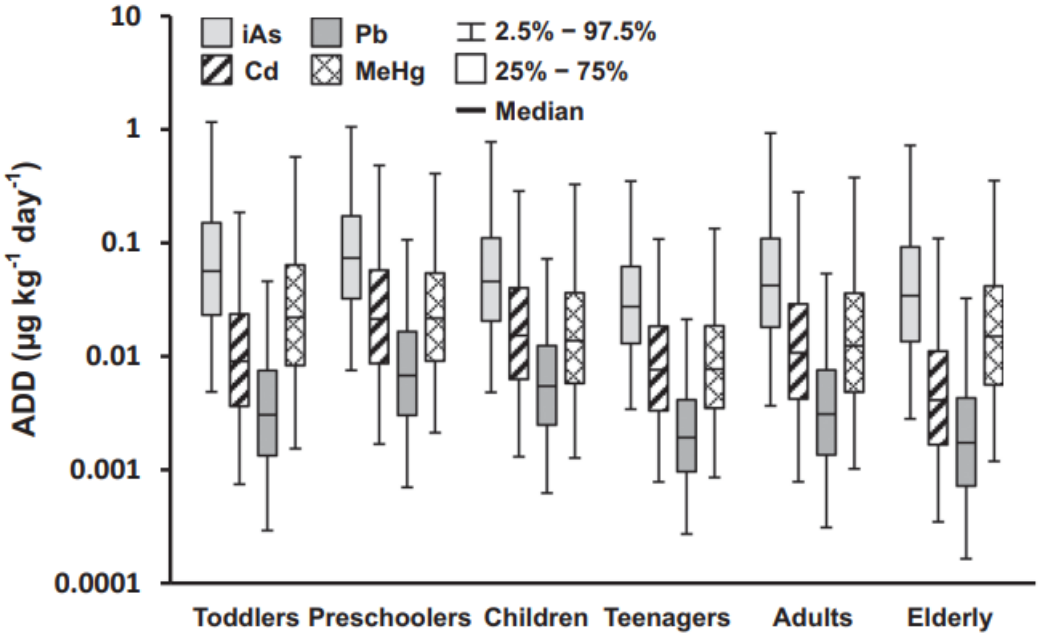
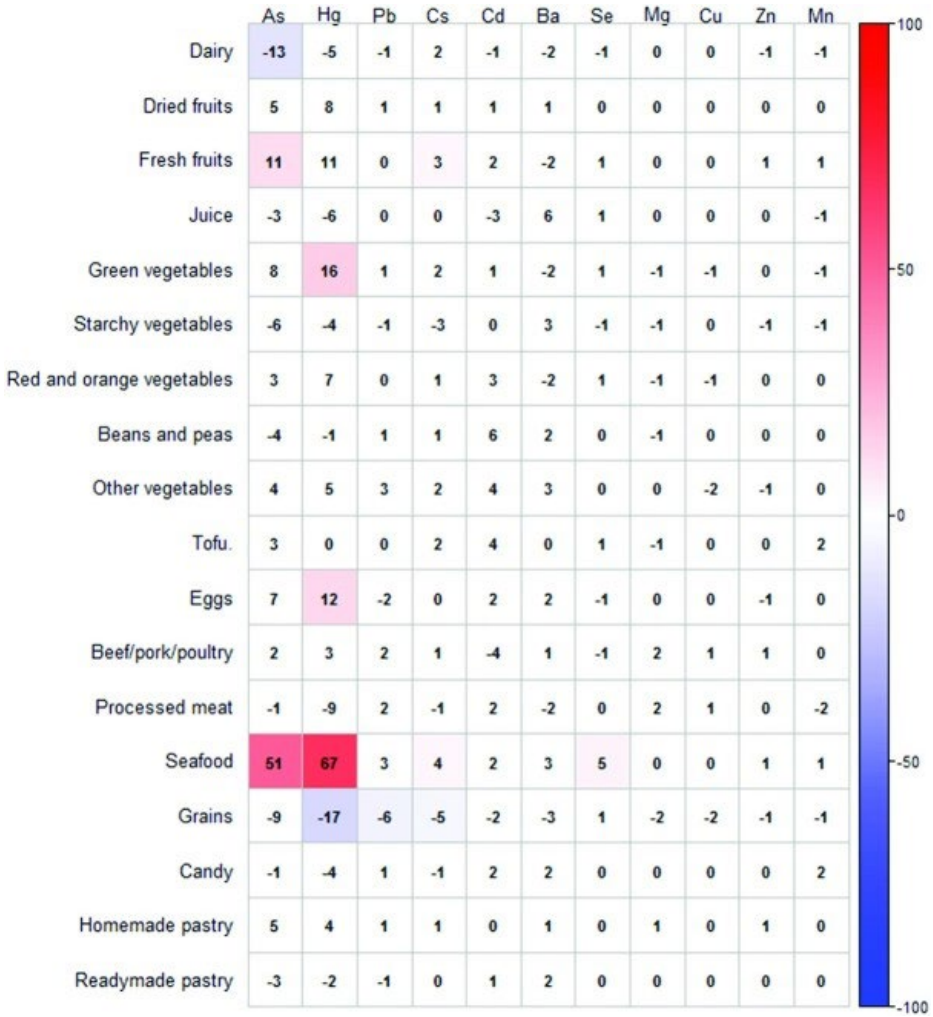


Fig. 3. Box-and-whisker plot representing average daily doses (ADD) of iAs, Cd, Pb, and MeHg by age populations.

Probabilistic Integrated Human Mixture Risk Assessment of Multiple Metals Through Seafood Consumption.
Risk Anal. 2019 Feb;39(2):426-438. PMID: 30176170Lin YJ, Lin P.

The concentrations of iAs, Cd, Pb, and MeHg in a variety of seafood sold in markets were obtained from the Taiwan Food and Drug Administration

Other metals and seafood

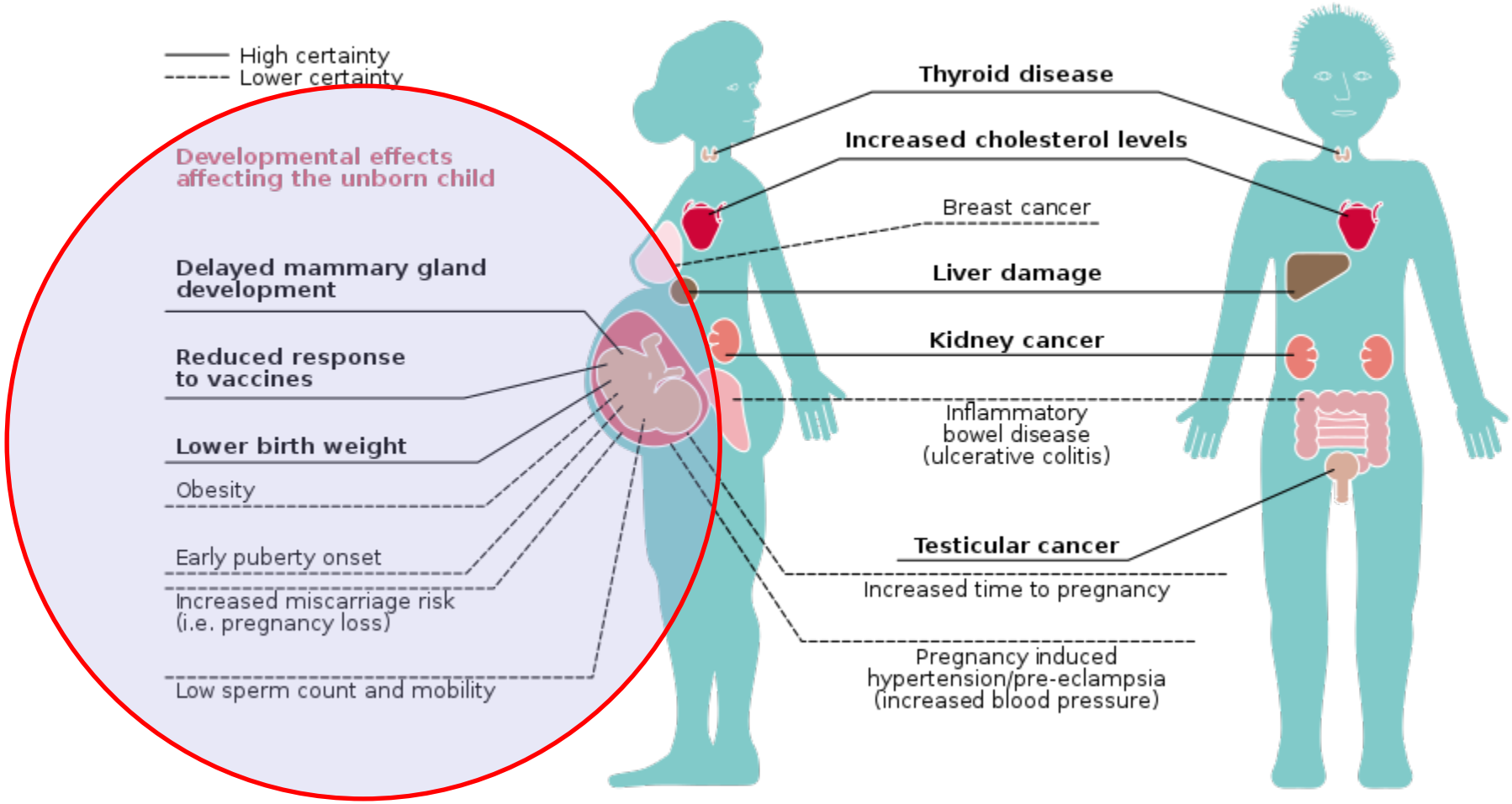


Numbers indicate the relative change (%) in median erythrocyte metal concentrations at early pregnancy per SD increase in intake, adjusting for age, race, education, income, smoking status, prepregnancy BMI, hemoglobin concentration, and total calorie intake.

Parameter estimates with false discovery rate–adjusted P values < 0.01 are shaded with colored backgrounds that correspond to the magnitude of the effect sizes.

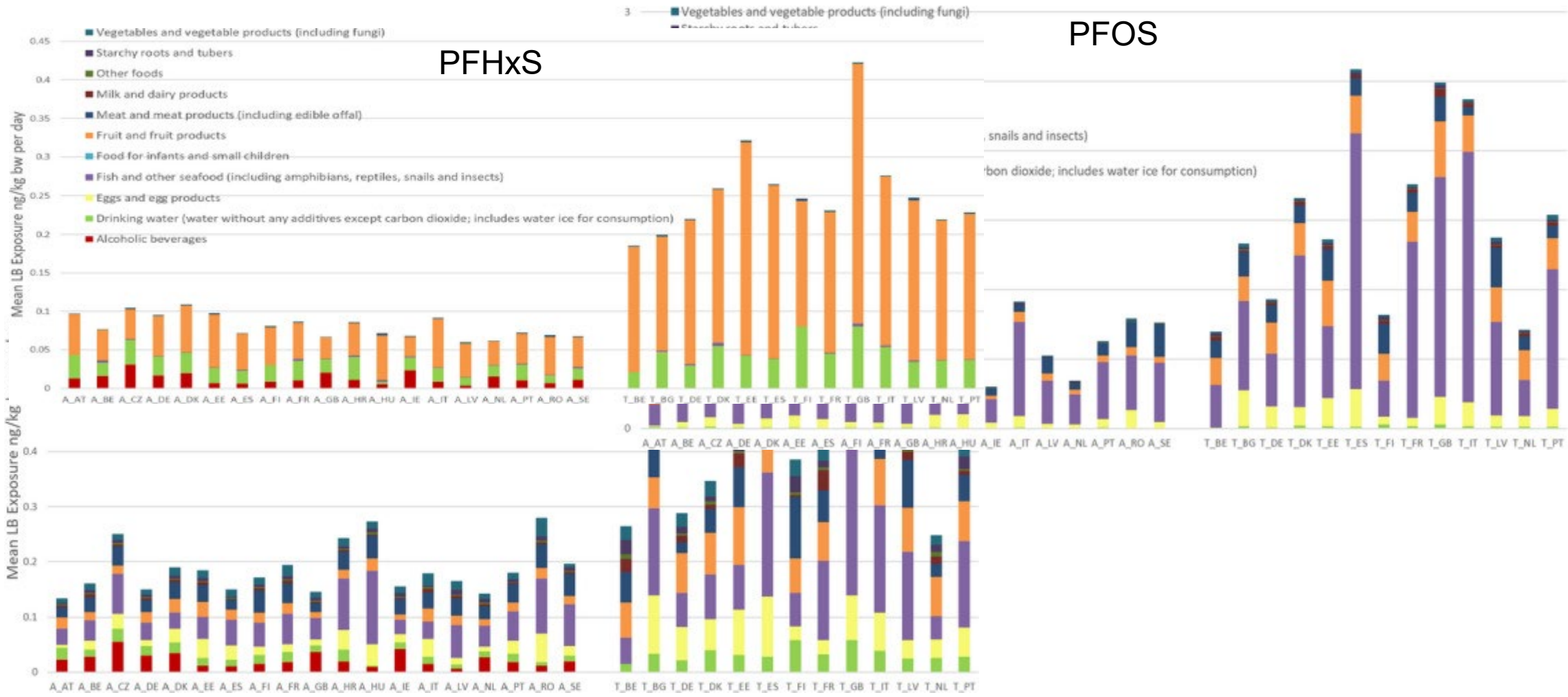
Diet and erythrocyte metal concentrations in early pregnancy-cross-sectional analysis in Project Viva. Lin PD, Cardenas A, Rifas-Shiman SL, Hivert MF, James-Todd T, Amarasiriwardena C, Wright RO, Rahman ML, Oken E. Am J Clin Nutr. 2021 Aug 2;114(2):540-549. PMID: 34038956

PFAS affect multiple health domains, including developmental effects



https://en.wikipedia.org/wiki/Per-_and_polyfluoroalkyl_substances

PFAS and diet



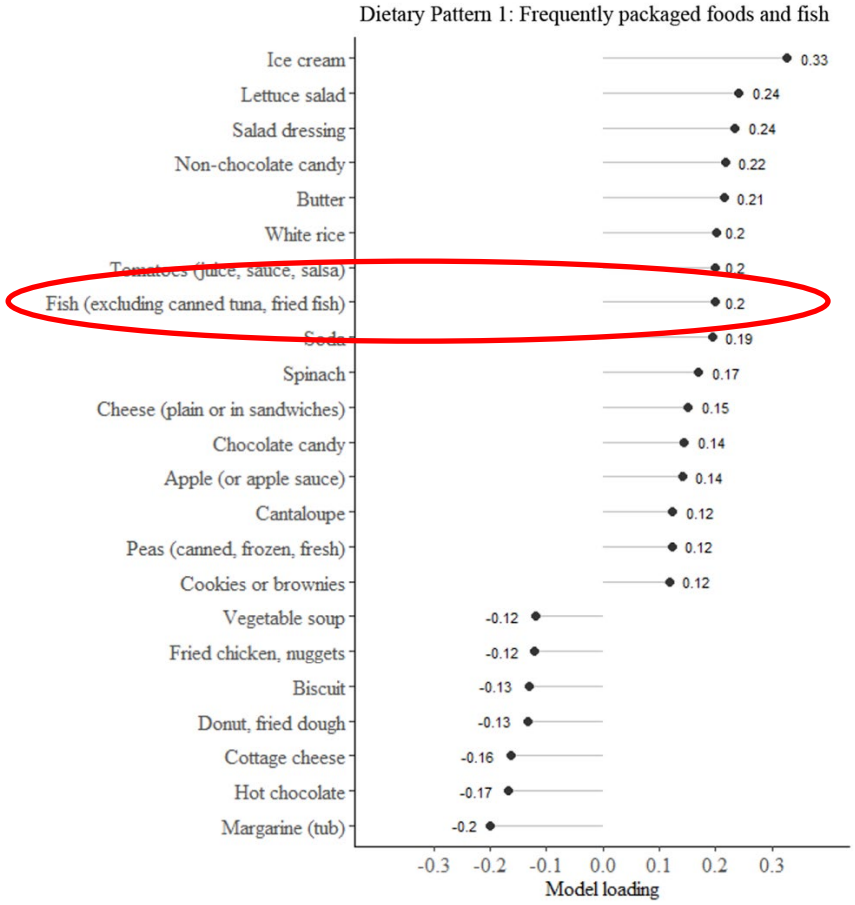
Risk to **human** health related to the presence of perfluoroalkyl substances in food. EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel); Schrenk D, et al.EFSA J. 2020 Sep 17;18(9):e06223. doi: 10.2903/j.efsa.2020.6223. eCollection 2020 Sep.PMID: 32994824

PFAS and diet

- For PFOS, ‘Fish and other seafood’ was the most important contributor to the mean lower bound exposure; to a lesser extent, ‘Fish and other seafood’ was also an important contributor for PFOA
- ‘Fish and other seafood’ was also among the main contributing food categories for most age groups for FOSA, PFPeA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA and PFTeDA.
- For the combined exposure to PFOA, PFOS, PFHxS and PFNA, the main contributing categories were ‘Fish meat’ and ‘Fruit and fruit products’ for all population groups

Risk to **human** health related to the presence of perfluoroalkyl substances in food. EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel); Schrenk D, et al.EFSA J. 2020 Sep 17;18(9):e06223. doi: 10.2903/j.efsa.2020.6223. eCollection 2020 Sep.PMID: 32994824

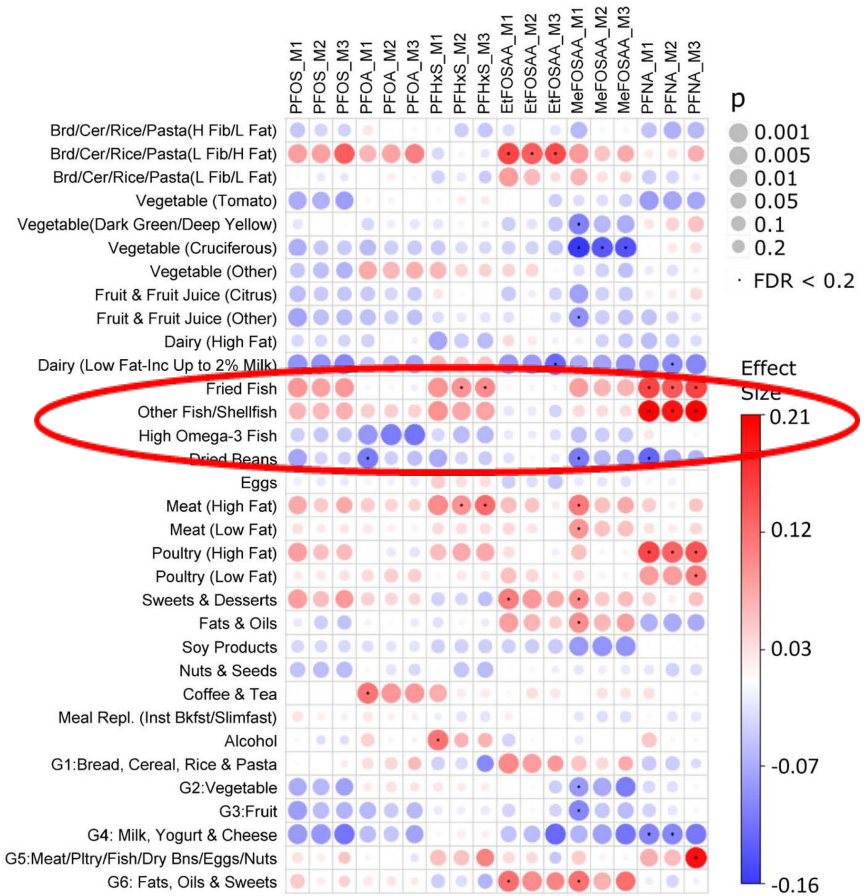
Dietary patterns and PFAS concentrations – children in Project Viva



- RR identified 6 dietary patterns that together explained 18% variation in the plasma concentrations of the 6 PFAS of which 50% was explained by a dietary pattern consisting of primarily packaged foods (including ice cream and soda) and fish.
- Children with higher intake of the packaged foods and fish dietary pattern had higher plasma concentrations of all PFAS, particularly MeFOSAA and PFOS.

Dietary patterns and PFAS plasma concentrations in childhood: Project Viva, USA. Seshasayee SM, Rifas-Shiman SL, Chavarro JE, Carwile JL, Lin PD, Calafat AM, Sagiv SK, Oken E, Fleisch AF. Environ Int. 2021 Jun;151:106415. doi: 10.1016/j.envint.2021.106415. Epub 2021 Mar 8. PMID: 33706127

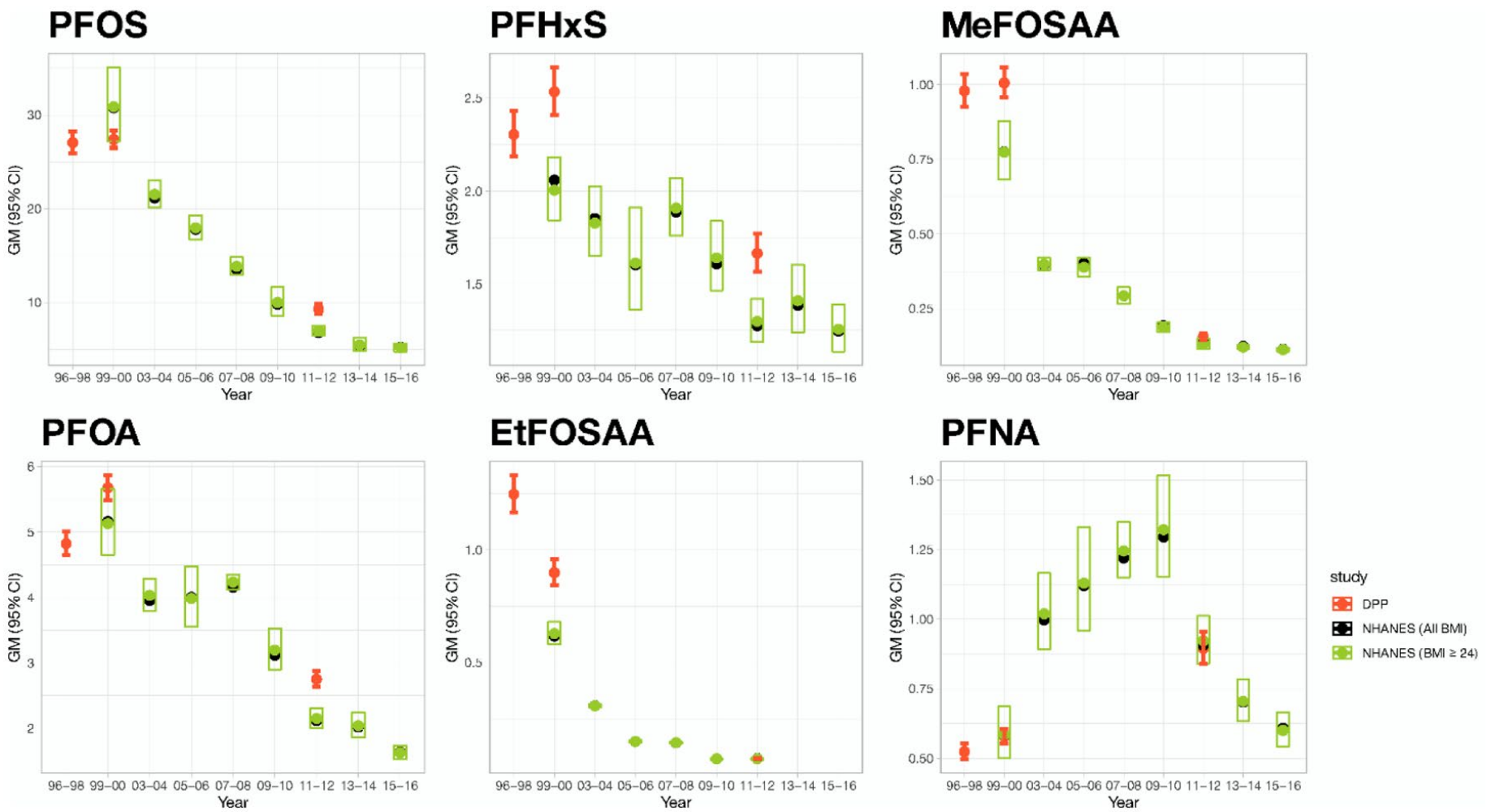
Dietary patterns and PFAS concentrations – adults in DPP



- We summarized four major dietary characteristics associated with variations in PFAS plasma concentrations in this population.
- Specifically, consuming more meat/fish/shellfish (especially fried fish, and excluding Omega3-rich fish), low-fiber and high-fat bread/cereal/rice/pasta, and coffee/tea was associated with higher plasma concentrations
- Dietary patterns of vegetables, fruits and Omega-3 rich fish were associated with lower plasma concentrations of some PFAS.

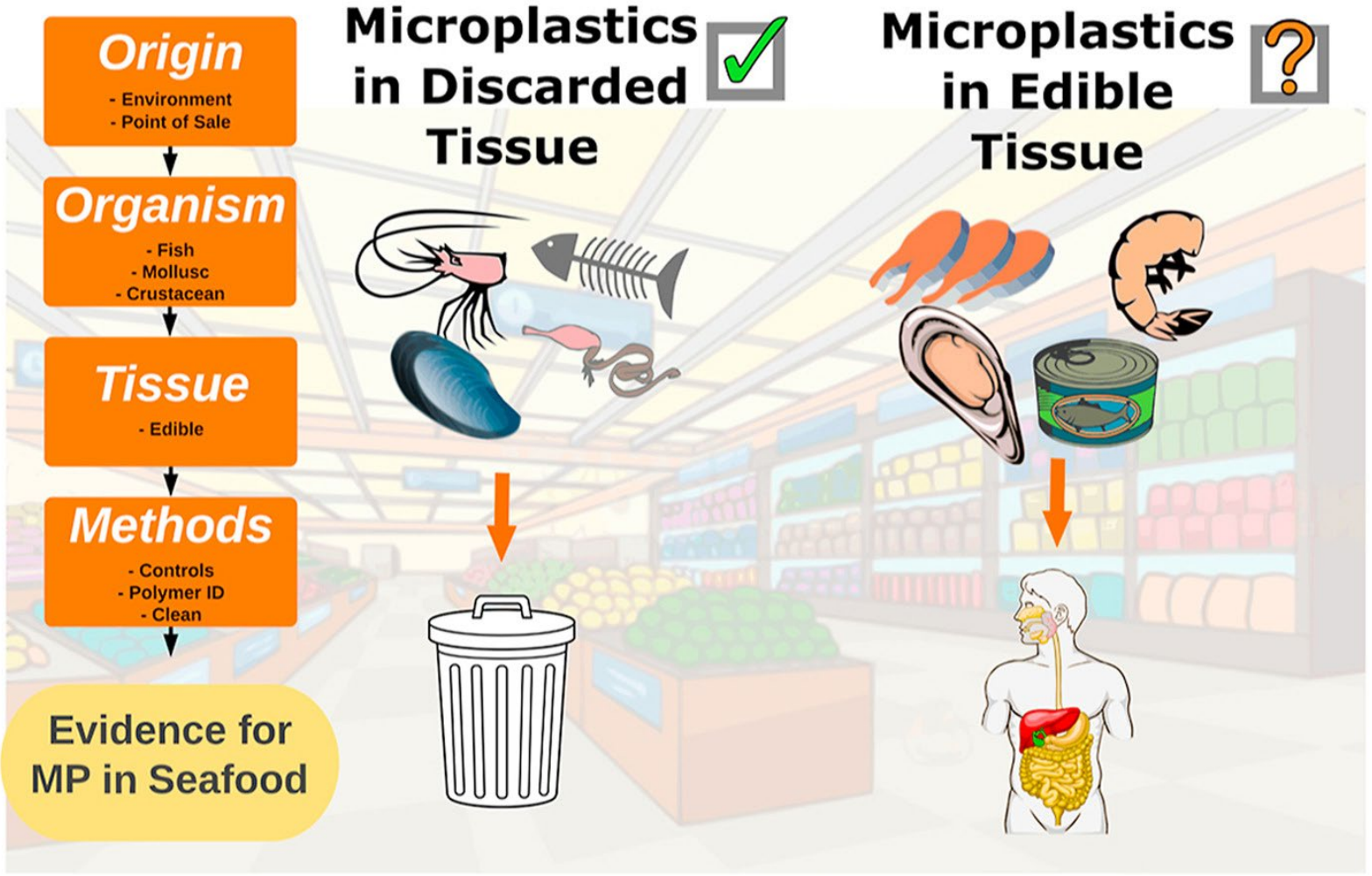
Dietary characteristics associated with plasma concentrations of per- and polyfluoroalkyl substances among adults with pre-diabetes: Cross-sectional results from the Diabetes Prevention Program Trial. Lin PD, Cardenas A, Hauser R, Gold DR, Kleinman KP, Hivert MF, Fleisch AF, Calafat AM, Sanchez-Guerra M, Osorio-Yáñez C, Webster TF, Horton ES, Oken E. Environ Int. 2020 Apr;137:105217. doi: 10.1016/j.envint.2019.105217. Epub 2020 Feb 18. PMID: 32086073

PFAS trends over time



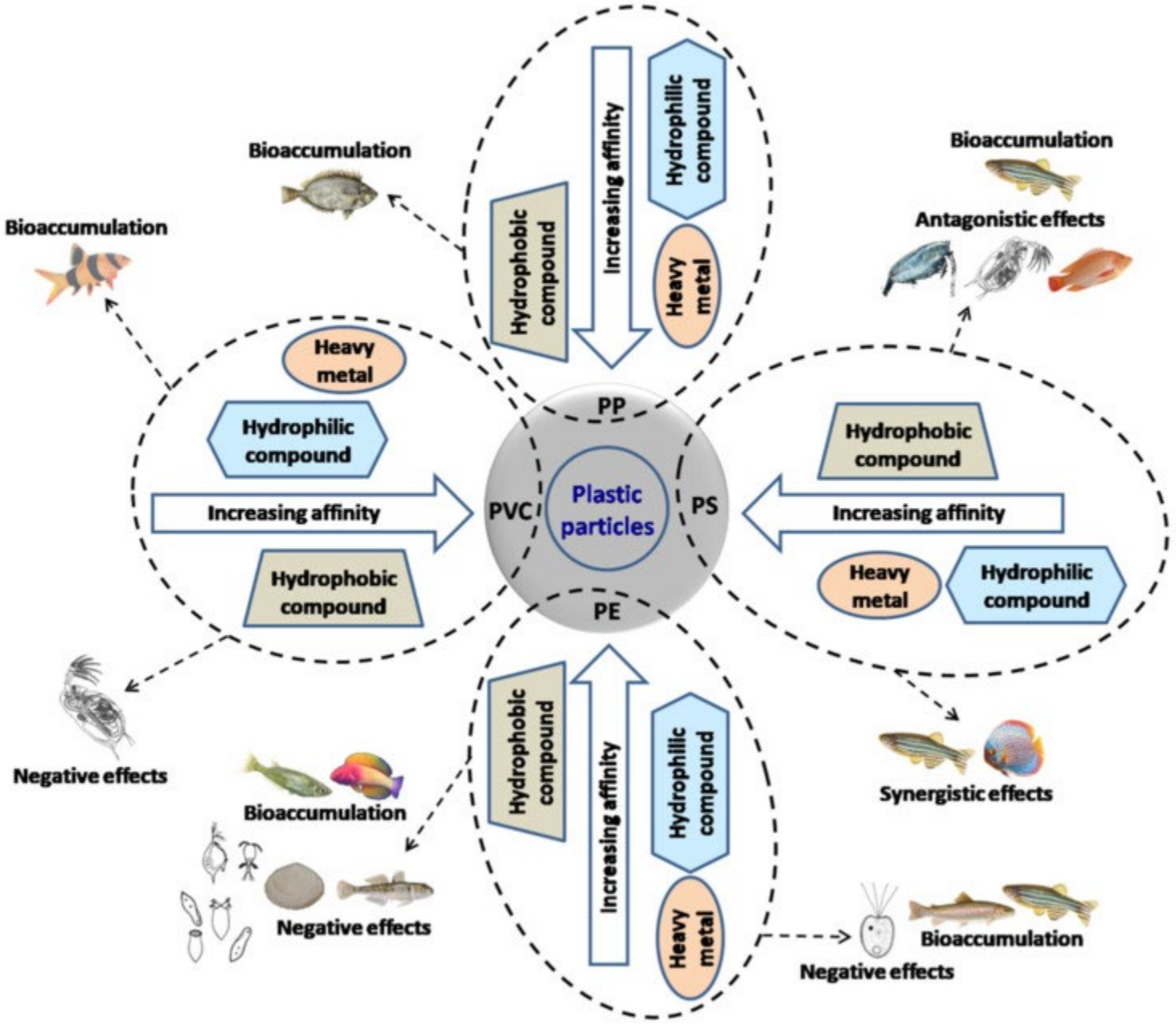
Lin PD, Cardenas A, Hauser R, Gold DR, Kleinman KP, Hivert MF, Calafat AM, Webster TF, Horton ES, Oken E. Temporal trends of concentrations of per- and polyfluoroalkyl substances among adults with overweight and obesity in the United States: Results from the Diabetes Prevention Program and NHANES. Environ Int. 2021 Dec;157:106789. doi: 10.1016/j.envint.2021.106789. Epub 2021 Jul 29. PMID: 34333293

Micro and nano plastics: Edible seafood likely not a major source, but limited data



Dawson AL et al. Relevance and reliability of evidence for microplastic contamination in seafood: A critical review using Australian consumption patterns as a case study. Environmental Pollution Volume 276, 1 May 2021, 116684. https://doi.org/10.1016/j.envpol.2021.116684

Plastics as a source of exposure to other contaminants



Plastic Interactions with Pollutants and Consequences to Aquatic Ecosystems: What We Know and What We Do Not Know.
Cássio F, Batista D, Pradhan A. Biomolecules. 2022 Jun 7;12(6):798. doi: 10.3390/biom12060798. PMID: 35740921

Contaminants of Emerging Concern (CECs)

Table 1. *Common Classes of CECs*

Class of CEC	Example	Definition
Antibiotics	Tetracycline, Erythromycin	Medications that fight bacterial infections, inhibiting or stopping bacterial growth
Antimicrobials	Triclosan	Biochemicals that kill or inhibit the growth of microorganisms including bacteria and fungi
Detergent metabolites	Nonylphenol	Chemical compounds formed when detergents are broken down by wastewater treatment or environmental degradation
Disinfectants	Alcohols, Aldehydes and oxidizing agents	A chemical agent used on non-living surfaces to destroy, neutralize, or inhibit the growth of disease-causing microorganisms
Disinfection by-products	Chloroform, Nitrosodimethylamine (NDMA)	Chemical substances resulting from the interaction of organic matter in water with disinfection agents such as chlorine
Estrogenic compounds	Estrone, Estradiol, Nonylphenol, Bisphenol A	Natural or synthetic chemicals that can elicit an estrogenic response
Fire or flame retardants	Polybrominated Diphenyl Ethers (PBDEs)	Any of several materials or coatings that inhibit or resist the spread of fire
Fragrances	Galaxolide	Chemical substances that impart a sweet or pleasant odor
Insect repellants	DEET (N,N-diethyl-meta-toluamide)	Chemical substances applied to skin or other surfaces to discourage insects from coming in contact with the surface
PAHs (poly-aromatic hydrocarbons)	Benzo(a)pyrene, Fluoranthene, Naphthalene	A large group of chemical substances usually found in the environment as a result of incomplete burning of carbon-containing materials like fossil fuels, wood, or garbage
Personal Care Products	Para-hydroxybenzoate	Chemical substances used in a diverse group of personal items including toiletries and cosmetics.
Pesticides or Insecticides	Permethrin, Fenitrothion, Bacillus thuringiensis israelensis (B.t.i.)	Chemical substances or microbiological agents that kill, incapacitate or otherwise prevent pests from causing damage
Pharmaceuticals	Fluoxetine (Prozac), Carbamazepine, Diphenhydramine	Chemical substances used in the prevention or treatment of physiological conditions
Plasticizers	Dioctyl Phthalate (DOP)	Chemical additives that increase the plasticity or fluidity of a material
Reproductive hormones	Dihydrotestosterone (DHT), Progesterone, Estrone, Estradiol	A group of chemical substances, usually steroids, whose purpose is to stimulate certain reproductive functions
Solvents	Ethanol, Kerosene	Chemical solutions, other than water, capable of dissolving another substance.
Steroids	Cholesterol, Coprostanol, Estrone, Progesterone	A large group of fat-soluble organic compounds with a characteristic molecular structure, which includes many natural and synthetic hormones
Surfactants	Sodium Lauryl Sulfate	Chemical substances that affect the surface of a liquid

ARROYO 2013

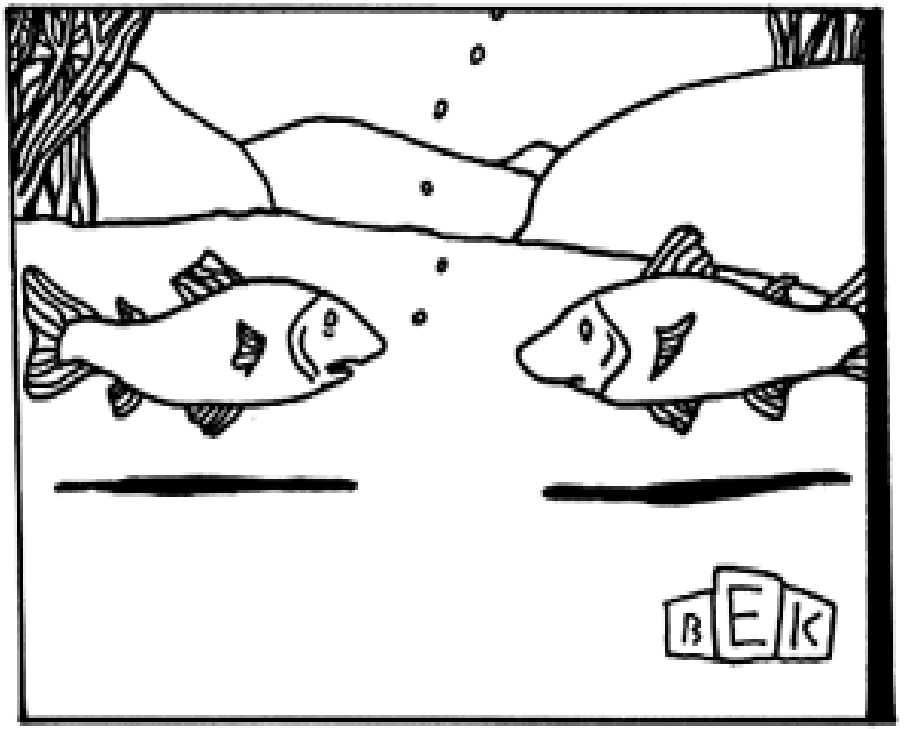
Raghav, M., Eden, S., Mitchell, K., Witte, B., 2013. Contaminants of emerging concern in water. ARROYO Available at:. https://repository.arizona.edu/handle/10150/325905 (Accessed: 3/28/23).

It’s complicated!

- Water body characteristics: oceans vs. coastal waters vs. fresh water
- Fish characteristics: species, age, size, location, aquaculture vs. wild, feed
- Variable individual consumer susceptibility: age, sex, lifestage
- Fish is not just a bag of mercury!
  - Other contaminants
  - Nutrients

Fish is the primary dietary source of omega-3 long-chain polyunsaturated fatty acids

- Omega-3 LCPUFA:
  - Essential nutrients – we can't synthesize them, have to eat them
  - Necessary for fetal optimal fetal brain, eye development (DHA)
  - Most women eat too little: US mean ~500 mg DHA/week, recommended 1400 mg/week
  - Seafood is the primary natural dietary source



"With all these omega-3 fatty acids, you'd think I'd feel better."

PROJECT Viva | A STUDY OF HEALTH FOR THE NEXT GENERATION

Maternal hair mercury at delivery and child cognition at ~6 months (n=135)

	Maternal 2nd tri fish intake (per svg/wk)	Maternal hair mercury at delivery (per ppm)
	Change in 6 month VRM score	
Fish	2.8 (0.2, 5.4)	---
Mercury	---	-4.0 (-10.0, 2.0)
Fish & mercury	4.0 (1.3, 6.7)	-7.5 (-13.7, -1.2)

Adjusted for maternal age, race/ethnicity, education, marital status; infant sex, gestational age, fetal growth, breastfeeding, age at testing

Oken E, et al. Env Health Perspect 2005;113:1376-80.

PROJECT Viva | A STUDY OF HEALTH FOR THE NEXT GENERATION

Maternal prenatal blood mercury and child cognition at ~age 3

Child test score	Age and sex	MV
Peabody Picture Vocabulary Test		
Hg top decile	-5.3 (-10.1, -0.5)	-4.0 (-8.0, 0.0)
Hg < 90th %ile	Referent	Referent
Wide Range Assessment of Visual Motor Abilities		
Hg top decile	-3.4 (-7.0, 0.2)	-3.5 (-7.2, 0.2)
Hg < 90th %ile	Referent	Referent

*MV adjustment = Child: fetal growth, gestation length, breastfeeding duration, birth order, language; Maternal: PPVT score, age, BMI, race/ethnicity, education, marital status, smoking; Paternal: education.

Oken, et al. AJE 2008

PROJECT Viva | A STUDY OF HEALTH FOR THE NEXT GENERATION

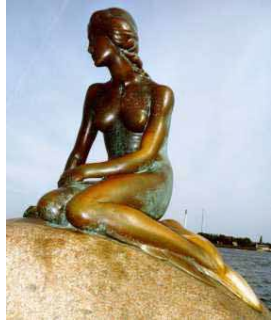
Maternal prenatal fish intake and child cognition at ~age 3

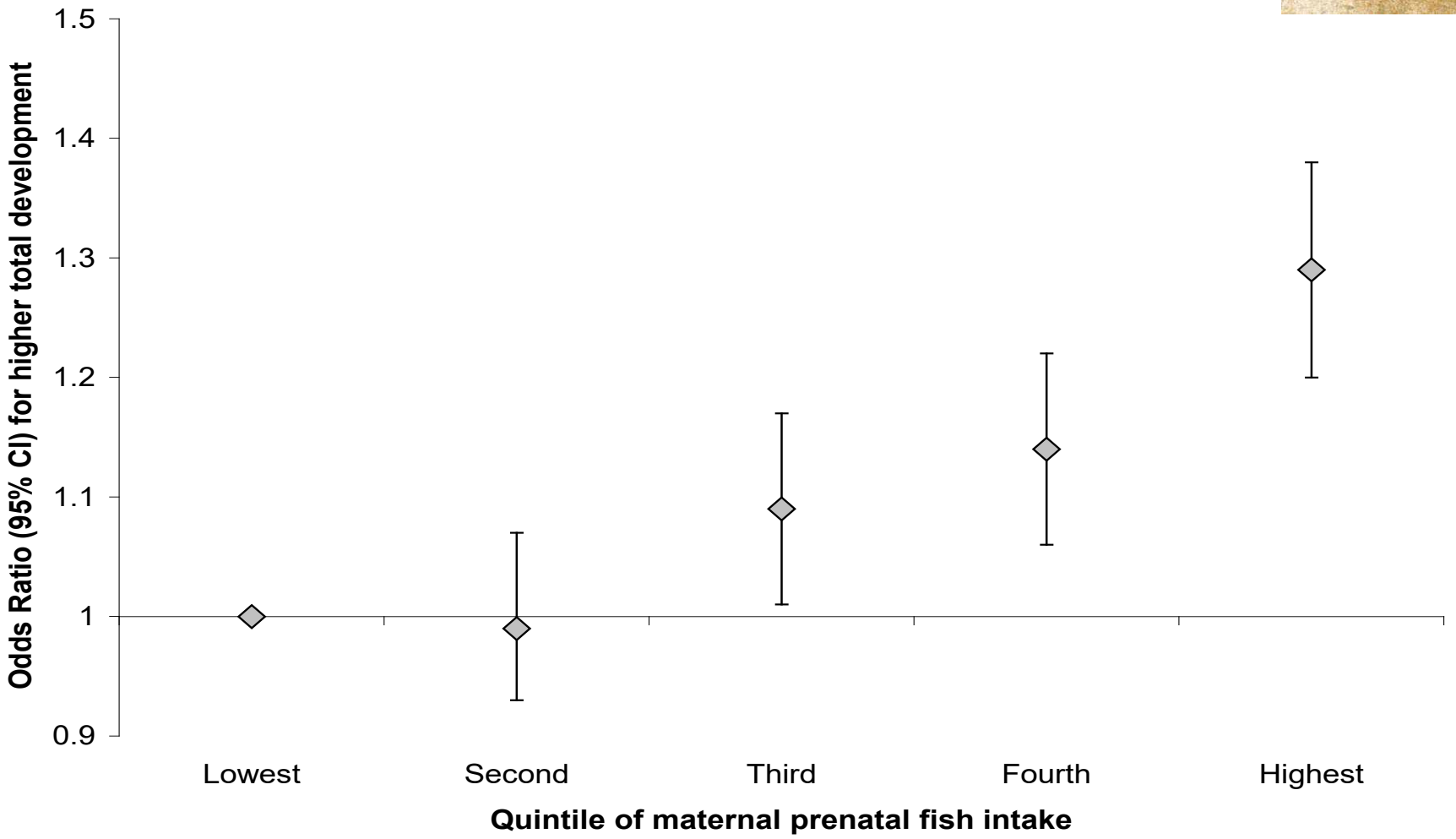
Child Test Score	Age and sex	MV
Peabody Picture Vocabulary Test		
Fish > 2x/wk	-1.5 (-7.3, 4.4)	1.2 (-3.5, 6.0)
Fish <= 2x/wk	-2.2 (-6.5, 2.2)	-2.1 (-5.7, 1.4)
Fish never	Referent	Referent
Wide Range Assessment of Visual Motor Abilities		
Fish > 2x/wk	3.7 (-0.7, 8.1)	5.3 (0.6, 9.6)
Fish <= 2x/wk	0.7 (-2.5, 4.0)	1.1 (-2.2, 4.4)
Fish never	Referent	Referent

*MV adjustment = Child: fetal growth, gestation length, breastfeeding duration, birth order, language; Maternal: PPVT score, age, BMI, race/ethnicity, education, marital status, smoking; Paternal: education.

Oken, et al. AJE 2008

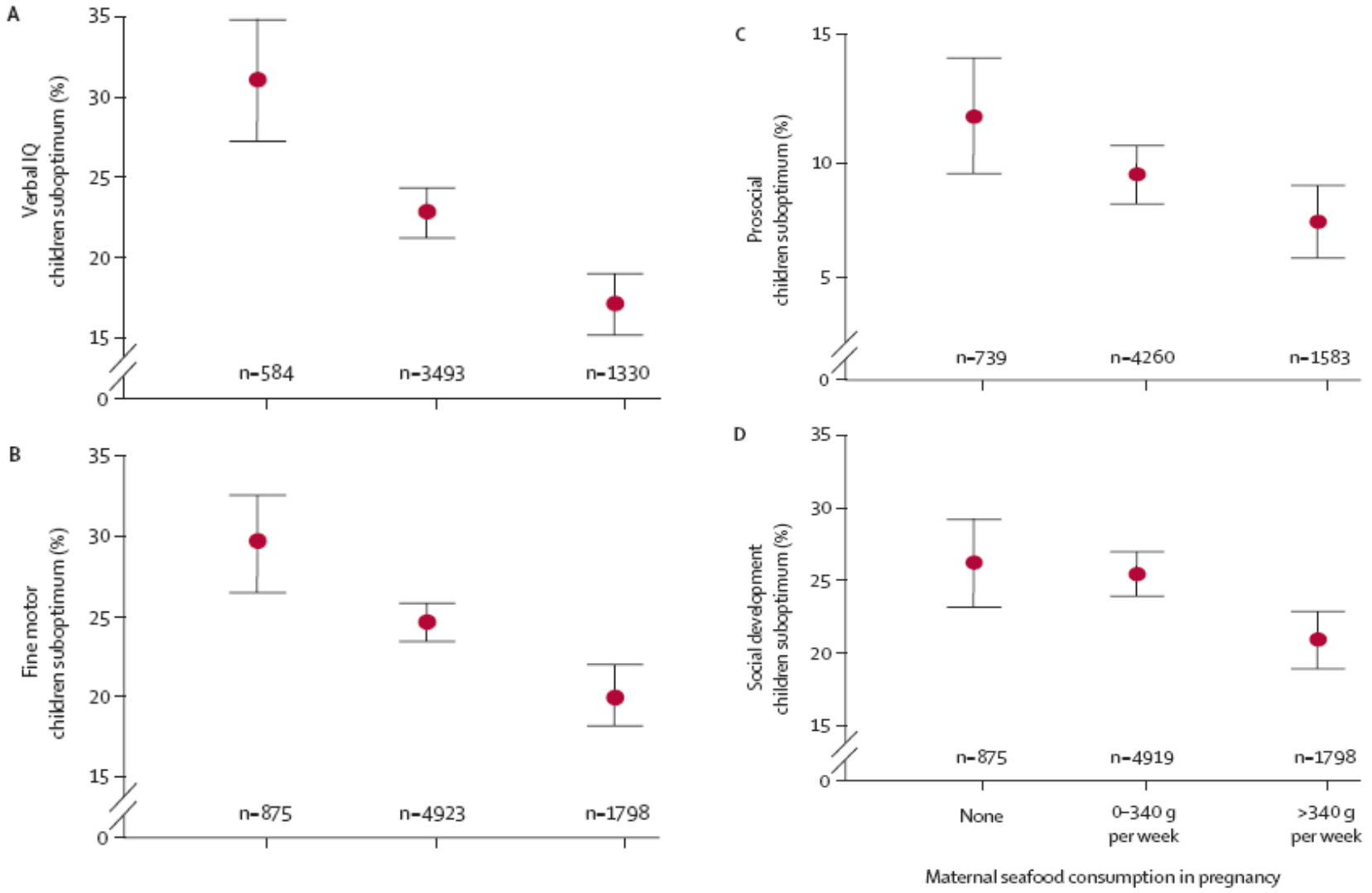
Danish National Birth Cohort





Oken, et al. Am J Clin Nutr 2009

Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study



Hibbeln JR, et al. Lancet 2007;369:578-85.

DHA Supplementation in Pregnancy, Birth Outcomes & Bayley Scores

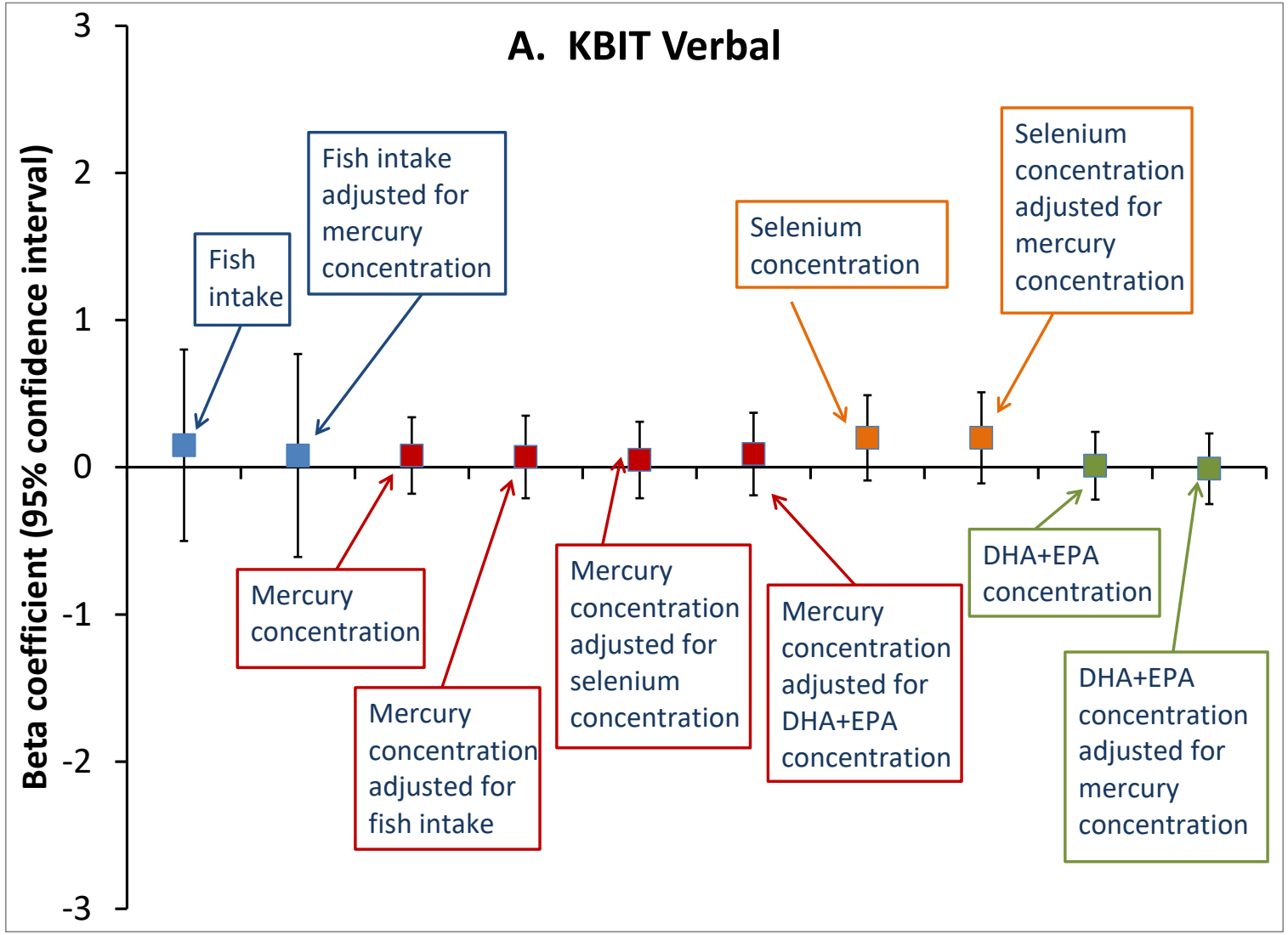
(Makrides et al, JAMA 2011)

Birth outcomes	**RR (95% CI)**
Birth <34wks	0.5 (0.3, 0.94)
Birth wt <2500 g	0.7 (0.4, 0.96)
NICU admission	0.6 (0.3, 0.97)

Cognition at 18 months	**Beta (95% CI)**
Cognition	0.01 (-1.4, 1.4)
Language	-1.4 (-3.1, 0.2)
Motor	0.08 (-1.2, 1.3)
Adaptive behavior	-1.5 (-3.2, 0.1)

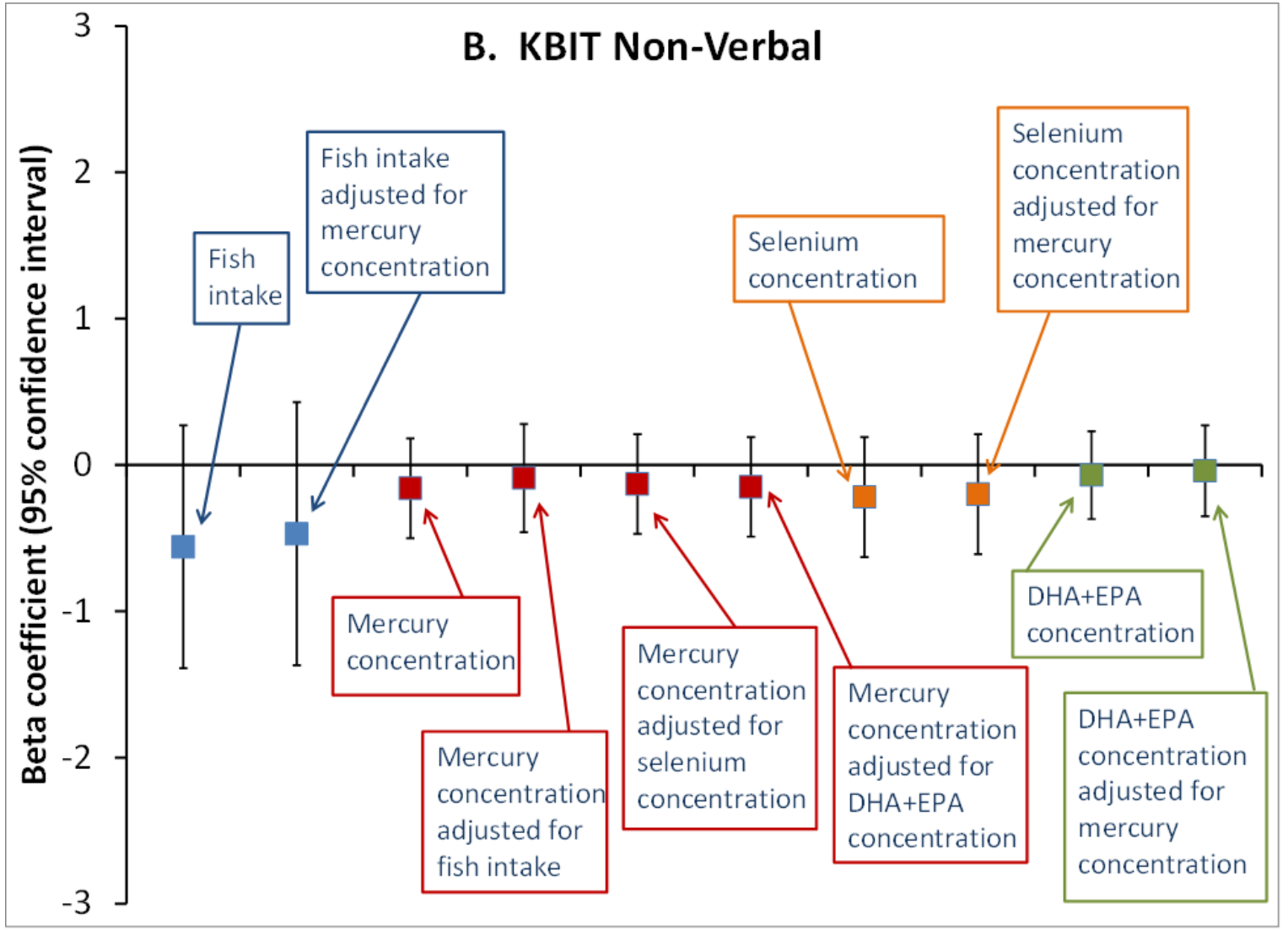
PROJECT Viva | A STUDY OF HEALTH FOR THE NEXT GENERATION

Results in mid-childhood

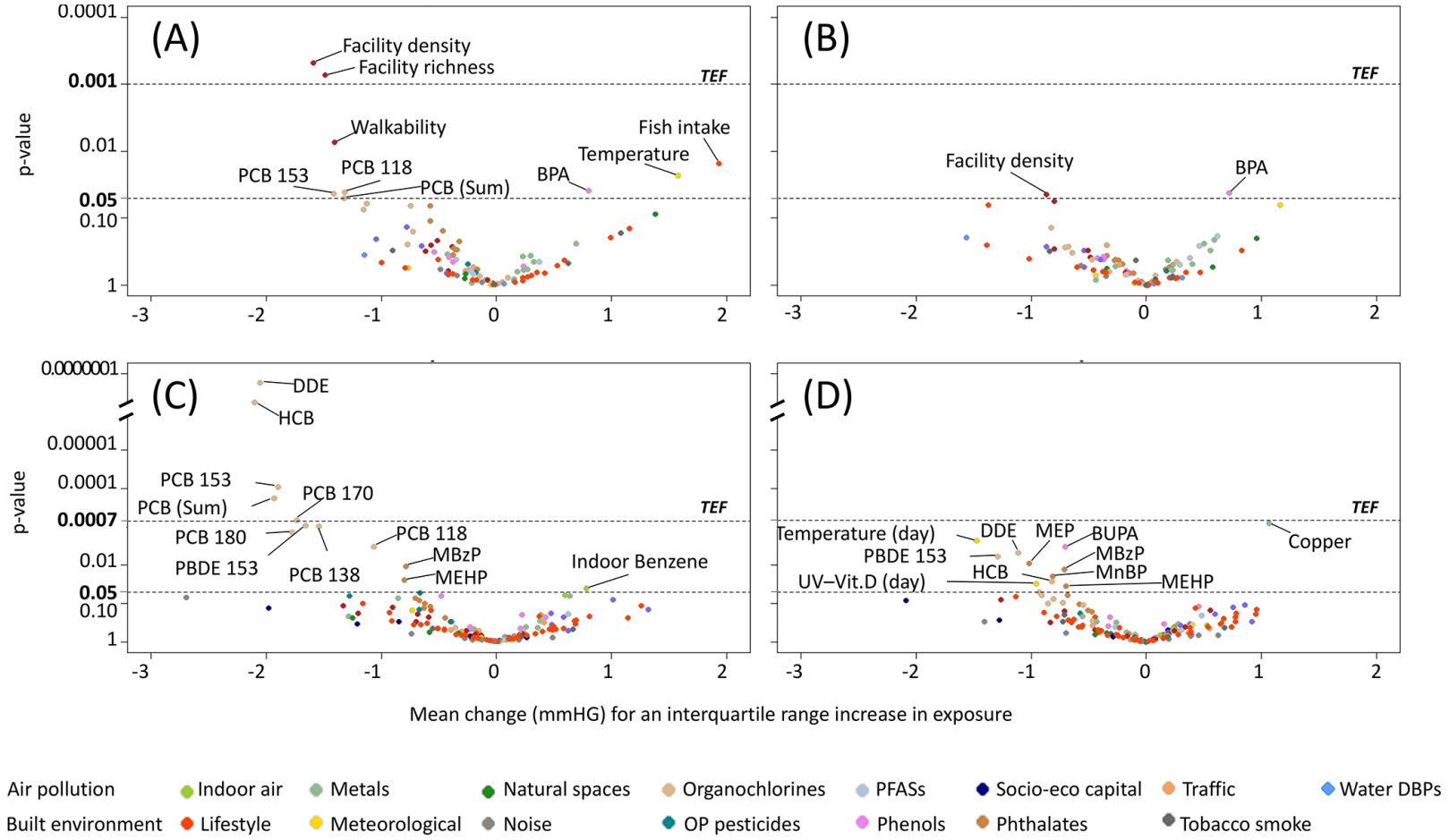


PROJECT Viva | A STUDY OF HEALTH FOR THE NEXT GENERATION

Results in mid-childhood



Exposome-wide associations of pre and post-natal environment with child BP



Early-Life Environmental Exposures and Blood Pressure in Children.Warembourg C, et al.
J Am Coll Cardiol. 2019 Sep 10;74(10):1317-1328. PMID: 31488269

No wonder women are confused

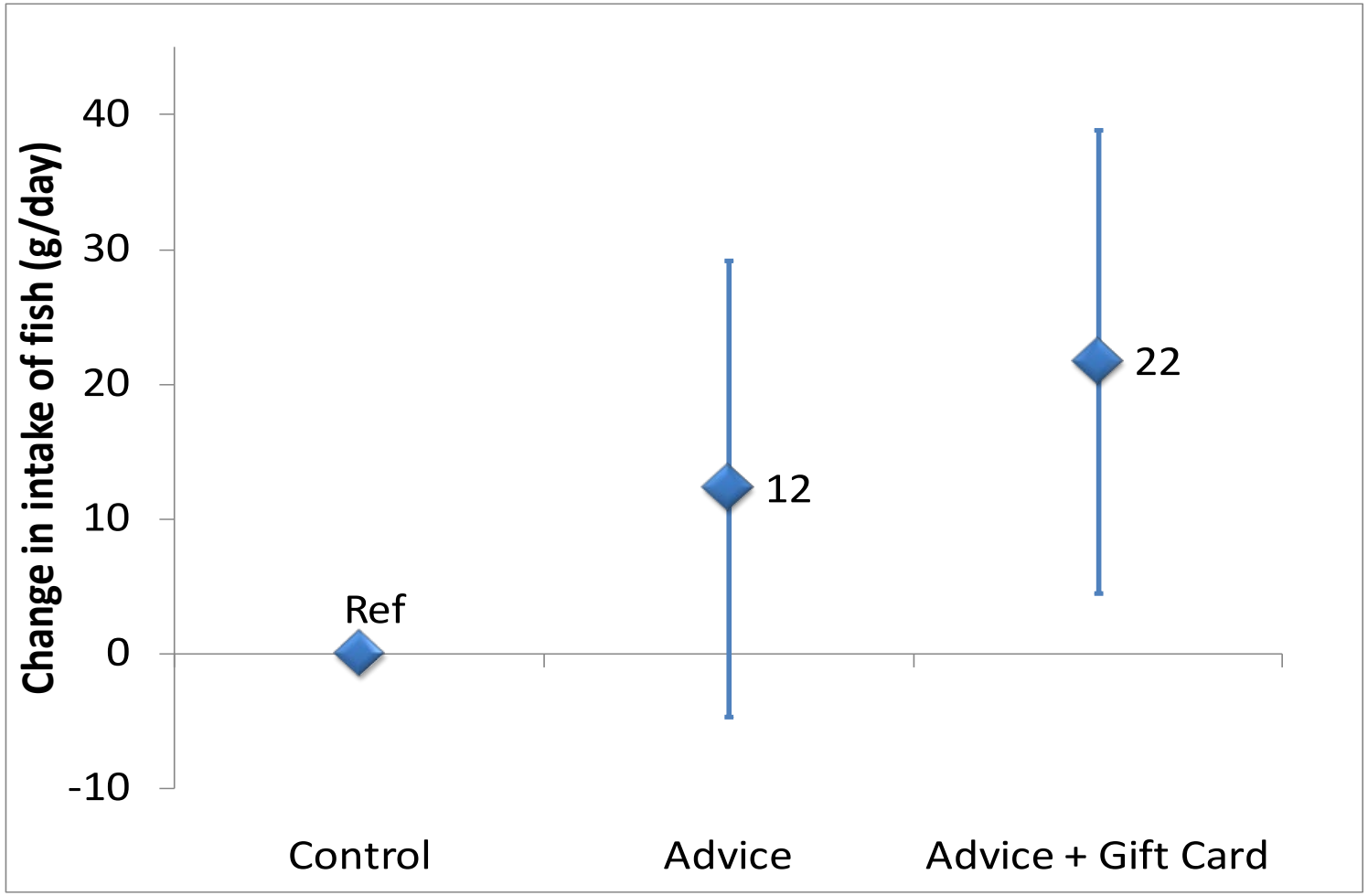
- "That's the main thing I find confusing – so, like, salmon, that's a pretty big fish, so maybe we shouldn't eat it, but then maybe we should eat it because, like it's higher in mercury but it's also higher in good fat, so don't eat it, but no, do eat it."

- "You hear that fish is so good for you, yet on the other hand it's filled with mercury and we need to look out for that…but yet we're supposed to eat it at least twice a week."

Bloomingdale A, Guthrie LB, Price S, Wright RO, Platek D, Haines J, **Oken E**.
A qualitative study of fish consumption during pregnancy. American Journal of Clinical Nutrition 2010 Nov;92(5):1234-40.

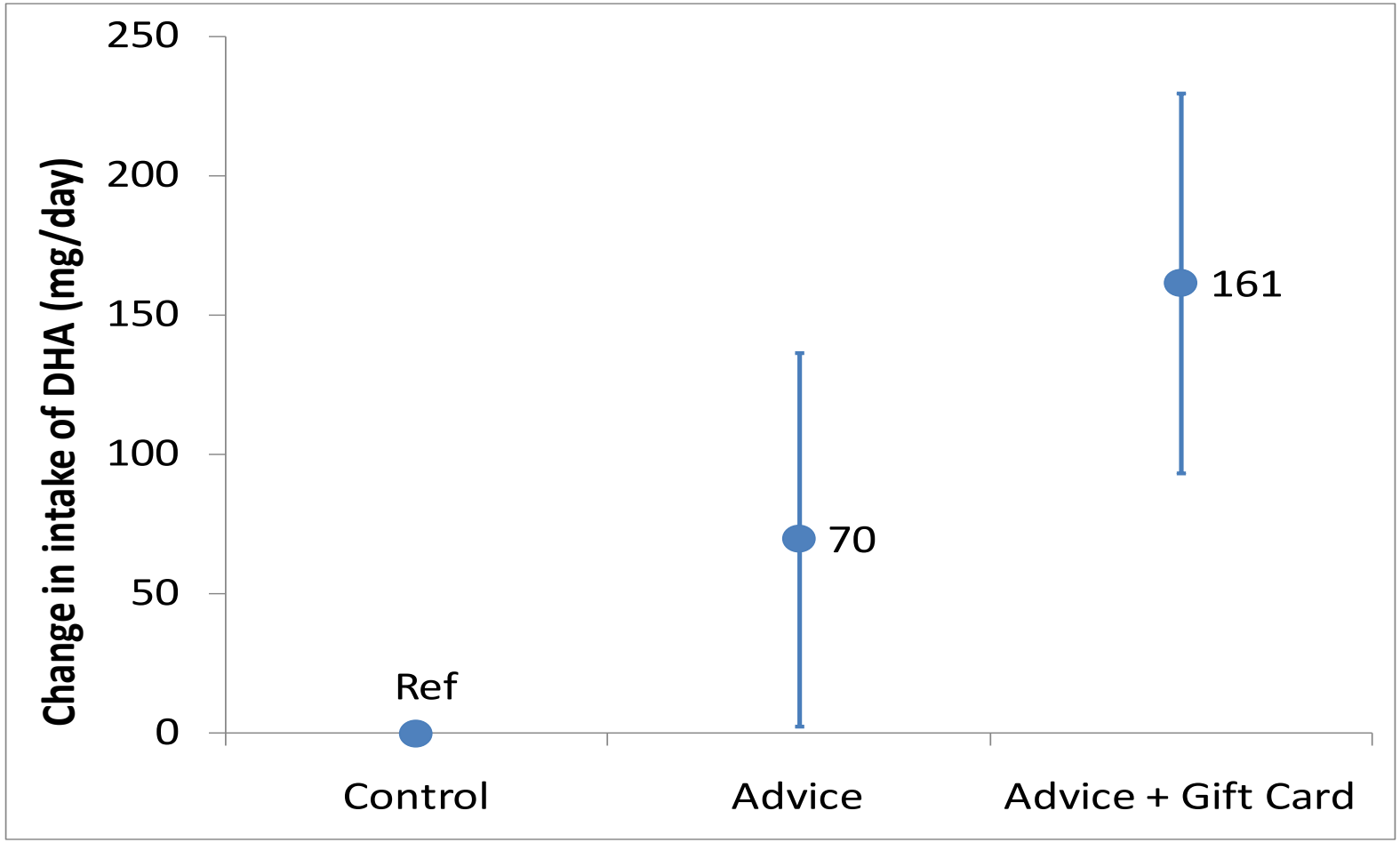
Can women act on a nuanced message?

Fish Intake



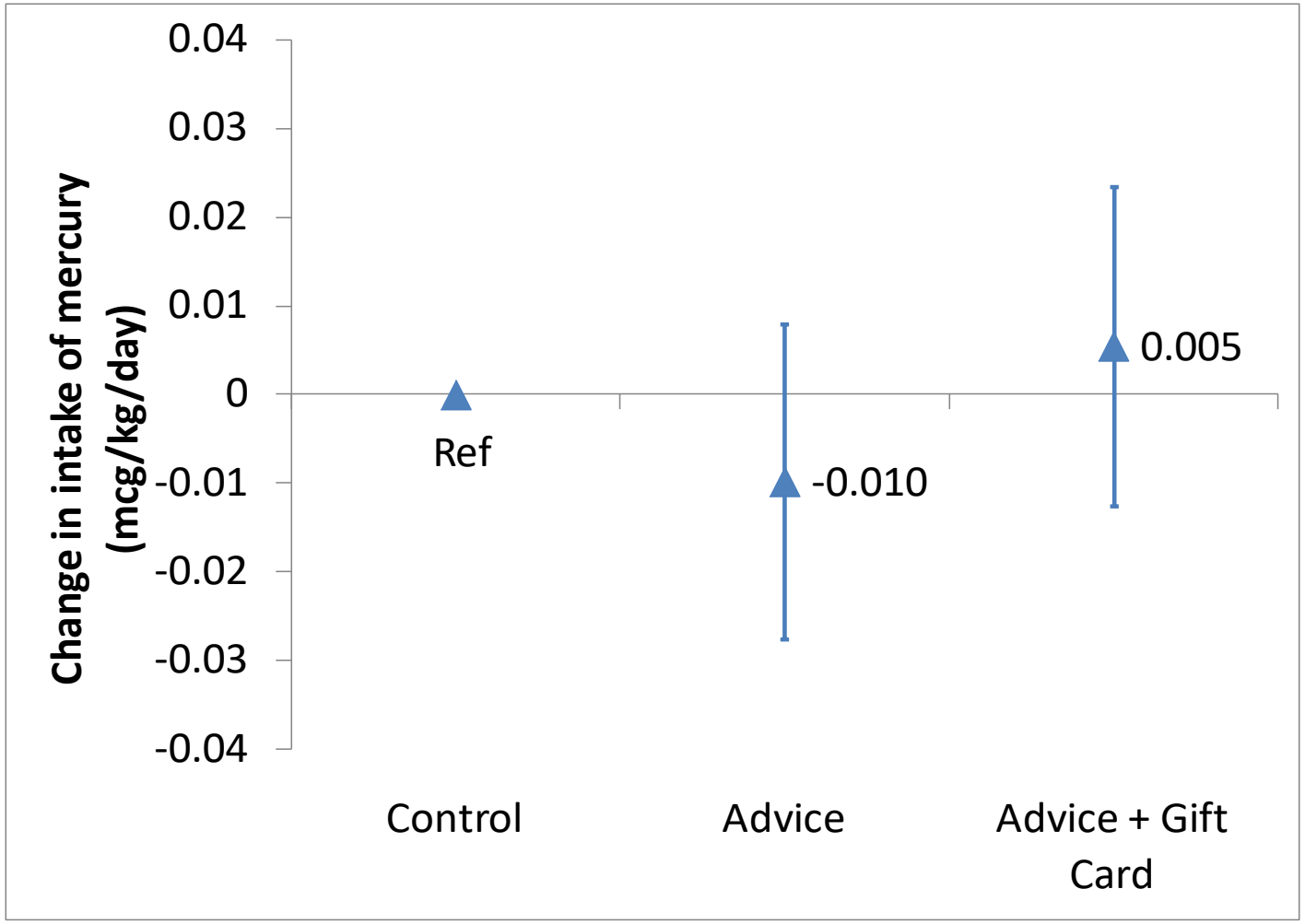
Oken et al. Nutrition Journal 2013, 12:33

DHA Intake



Oken et al. Nutrition Journal 2013, 12:33

Mercury Intake



Oken et al. Nutrition Journal 2013, 12:33

Forthcoming ECHO analyses

- Demographic and health characteristics associated with fish and n-3 fatty acid supplement intake during pregnancy: results from pregnancy cohorts in the ECHO program

- Associations of maternal fish consumption and omega-3 supplement use during pregnancy with child autism-related outcomes: Results from the ECHO program.