

Epidemiology of fish intake benefits and PFAS risks: A focus on EPA's RfDs

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Outline

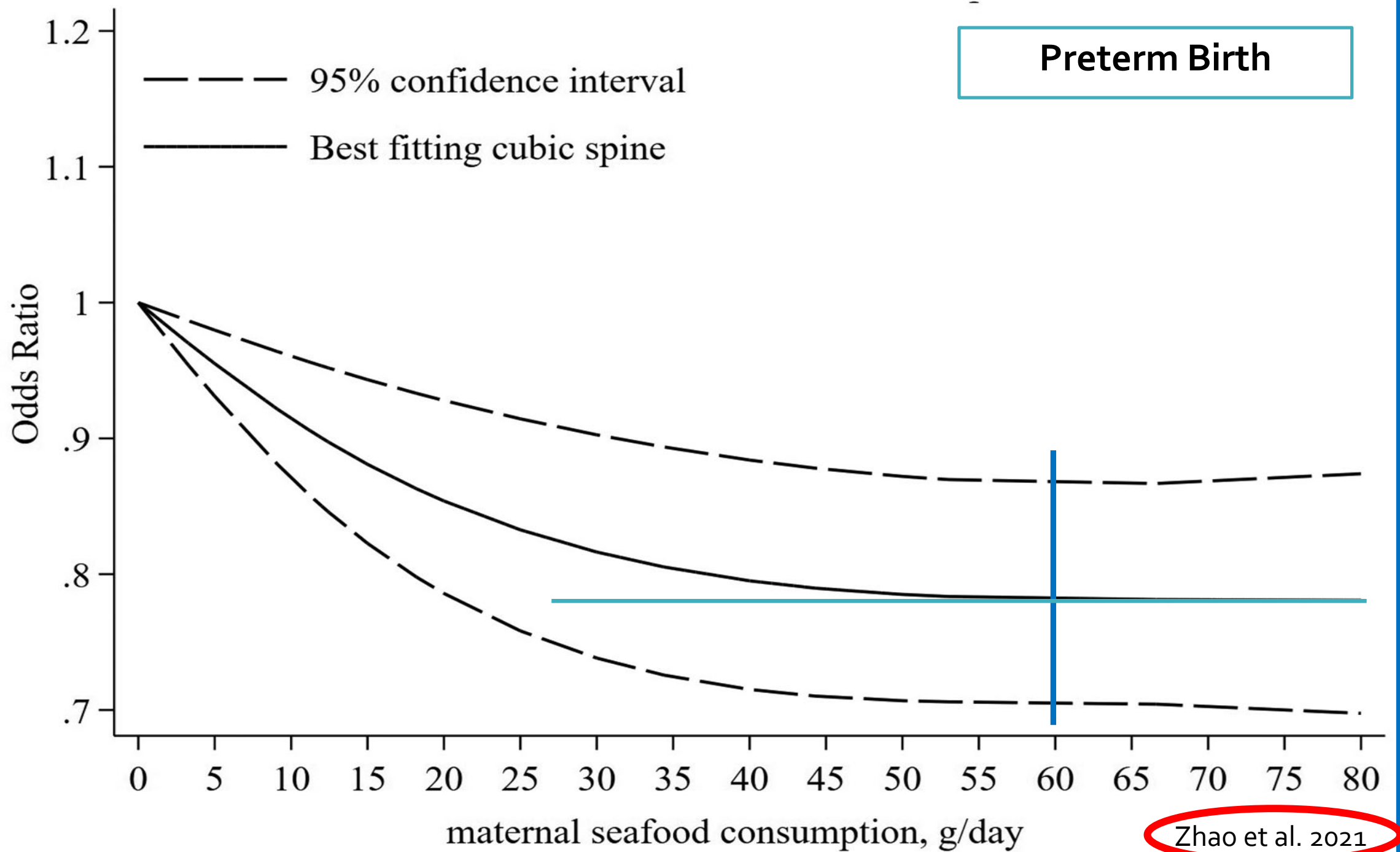
- Health endpoints used by EPA to develop RfDs
 - PFAS studies used by EPA by endpoint (**focus on PFOS/PFOA**)
 - PFAS meta-analyses
 - Fish intake studies by endpoint
- Fish contaminant studies and population PFAS exposures
- Needs, considerations, and conclusions

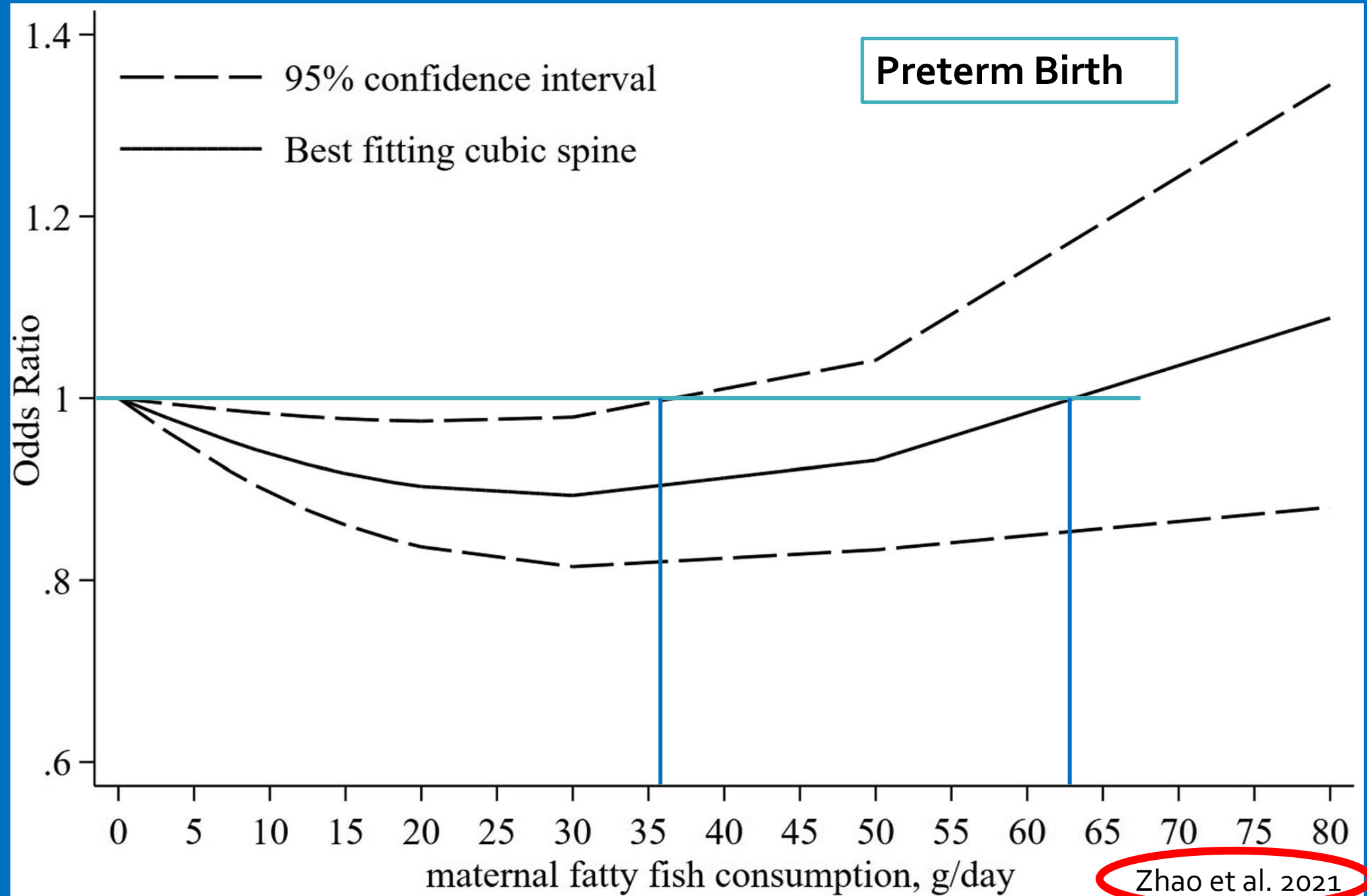
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Critical health endpoint	EPA evidence confidence
Birthweight	High
Cardiovascular	Medium
Immune	Medium
Liver	Medium

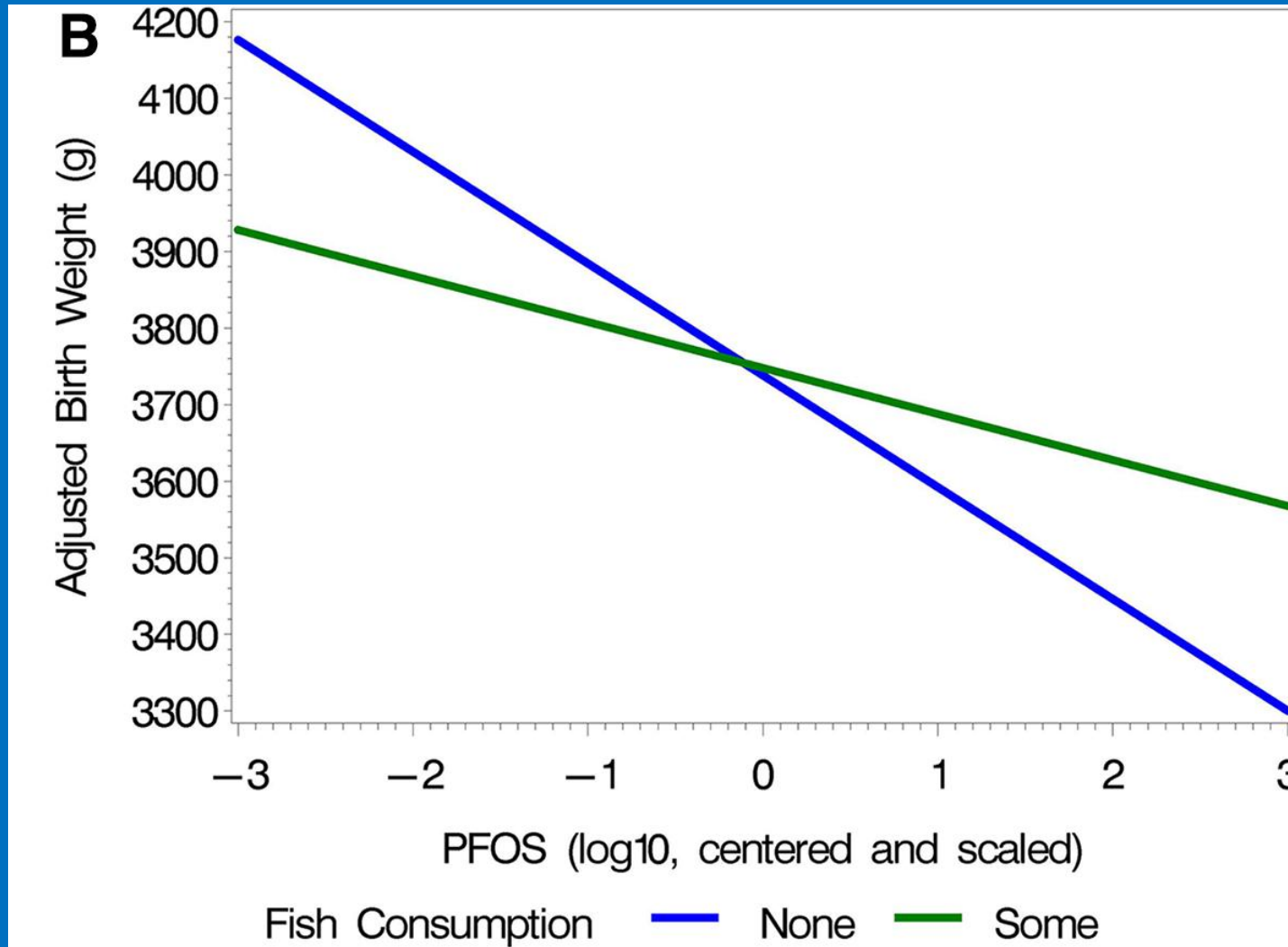
Birth outcomes

Study	Birthweight (BW)	Other birth outcomes	Magnitude
Wikström 2020	(only girls) • PFOS: ↓ • PFOA: ↓	↑ odds small for gestational age (birth weight <10 th %ile)	Quartile 4 vs Quartile 1 (only girls) • PFOS: -142 g • PFOA: -136 g
Sagiv 2018	• PFOS: ↓ • PFOA: ↓ p>.05 for both	↑ odds of preterm birth (gestation <37 weeks)	Change per 1 ng/mL increment • PFOS: -1.1 g • PFOA: -4.9 g
Darrow 2013	• PFOS: ↓ • PFOA: –	No association with preterm birth or low birthweight (<2.5 kg)	Change per IQR increase • PFOS: -29 g • PFOA: +1 g
PFAS meta-analyses	• PFOS: ↓ • PFOA: ↓	Larger decrease in BW when blood collected later in pregnancy (e.g., -7 g vs -1 g Dzierlenga 2020)	Change per 1 ng/mL increment • PFOS: -1 to -5 g • PFOA: -10 to -19 g
Fish intake meta-analyses	↑	↓ odds small for gestational age ↓ odds of preterm birth ↓ odds low birthweight	Eating fish ≥3x/wk vs. <1x/wk: +15.2 g (Leventakou 2014)





PFAS/fish studies



- Gennings 2020 (same cohort as Wikström)
- Slope change from -120 to -49 with eating >0.35x/week of freshwater fish vs. less

ALSPAC study (UK) Taylor 2016

Maternal Hg vs birthweight

All women	-3.1 g (-18.9, 12.8)
Fish eaters	-1.5 g (-18.6, 15.6)
Non fish eaters	-58.4 g (-113.8, -3.0)

Other studies:

Lauritzen 2017: No effect with or without fish intake

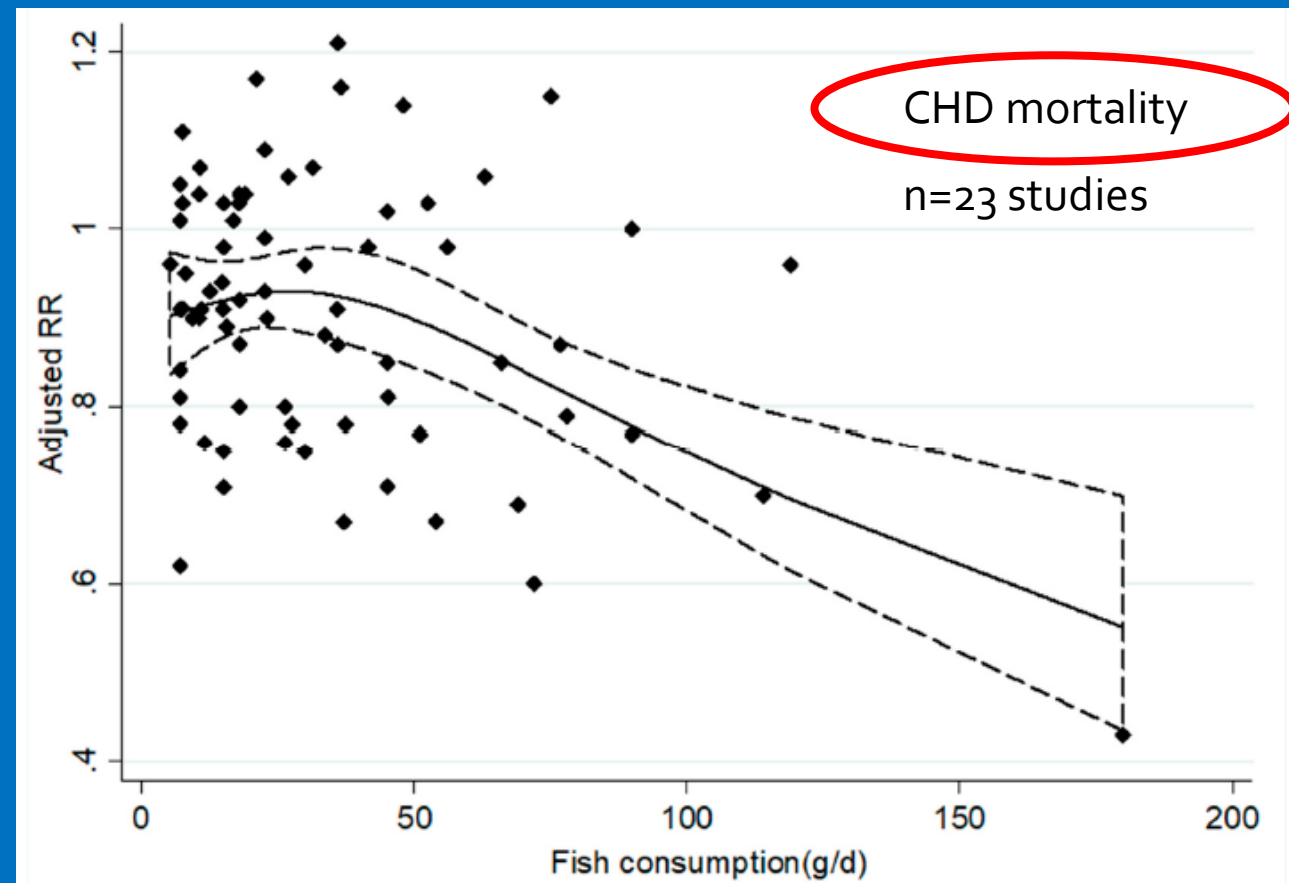
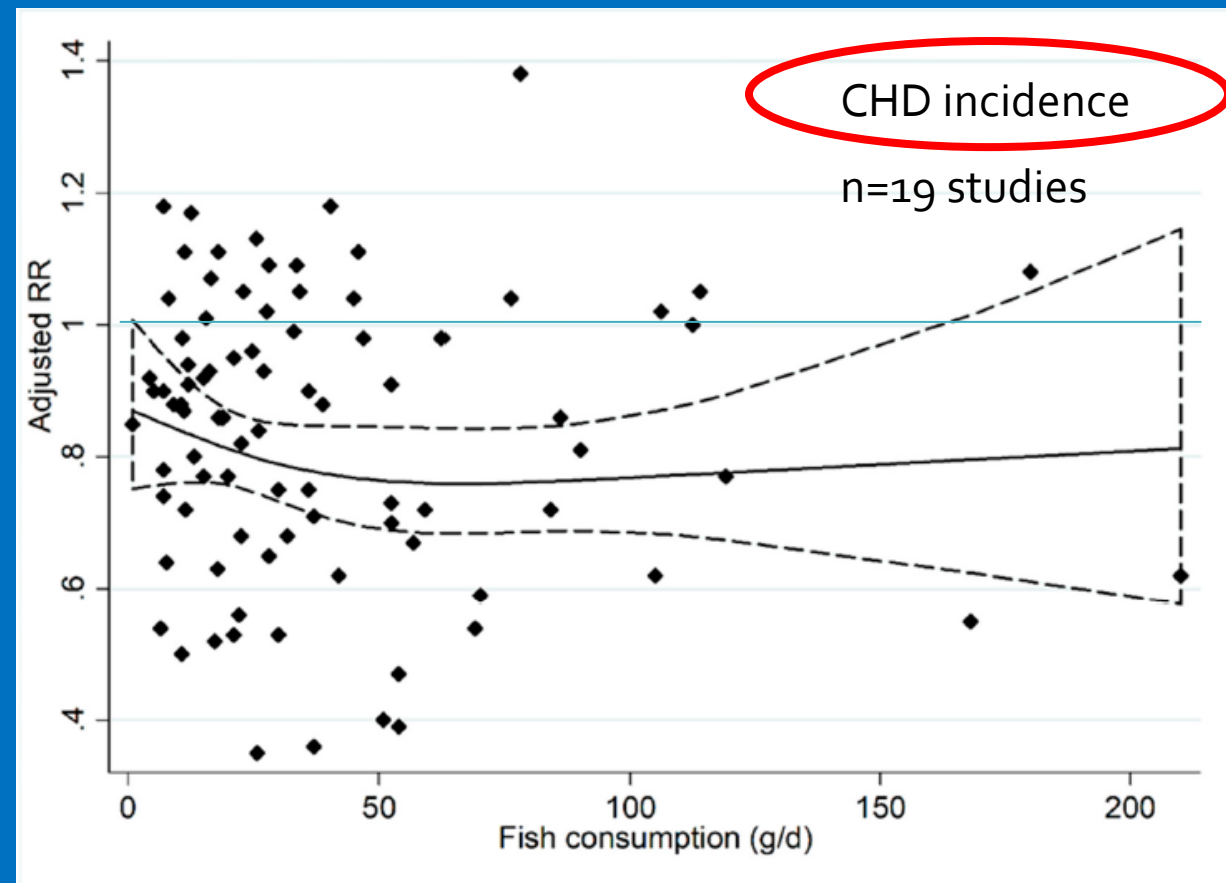
Meng 2008: Adjusting for fish intake in small sample did not affect LBW and PTB association w PFAS

Birth outcomes (summary)

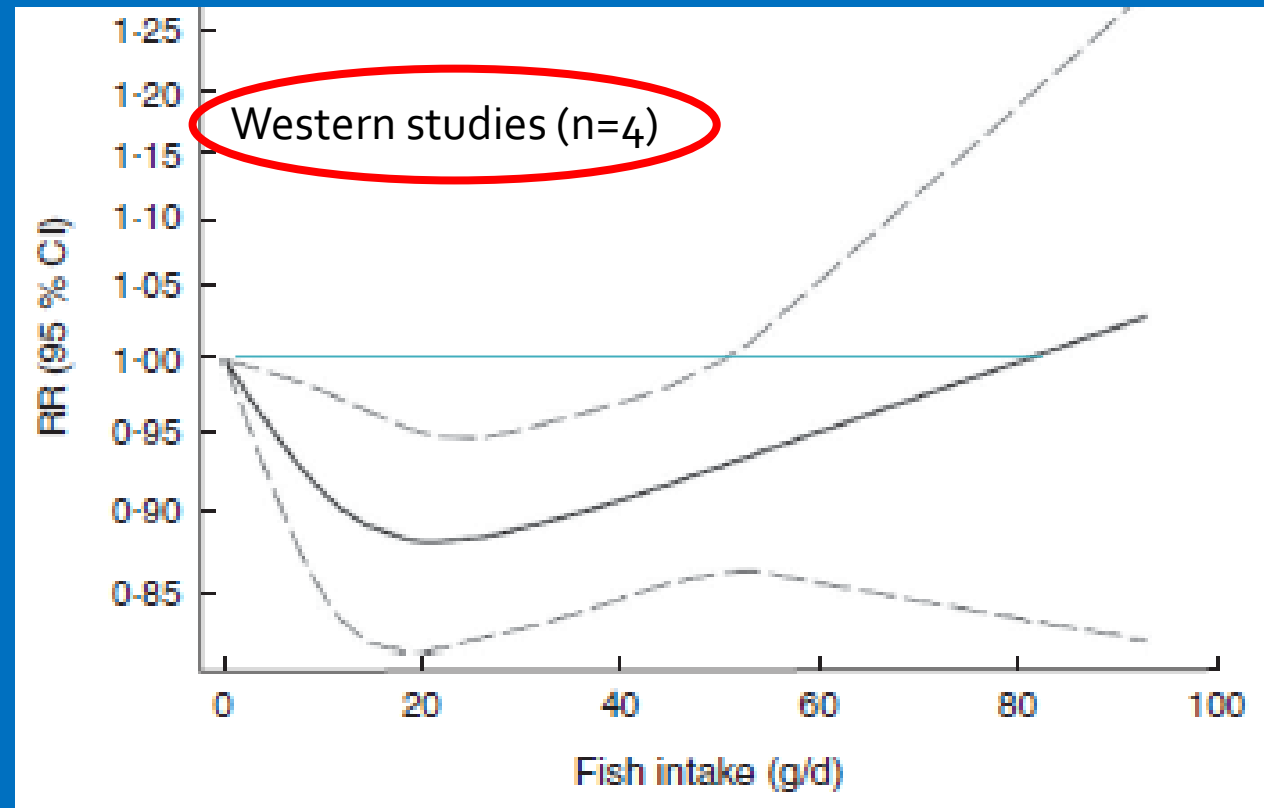
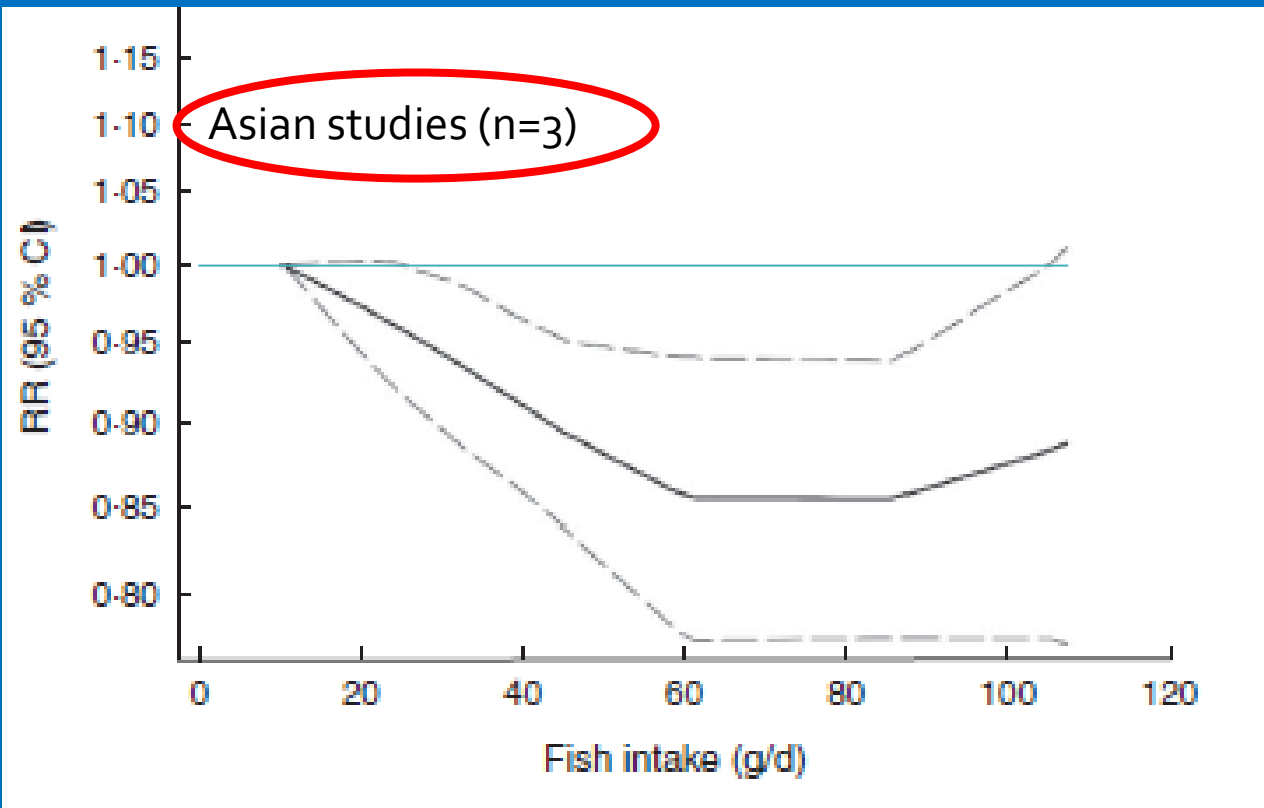
- Adverse associations between maternal PFAS exposure and birth weight but not consistent for other birth outcomes
- Effect of maternal serum sample timing (pregnancy hemodynamics)
- Maternal fish intake associated with higher birthweight and lower odds of SGA, PTB, and LBW
 - Exceptions in few studies with consumption of lean fish, large oily fish, and shellfish, sometimes related to high PCB or mercury content
 - Frying lean fish might have contributed to adverse outcomes.

Cholesterol/Cardiovascular diseases

Study	Total cholesterol	Cardiovascular disease outcomes	Magnitude
Dong 2019	- PFOS: ↑ - PFOA: ↑	Not investigated	Increase per 1 ng/mL PFAS PFOS: +0.4 mg/dL PFOA: +1.5 mg/dL
Steenland 2019	- PFOS: ↑ - PFOA: ↑	No association with cardiovascular disease	Highest vs Lowest decile of PFAS +11-12 mg/dL
PFAS meta-analyses	- PFOS: ↑ - PFOA: ↑	Generally mixed association with cardiovascular diseases.	Increase per 1 ng/mL in adults (Ji et al., 2025) PFOS: 0.51 mg/dL PFOA: 0.98 mg/dL
Fish intake meta-analyses	Mixed results	↓ risk of coronary heart disease, heart failure, myocardial infarction, stroke ↑ HDL-cholesterol	



Coronary heart disease and fish intake
(Zhang 2020)



Cardiovascular mortality and fish intake (Jayedi 2018)

Cardiovascular outcomes (summary)

- Association between PFAS exposures and increased TC, LDL
 - No consistent evidence of association with cardiovascular diseases.
 - Associations varied by study and endpoint among neutral, beneficial, and adverse associations
- Fish intake associated with neutral or favorable cardiovascular outcomes.
 - Adverse associations in few studies with intake of fried fish and lean fish, which require further investigation into fish type, preparation method, and contaminant profiles

Immune outcomes

Study	[Antibody]	Other immune outcomes	Magnitude
Budtz-Jorgensen and Grandjean 2018	- PFOS: ↓ - PFOA: ↓	Not assessed	Per doubling PFAS: -19% to -38% (diphtheria/tetanus)
Timmermann 2020	- PFOS: ↓ - PFOA: ↓ >.05	Not assessed	Per 1 ng/mL serum increase: PFOS: -9% (diphtheria) PFOA: -22% >.05 (diphtheria) PFHxS: -78% (diphtheria)
Zhang 2023	- PFOS: ↓ - PFOA: ↓	Not assessed	Per 2.7x increase in PFAS: -11% (rubella – PFOS/PFOA) -15% (mumps – PFOA) (only with low folate status)
PFAS meta-analyses	- PFOS: ↓ - PFOA: ↓	Not assessed	-10% to -20% tetanus and diphtheria antibodies with PFOS/PFOA/PFHxS
Fish intake studies	Not assessed	Potential benefits on autoimmune disease, hypersensitivity, little on immunosuppression	

Other vaccines and variation within studies

- Some studies found association with one antibody type but not others (e.g., yes rubella; no measles/*H. infl* type b/tetanus)
 - No association with COVID-19 antibodies
- Some studies showed increase antibodies with increased PFAS in serum
- What are the determinants for an association
 - Vaccine/disease specific? E.g., toxoid strength
 - PFAS concentration?
 - Other factors?

Is there increased susceptibility to infection?

Number of infections per year 2012-2022 (WHO)			
Vaccine-preventable diseases	USA	Norway	Denmark
Tetanus	≤37	≤3	≤2
Diphtheria	≤2	≤8*	≤1
Rubella	≤9	≤3	0
Measles	≤1,275**	≤18	≤27

*≤2 except for 2022

** highest in 2020

What do some PFAS immunology reviews find?

- DeWitt et al. (2019) – Review of toxicology and epi studies
 - Strong evidence for risk of immunosuppression
- ATSDR (2021) No consistent evidence for a PFAS-infectious disease association. Evidence of decreased antibody response.
- EPA (2024) Decreased childhood antibody responses. Observed increased risk of upper and lower respiratory infections.
- Crawford et al. (2023) – Systematic review and meta-analysis of vaccine response epi
 - Suggests antibody association, multiple antigens, particularly Diphtheria, Rubella, and Tetanus. Low to moderate risk of bias.
- Antoniou and Dekant (2024) – Systematic review and meta-analysis of epi studies
 - Suggestive evidence for PFAS increased infection risk
 - Moderate to no evidence for antibody titer reduction
- Wikoff et al. (2025) – Uncertainty assessment of epi studies
 - High uncertainty in magnitude/direction of effect in PFAS exposure- vaccine studies
 - Data not good for causal dose-response assessment

Immune outcomes (summary)

- Association between PFAS exposure and decreased antibodies after vaccination
 - Variation among studies and by vaccine [decrease (mostly), increase, neutral]
- Fish intake studies showed possible favorable outcomes on autoimmunity and hypersensitivity, but scant evidence on immunosuppression
- Several factors can affect the immune response to vaccine (e.g., sex, gut flora, physical activity, nutrients, location, BMI, income, mood, stress)
 - Circadian rhythm dependent vaccine response (Fernandes 1976, Wang 2022)
 - Maternal blood lead and arsenic in drinking water (Welch 2020)

Implications for fish consumption recommendations

What do states use?

RfD source	RfD (ng/kg bw-d)	Fish PFOS conc (ng/g wet weight)*	Recommended fish meals/week (8 oz)
MN	3.1	3.07	2.2
NJ	1.8	3.07	1.3
Oregon	4.1	3.07	2.9
WA	3.1	3.07	2.2
EPA, 2024	0.1	3.07	0.07
EPA, 2016	20	3.07	14
Dourson et al. 2025	20-100	3.07	14 - 70

*median in fish from the Nat'l Rivers and Streams Assessment (2018/9 data) (Stahl et al. 2023). Mean ~ 6 ng/g

None of these numbers account for the benefits of fish consumption

Fish contaminant profiles

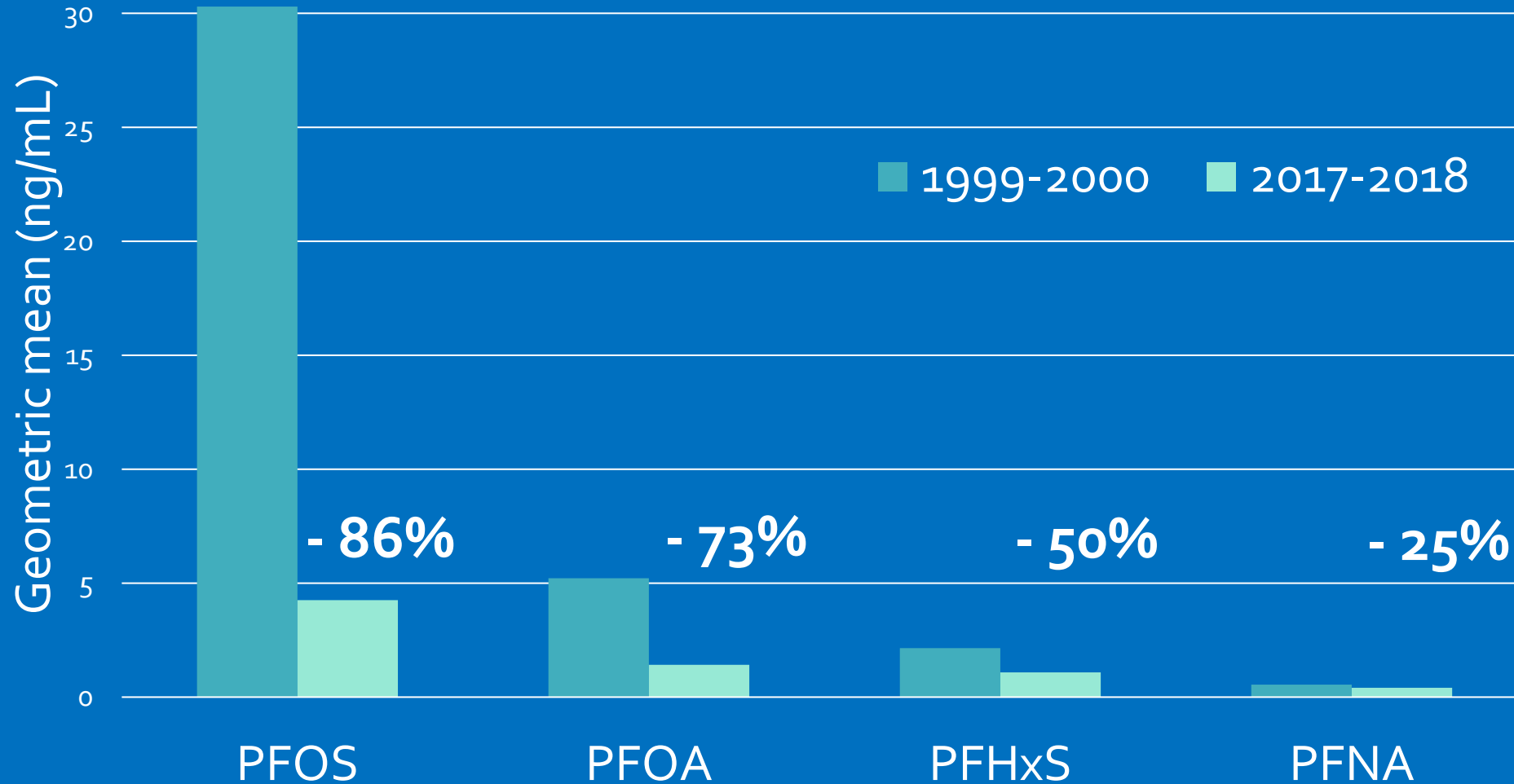
Stahl 2023: National Rivers and Streams Assessment (2013/4 – 2018/9)

- maintained half sampling locations
- PFOS = most frequently detected (median decreased >50%)

MacGillivray 2021: Delaware River (2004 – 2018)

- decrease in PFOS in select species. Others PFAS decreased or unchanged

NHANES adult population exposures



Public health considerations

- Reference doses do not consider the benefits of fish intake
 - Approaches (Dourson 1987; FDA 2014; Ginsberg 2015)
- Are the recommendations we make effective? (consider timing, population of interest, loss of benefit, risk)
- Is there room for a “reverse uncertainty factor” (or benefit factor)

Hamade. Fish consumption benefits and PFAS risks: Epidemiology and public health recommendations. Toxicol Rep. 2024 Sep 19;13:101736.

Needs

- More monitoring of finfish, shellfish, marine mammals
 - Marine and freshwater
 - Tissue-specific measurements
 - Preparation method
- Studies of PFAS exposure that monitor fish intake
 - Food frequency questionnaire
 - Biomarkers
- Assessing the toxicology and epidemiology of the many other PFAS
 - + Investigating additive effects
- Exploring exposure and effects on subpopulations
- Continued reduction of PFAS release and exposure

Conclusions

- For many populations, PFAS and other contaminants generally pose no net risk from consuming 200-500 g/week (or more) of a variety of fish
 - In line with several U.S. national recommendations
 - In some studies, very high intake, fish type, frying, PCBs, Hg, associated with adverse outcomes
- Epidemiology studies used by EPA for RfD development have small effect magnitudes, do not have clear associations with health conditions, or contrast with benefits
 - Clear toxicity in animal studies, but what is relevant for fish consumption and human health?
 - Needs thoughtful assessment including engagement of health care professionals

*Half of food sustains and
half of it kills*

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