Reduced immune response to vaccinations in children with elevated exposure to perfluorinated compounds

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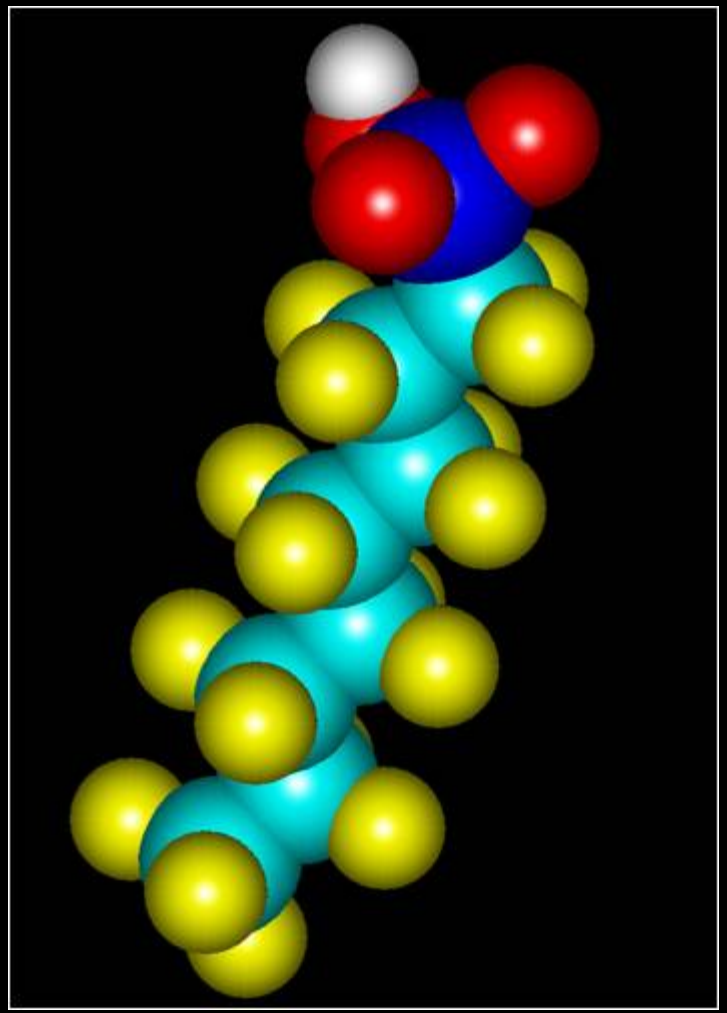

The Interplay Between Environmental Exposures and Infectious Agents:
Environmental Chemicals and Immune Response
NIEHS Superfund Research Program
Webinar, 31 October 2016

Perfluorinated alkyl substances (PFAS) characteristics

Highly **persistent** in the environment, global dissemination
Slightly water soluble, low vapor pressure
Easily absorbed in humans
Elimination half-time in humans: several years
Pass the placental barrier
Lactational transfer results in peak exposures in infancy

Major adverse effects documented in laboratory animals and also reported in humans:
Carcinogenicity
Liver enzymes and serum lipids
Immunotoxicity
Endocrine disruption, including delayed breast development
Fetal toxicity and adverse pregnancy outcomes

Immunotoxicity

Reported in mice and Rhesus monkeys

Outcomes are fairly crude:
Decreased spleen and thymus weights, lowered total immunoglobulin, and decreased immunocyte cell counts

Decreased antibody responses shown in both mice and monkeys
Mediated through PPARα and non-PPARα dependent pathways

NTP on PFOS and PFOA: "*presumed to be an immune hazard to humans… – high level of evidence… from animal studies… and moderate level of evidence from studies in humans*"

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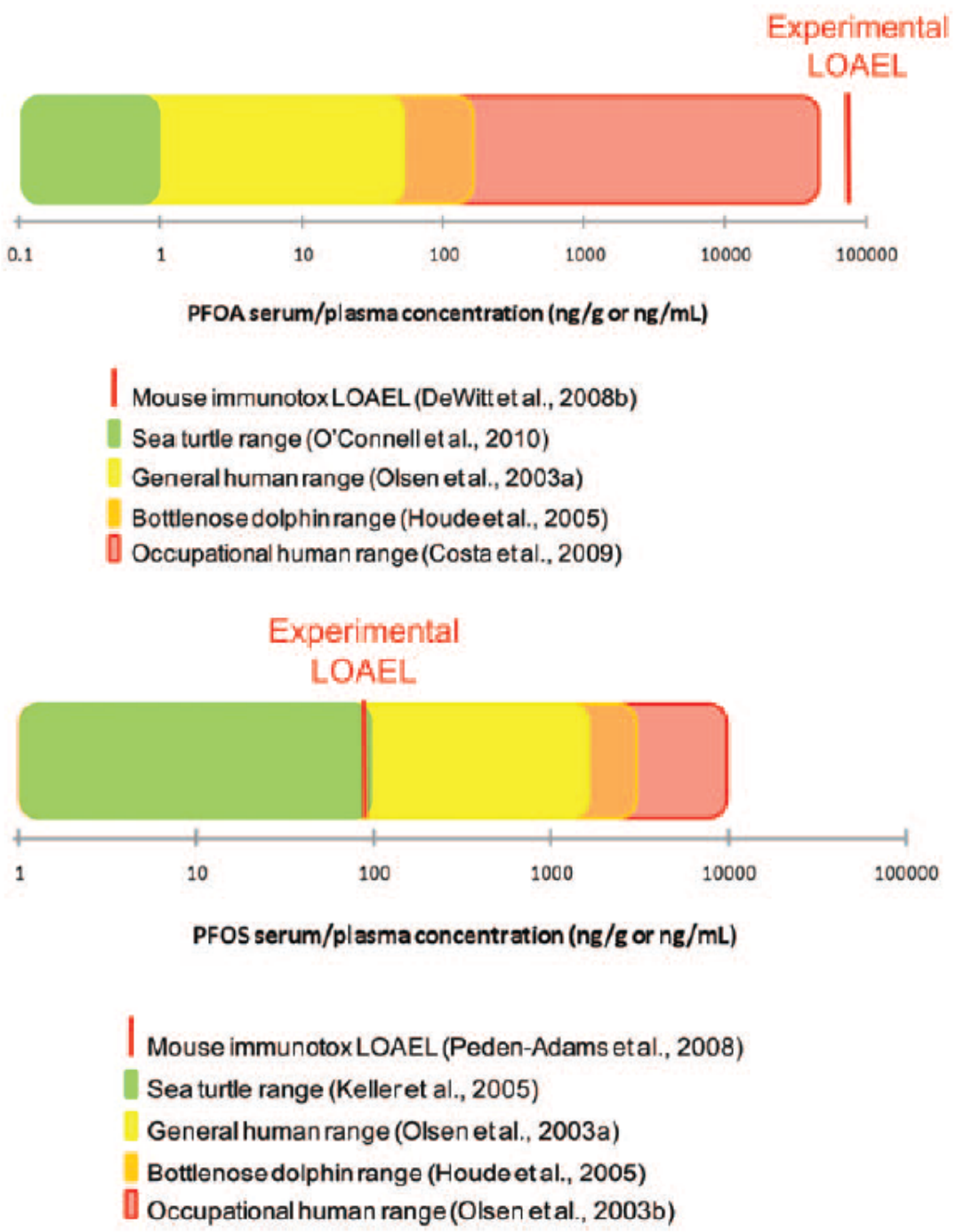
RESEARCH ARTICLE

Suppression of antigen-specific antibody responses in mice exposed to perfluorooctanoic acid: Role of PPARα and T- and B-cell targeting

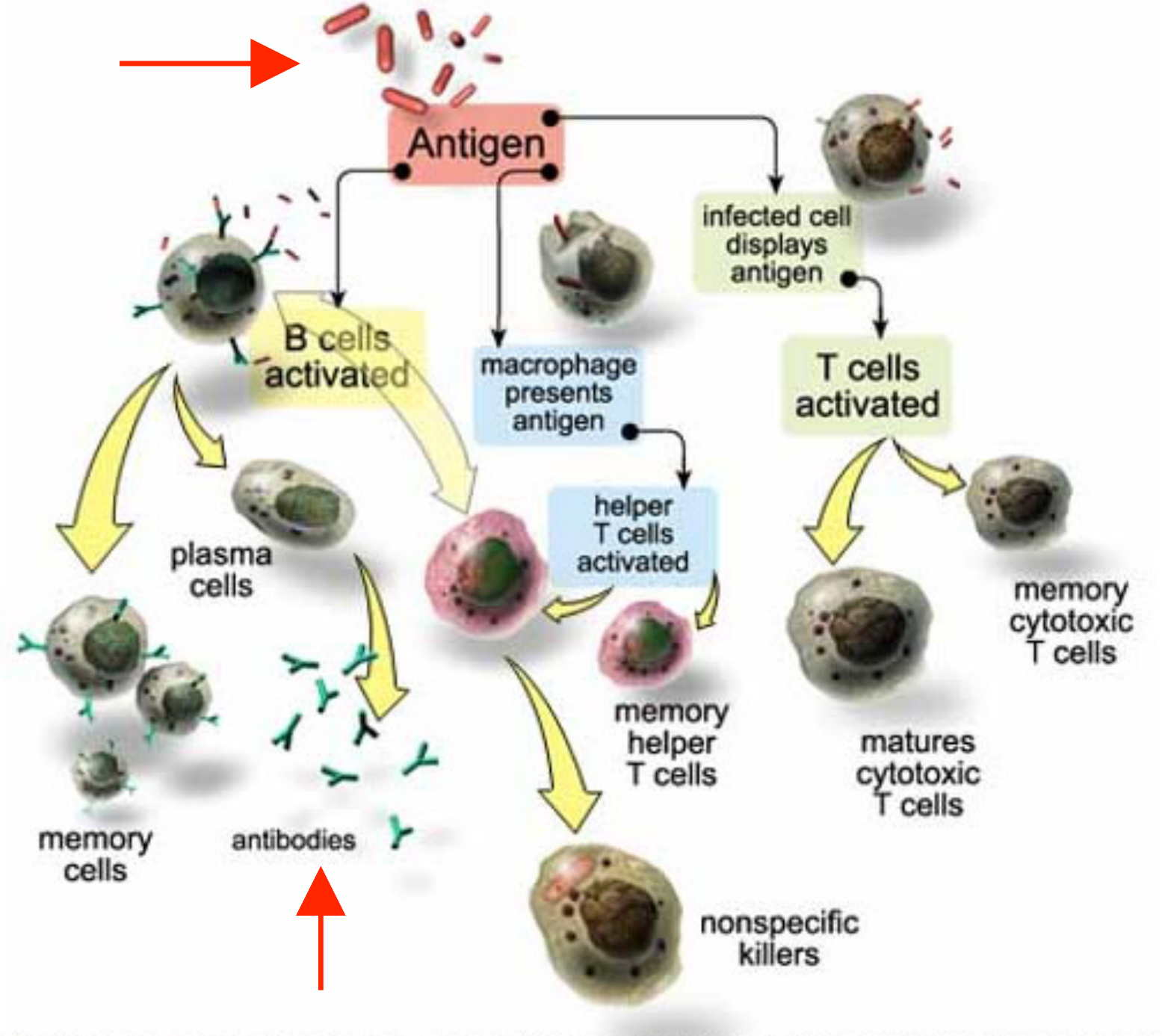
Jamie C. DeWitt[1], Wanda C. Williams[2], N. Jonathan Creech[3], and Robert W. Luebke[2]



PFOA:
LOAEL higher than highest exposures

PFOS:
LOAEL similar to human exposures

(DeWitt et al., 2012)



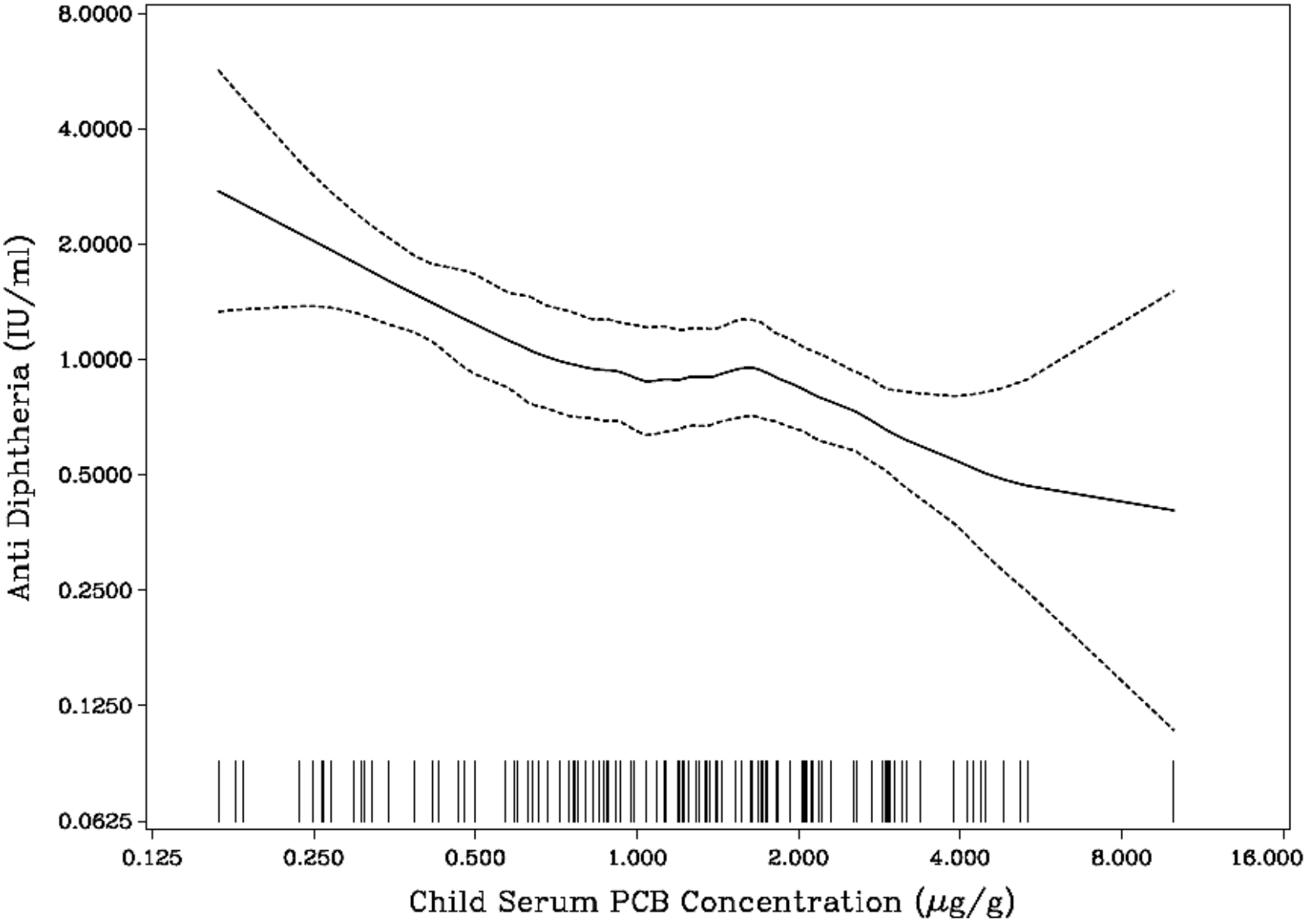
(Source: the Human Immune Response System www.uta.edu/chagas/images/immunSys.jpg)

Human immunotoxicity:
Advantages of vaccine responses in epidemiological studies:

- 'Natural experiment'
- Same dose of antigen
- Same age at exposure
- Routine antibody assay
- Clinical relevance

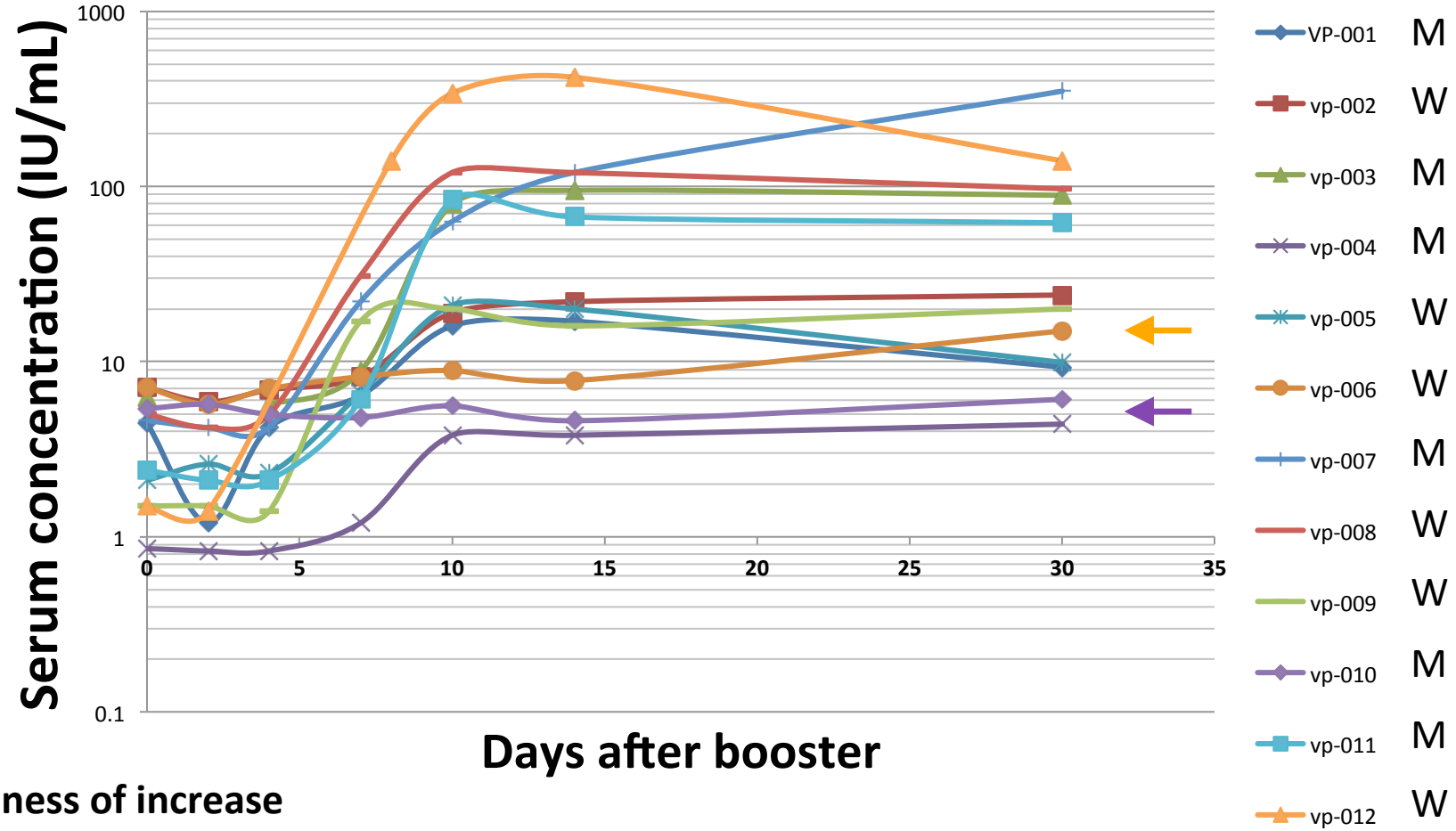
Colourbox.com

The higher the PCB exposure, the less efficient the response to childhood immunization (here the diphtheria antibody response at 18 months)



Heilmann et al., PLoS Medicine, 2006

Change in tetanus antibody concentration after booster



Steepness of increase inversely associated with serum-PFAS

(Kielsen et al., 2015)

Faroe Islands

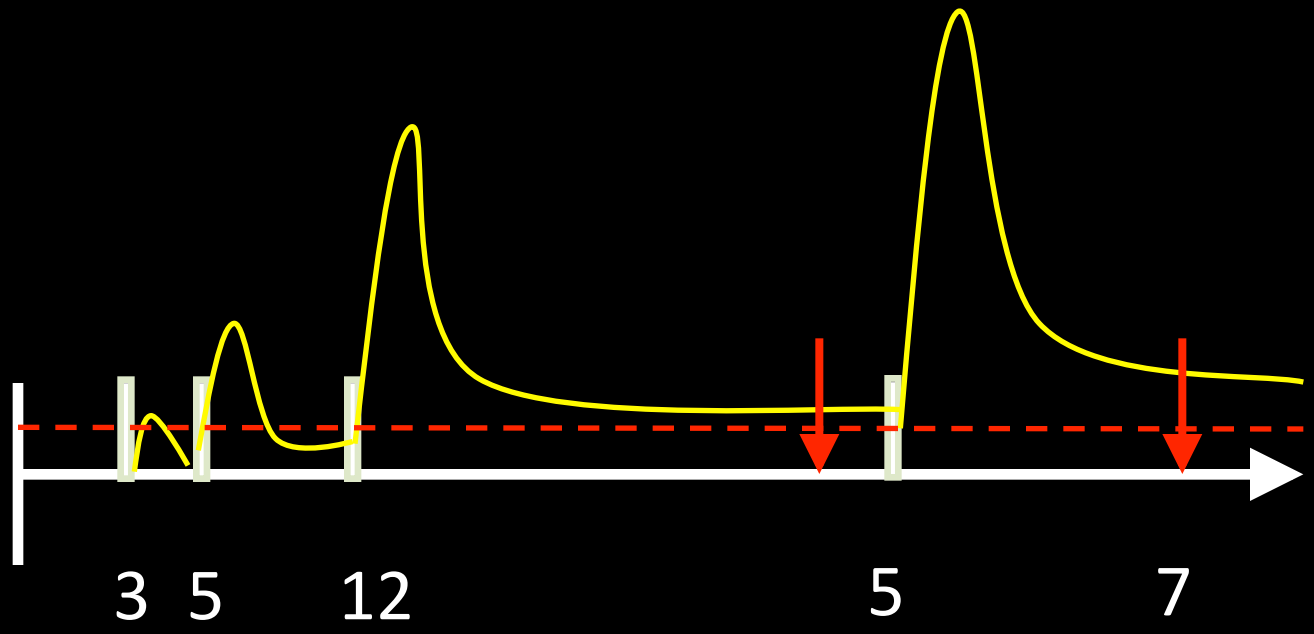
- **Homogeneous, western culture**
- **High participation rate in prospective studies**
- **Fishing community with high seafood intake**
- ***Wide range of exposures from traditional food (pilot whale)***
- **Total population - 48,000**

From NASA

Vaccination

Blood sample

Antibody concentration responses to vaccinations



Serum Vaccine Antibody Concentrations in Children Exposed to Perfluorinated Compounds

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Context Perfluorinated compounds (PFCs) have emerged as important food contaminants. They cause immune suppression in a rodent model at serum concentrations similar to those occurring in the US population, but adverse health effects of PFC exposure are poorly understood.

Objective To determine whether PFC exposure is associated with antibody response to childhood vaccinations.

Design, Setting, and Participants Prospective study of a birth cohort from the National Hospital in the Faroe Islands. A total of 656 consecutive singleton births were recruited during 1999-2001, and 587 participated in follow-up through 2008.

Main Outcome Measures Serum antibody concentrations against tetanus and diphtheria toxoids at ages 5 and 7 years.

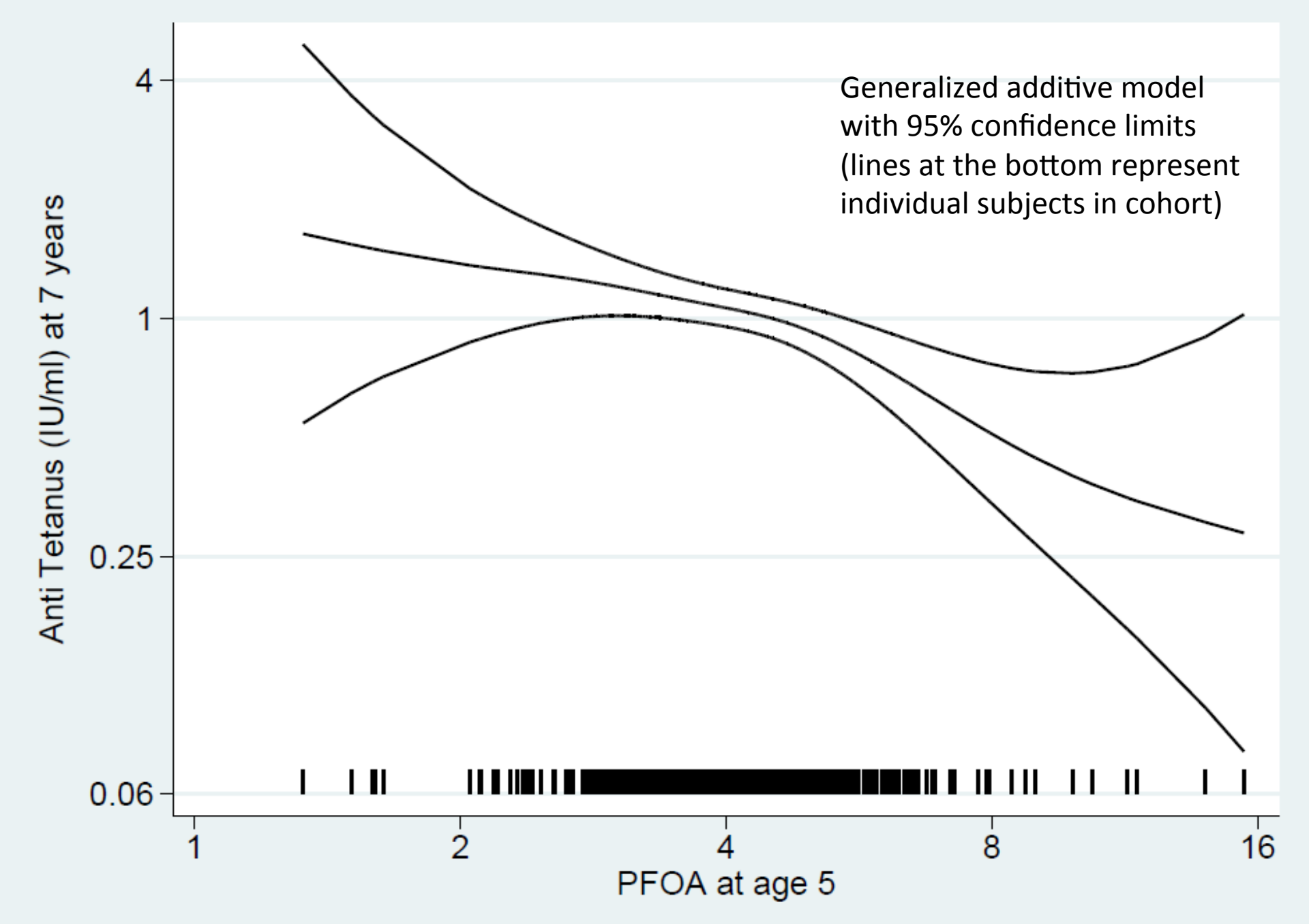
Results Similar to results of prior studies in the United States, the PFCs with the highest serum concentrations were perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). Among PFCs in maternal pregnancy serum, PFOS showed the strongest negative correlations with antibody concentrations at age 5 years, for which a 2-fold greater concentration of exposure was associated with a difference of –39% (95% CI, –55% to –17%) in the diphtheria antibody concentration. PFCs in the child's serum at age 5 years showed uniformly negative associations with antibody levels, especially at age 7 years, except that the tetanus antibody level following PFOS exposure was not statistically significant. In a structural equation model, a 2-fold greater concentration of major PFCs in child serum was associated with a difference of –49% (95% CI, –67% to –23%) in the overall antibody concentration. A 2-fold increase in PFOS and PFOA concentrations at age 5 years was associated with odds ratios between 2.38 (95% CI, 0.89 to 6.35) and 4.20 (95% CI, 1.54 to 11.44) for falling below a clinically protective level of 0.1 IU/mL for tetanus and diphtheria antibodies at age 7 years.

Conclusion Elevated exposures to PFCs were associated with reduced humoral immune response to routine childhood immunizations in children aged 5 and 7 years.

JAMA. 2012;307(4):391-397 www.jama.com

FLUORINE-SUBSTITUTED ORganic compounds have thousands of important industrial and manufacturing applications and occur widely in surfactants and repellants in food packaging and textile impregnation.[1] The perfluorinated compounds (PFCs) are highly persistent and cause contamination of drinking water, food, and food chains.[1] The most common PFCs, perfluorooctanoic acid (PFOA, sometimes called C8), perfluorooctane sulfonic acid (PFOS), and perfluorohexane sulfonic acid (PFHxS), have elimination half-lives in humans of at least 4 years[2] and are commonly detected in human serum.[3]

Perfluorinated compounds are transferred through the placenta,[4] and post-



Grandjean et al., 2012

Odds ratios (ORs) for doubling in child's **age-5** serum-PFAS as predictor of antibodies *below 0.1 IU/mL* at **age 7** years (i.e., *the vaccine did not protect against the disease*)

	Tetanus (N=18)		**Diphtheria (N=32)**	
	PFOS	**PFOA**	**PFOS**	**PFOA**
OR	2.61	4.20	2.38	3.27
95%CI	*0.77; 8.92*	*1.54; 11.44*	*0.89; 6.35*	*1.43; 7.51*
p	0.12	0.006	0.08	0.006

PFOA showed the strongest effect - ORs below 2.0 for other PFASs

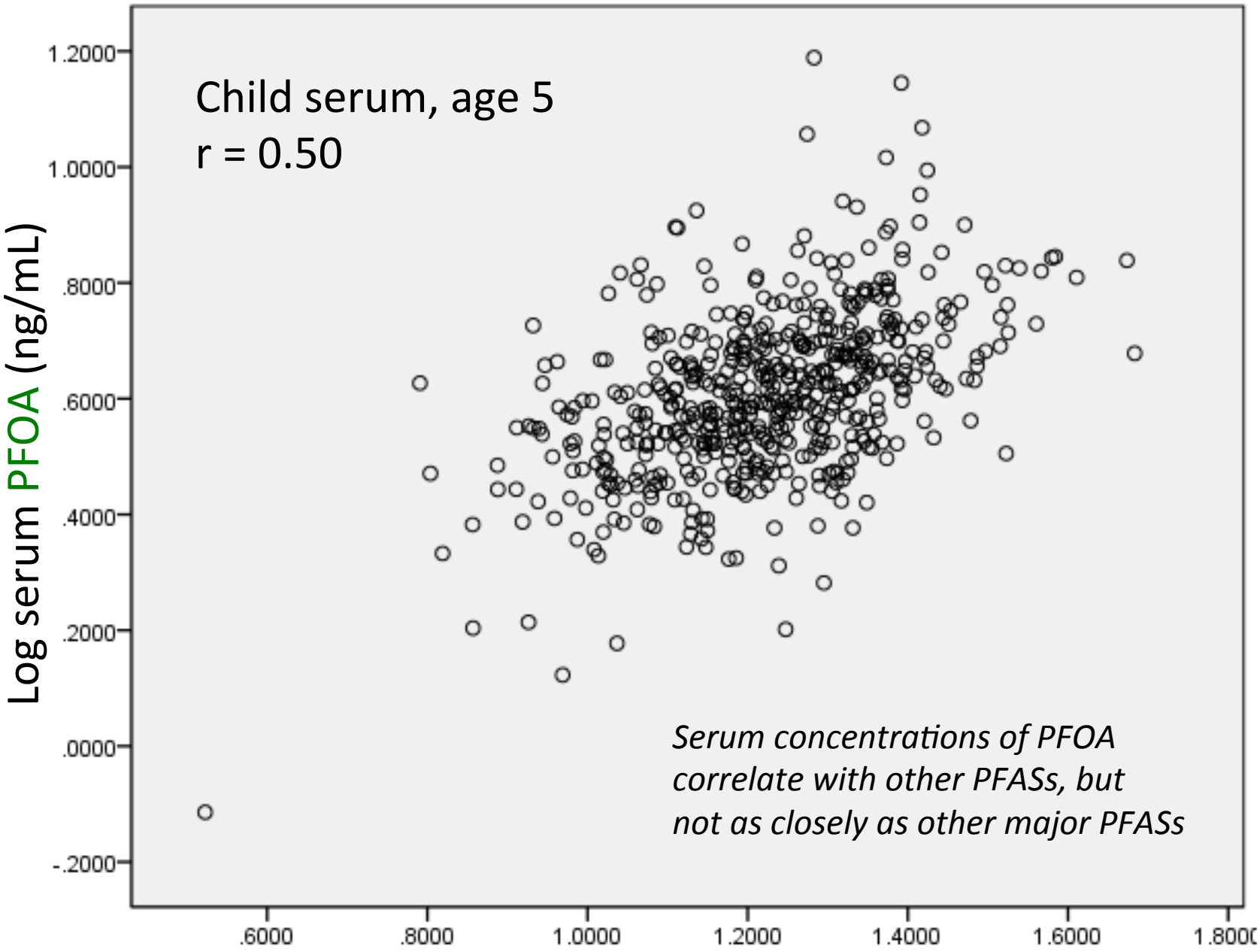
Grandjean et al, 2012

Effect of a doubled serum-***PFOA*** at ages 5 and 7 years on serum antibodies (%) at age 7 years

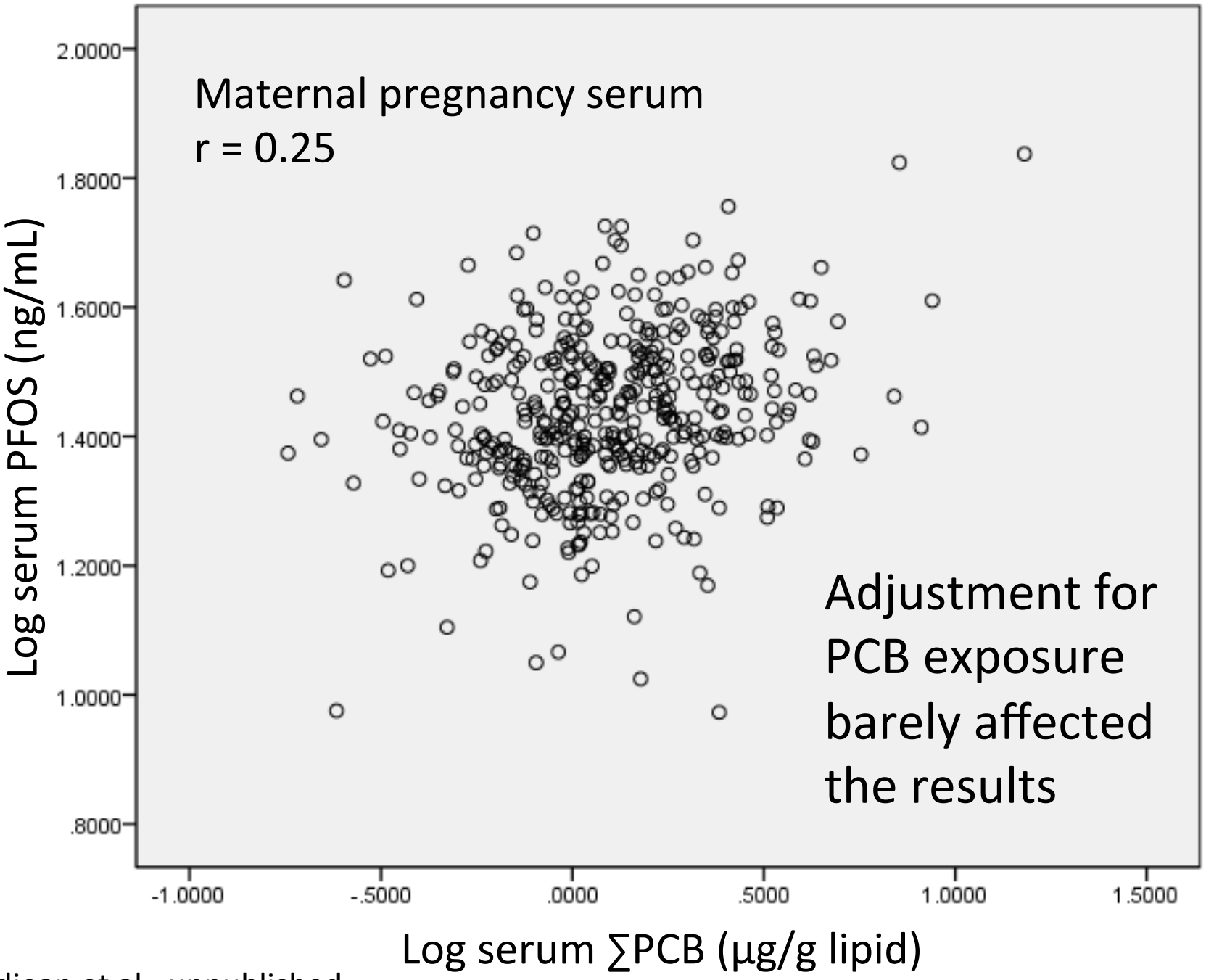
	Tet	**95% CI**	**Diph**	**95% CI**
Regression (7)	-20.5	-38.2; 2.1	-25.4	-40.9; -5.8
SEM (5+7)	-38.2	-56.1;-13.0	-34.7	-52.5; -10.2
Adjusted*	-29.6	-50.6; 0.4	-26.9	-47.4; 1.5

*adjusted for other PFASs (almost unchanged)

Mogensen et al., 2015

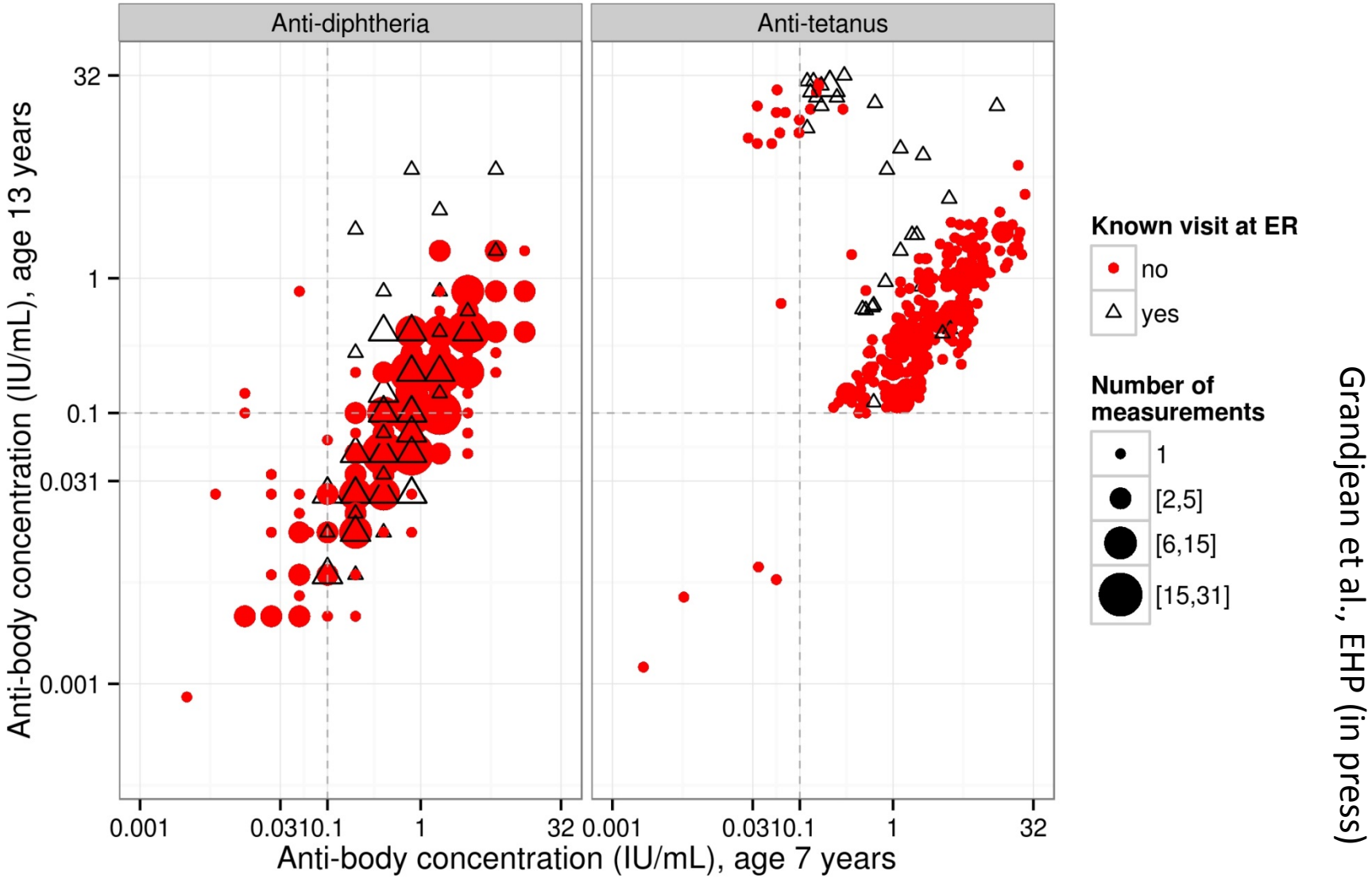


Grandjean et al., unpublished

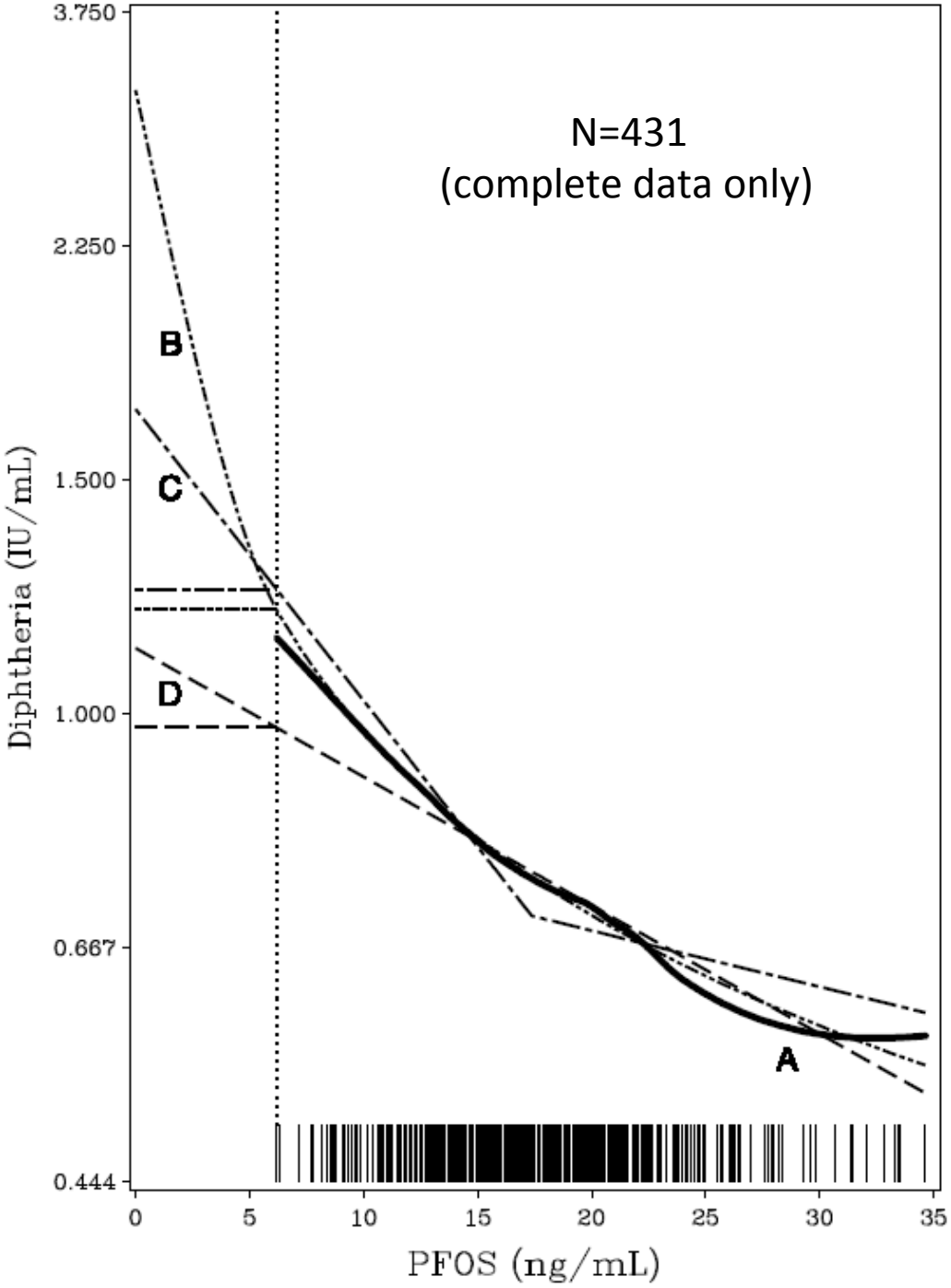


Grandjean et al., unpublished

Follow-up at age 13 years: Antibody concentrations are affected by (unscheduled) booster vaccinations



Grandjean et al., EHP (in press)



BMC calculations
Serum-PFAS at age 5
Serum antibody at age 7

BMCL at BMR = 5%
~1.3 ng PFOS/mL serum
~0.3 ng PFOA/mL serum
for linear curve

Lower for log curve
Higher for BMR = 10%

Environmental Health 2013, **12**:35

Increased risk of infection?

- In the Odense Child Cohort (Denmark), 359 children aged 1-3 years were monitored for fever and symptoms every 2 weeks for 1 year (by text messages)
- Days with fever >38.5º (101.3ºF), comparison of high and low tertiles of maternal pregnancy serum concentrations:
  - Odds of experiencing days with fever above median for **PFOS** OR: 2.35 (95%CI: 1.31, 4.11) and **PFOA** OR: 1.97 (95%CI: 1.07, 3.62)
- Higher exposures to **PFOA** and **PFOS** tended to increase the proportion of episodes with fever and nasal discharge: for medium tertile **PFOA** exposure as compared to the low tertile (IRR: 1.38 (95% CI: 1.03,1.86)).
- Likewise, higher exposures to **PFOA, PFOS** and **PFHxS** tended to increase the proportion of episodes with fever and coughing.

Dalsager et al., Environment International, 2016

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informa healthcare

RESEARCH ARTICLE

Pre-natal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood

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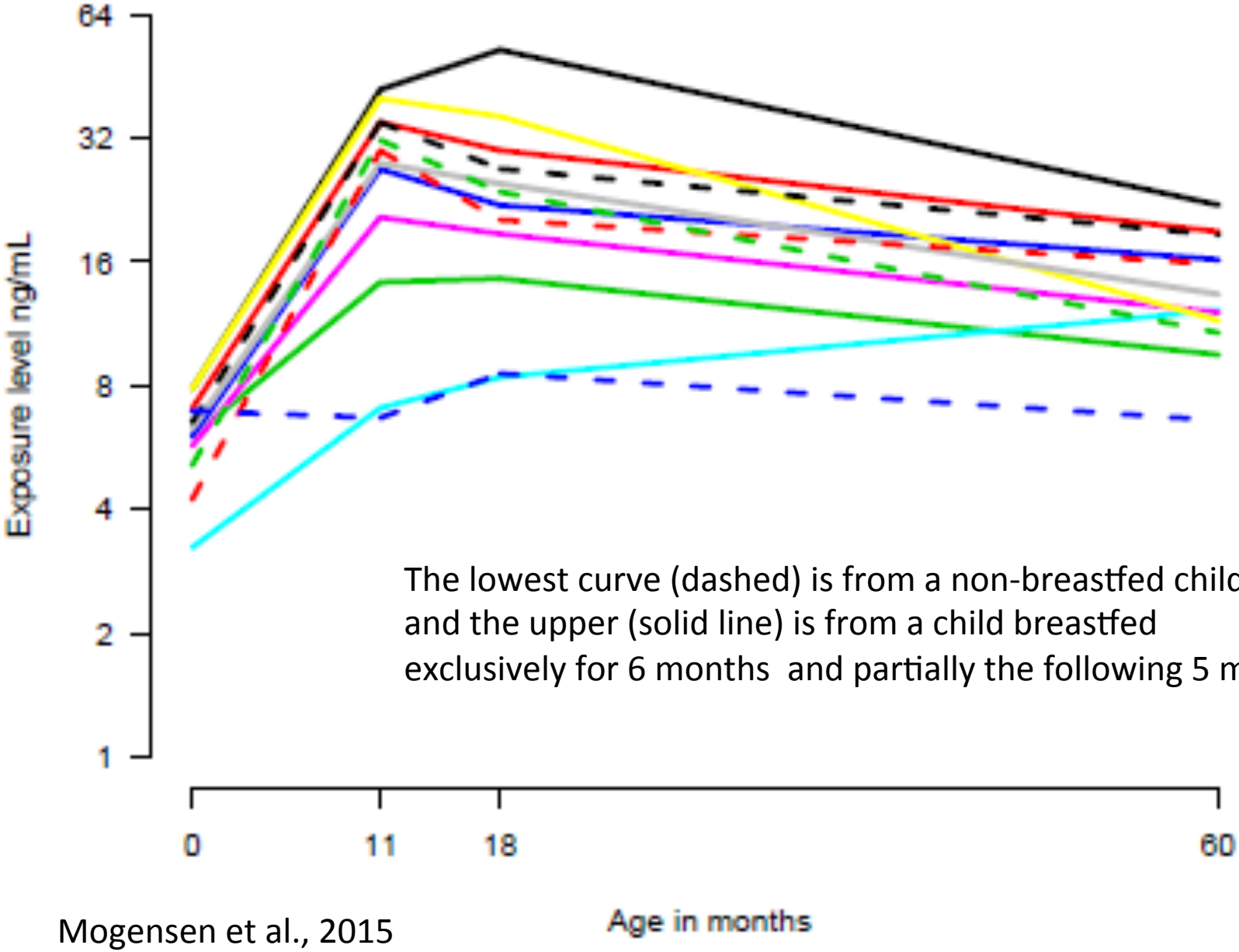
There was an inverse association between the level of anti-rubella antibodies in the children's serum at age 3 years and the concentrations of the four PFAS. Furthermore, there was a positive association between the maternal concentrations of **PFOA** and **PFNA** and the number of episodes of common cold for the children, and between **PFOA** and **PFHxS** and the number of episodes of gastroenteritis (assessed by questionnaire).

Conclusions

- PFASs are *immunotoxic at current exposures*
- Vaccine antibody concentrations are sensitive indicators of immunotoxicity
- Effects of individual PFASs may be difficult to separate in epidemiological studies
- Early development likely represents a highly vulnerable stage (with lactational transfer)
- Likely consequences for infectious disease – and perhaps other adverse health effects

PFOS transfer via human milk



The lowest curve (dashed) is from a non-breastfed child, and the upper (solid line) is from a child breastfed exclusively for 6 months and partially the following 5 months

Mogensen et al., 2015