CHE call on PFASs
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A brief discussion of some recent epidemiologic studies of PFAS

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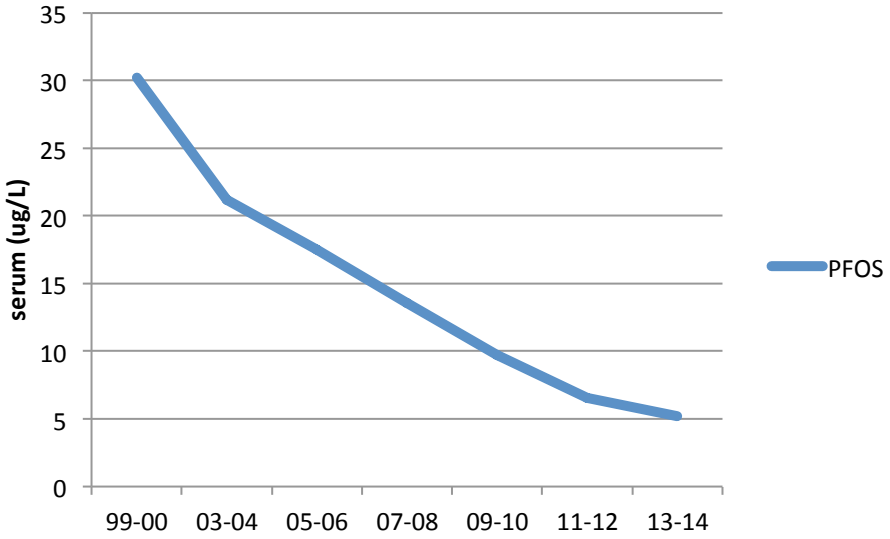
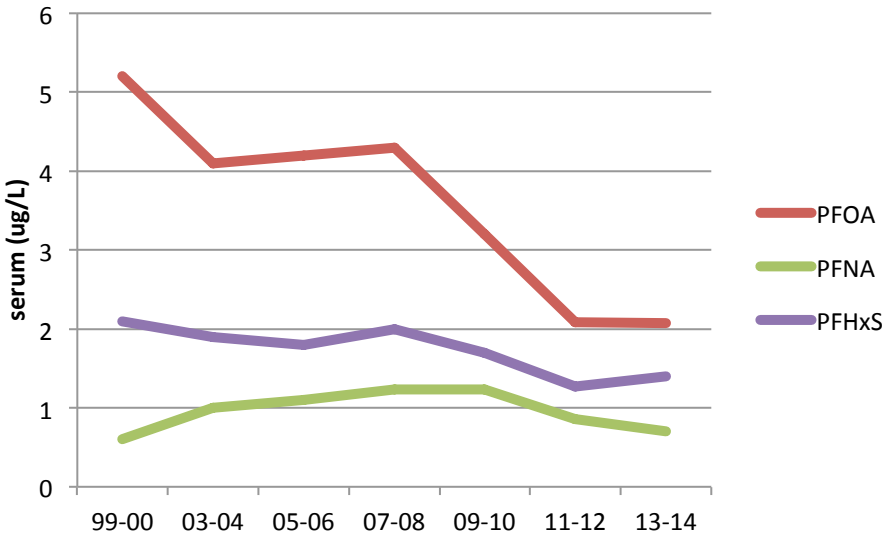
Some things to note about PFAS

- large & complicated class of compounds
- moving target (changing regulations & production -> shorter chain or altered structures)
- occur as mixtures
- structurally related to fatty acids—one of the reasons researchers are interested in metabolic effects (e.g., obesity, diabetes, cholesterol, etc.)

Human serum levels

- widely found in human serum
- North America ~ Europe
- men > women
- time trends of 4 PFAS currently measured in US serum by CDC (NHANES)





CDC—March 2018 update
Scales differ

- PFAS in whole blood can differ from serum
- *unidentified* organofluorine compounds in human blood

Quantifiable PFAS accounted for 31-100% of total extractable organic fluorine, with a trend towards more unidentified compounds (German & Chinese samples)(Yeung & Mabury 2016)

Exposure

- exposure usually measured using samples of serum or plasma
- levels in blood reflect exposure to those compounds & *precursors*
- for most people, exposure is estimated to be predominantly via diet followed by indoor exposure with water small (e.g., Gebbink et al 2015). Needs follow-up
- for some populations, water is a dominant source of exposure

Explosion of human epidemiologic research published since we gave the last CHE call Dec 2016

~ 40 published PFAS epidemiology papers since then!

- **metabolic effects (obesity, lipids, diabetes related, etc.),**
- **birth outcomes**
- **neurodevelopmental**
- **immune system**
- **other (thyroid hormones, reproductive, etc.)**

I will briefly discuss today some of these new studies, particularly PFAS & Project Viva. I am not providing a full literature review, e.g., evaluating these new studies in comparison to previous literature.

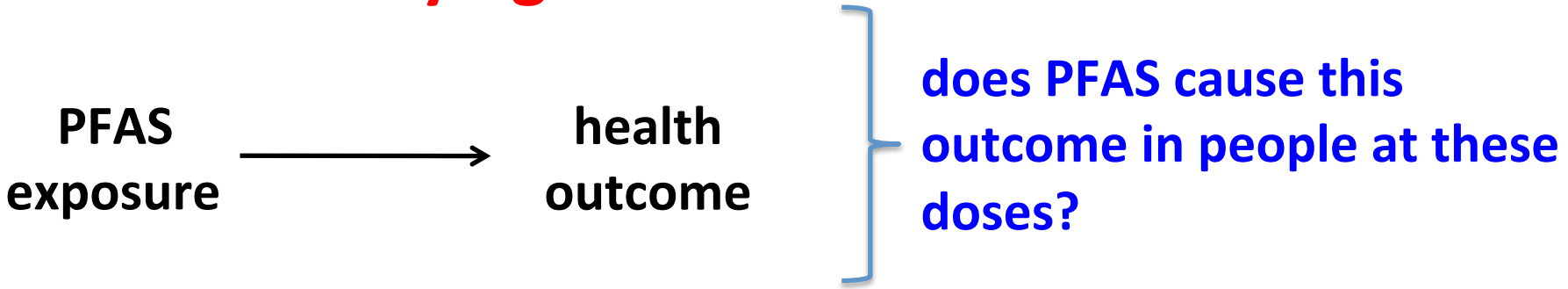
Some important things to know about environmental epidemiology

- **Epidemiology and animal toxicology are complementary—they tell us different facets of the story**
- **Hard & expensive!**
- **A good epidemiology paper discusses strengths & weaknesses of the study (nothing is perfect).**
- **The proper design of studies and methods to mitigate potential weaknesses is a major part of the work**
- **Environmental epidemiologists rarely if ever rely on a single study. Evidence can be inconsistent. It typically takes a substantial body of studies to come to scientific conclusions (which should not preclude policy!)**

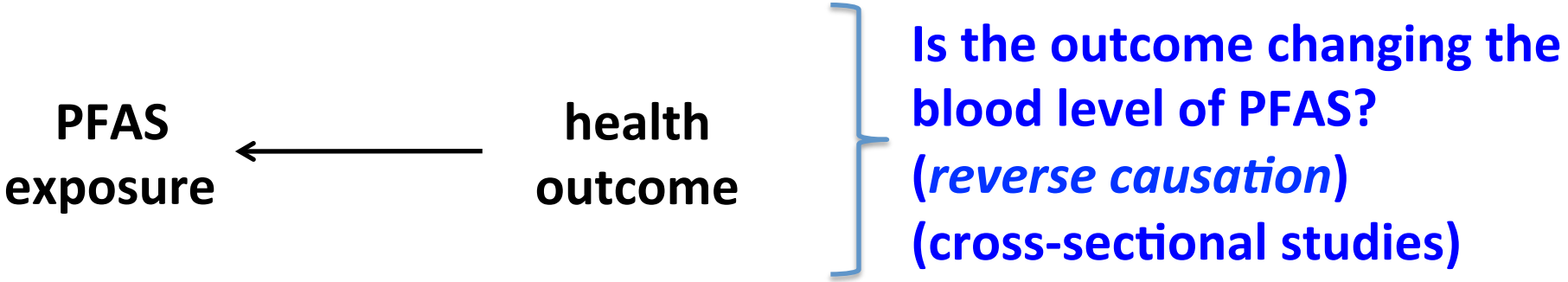
Some important things to know about environmental epidemiology

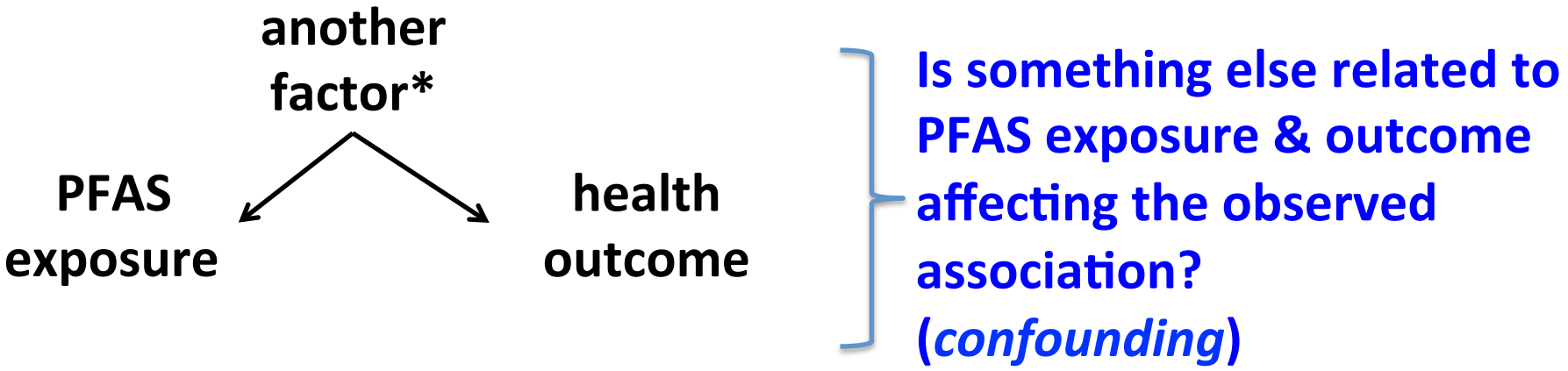
- ***cross-sectional study:*** **measure exposure and outcome at the same time**
- ***follow-up study:*** **measure exposure at beginning and follow-up to determine who develops the outcome**

What we're trying to determine



A few of the things to worry about (among many!)





* e.g., SES, behavioral, physiology…

PFAS and Project Viva

- about 1000 mother-child pairs from Boston area (numbers depend on particular study)
- recruited during pregnancy 1999-2002, ~ peak serum levels for most PFAS typically measured in USA
- PFAS measured in mother's plasma from early in pregnancy and in children ~8 yrs old
- primary focus on PFOS, PFOA, PFNA, PFHxS (depending on study)
- follow over time: examining birth outcomes and child health
- large, well designed study

PFAS and Project Viva: Results

Preterm and birth weight (Sagiv et al 2018)

- **prenatal PFAS: increased risk of preterm birth**
- **also decreased birth weight (after adjusting for gestational age)**
- **NOT confounded by maternal physiology (e.g., kidney function)**

Thyroid hormone disruption (Preston et al 2018)

- **prenatal PFAS: decreased free T4 (a main thyroid hormone) in moms (cross-sectional)**
- **also decreased T4 in *male infants***

Obesity-related outcomes in children (Mora et al 2017)

- **prenatal PFAS: small increases in *girls, not boys* (e.g, BMI, waste circumference, skinfold thickness, DXA)**
- **outcomes not related to childhood PFAS levels**

PFAS and Project Viva: Results

Metabolic function in children (Fleisch et al 2017)

- studied markers related to insulin resistance (e.g., HOMA-IR), etc.
- no evidence for adverse effect with PFAS
- indeed children with higher PFAS had lower (*better*) HOMA-IR in girls, no effect in boys (cross-sectional)
- some toxicology data suggest mechanisms that may work in opposite directions; possibility of reverse causation

Blood lipid/cholesterol levels in children (Mora et al 2018)

- prenatal PFAS: improved blood lipid profile in girls, no effect in boys (e.g., "good" and "bad" cholesterol)
- childhood PFAS: increased "good" and "bad" cholesterol; possibility of reverse causation

PFAS and Project Viva: Results

Neurodevelopmental outcomes (Harris et al 2018)

- **published only last week!**
- **cognitive testing in early childhood (median age 3.2) & mid-childhood (median age 7.7)**
- **some evidence for decreased visual motor ability**
- **other results in the study were inconsistent, sometimes associated with better cognitive outcomes**

PFAS and the Diabetes Prevention Program Trial

- **study of prevention of type 2 diabetes among high-risk people: lifestyle or drug intervention or placebo (PFAS study added later)**
- **PFAS measured in plasma of 957 people at baseline (1996-1999)**
- **follow-up 2 - 5 yr**

<u>PFAS & diabetes (Cardenas et al 2018)</u>

- **at baseline, small associations between PFAS & markers of insulin resistance etc. (cross-sectional)**
- **no strong evidence of association between PFAS & diabetes incidence (some evidence for branched PFOA) or prospective changes in glycemia indicators**

Stay tuned: something interesting currently in review

Conclusions

Of the outcomes I discussed today, I think birth weight is the best established by the existing literature (e.g., this study and others on birth weight)

If real, some interesting differences in effects on boys and girls

Lots more, high quality epidemiology under way. We will know more reasonably soon

Environmental epidemiologists rarely if ever rely on a single study. Evidence is often inconsistent. It typically takes a substantial body of studies to come to scientific conclusions (which should not preclude policy!). I did not present a full literature review today.

Thanks to NIEHS for funding this kind of research

References

Project Viva

- Fleisch AF, et al. Early-Life Exposure to Perfluoroalkyl Substances and Childhood Metabolic Function. *Environ Health Perspect.* 2017; 125(3):481-487.
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- Sagiv SK, et al. Early-Pregnancy Plasma Concentrations of Perfluoroalkyl Substances and Birth Outcomes in Project Viva: Confounded by Pregnancy Hemodynamics? *Am J Epidemiol*. 2018; 187(4):793-802.

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- Cardenas A, et al. Plasma Concentrations of Per- and Polyfluoroalkyl Substances at Baseline and Associations with Glycemic Indicators and Diabetes Incidence among High-Risk Adults in the Diabetes Prevention Program Trial. *Environ Health Perspect*. 2017; 125(10):107001