National Institute of Environmental Health Sciences
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DISENTANGLING HETEROGENEOUS OUTCOMES TO BETTER UNDERSTAND ENVIRONMENTAL IMPACTS ON PREGNANCY AND CHILD HEALTH

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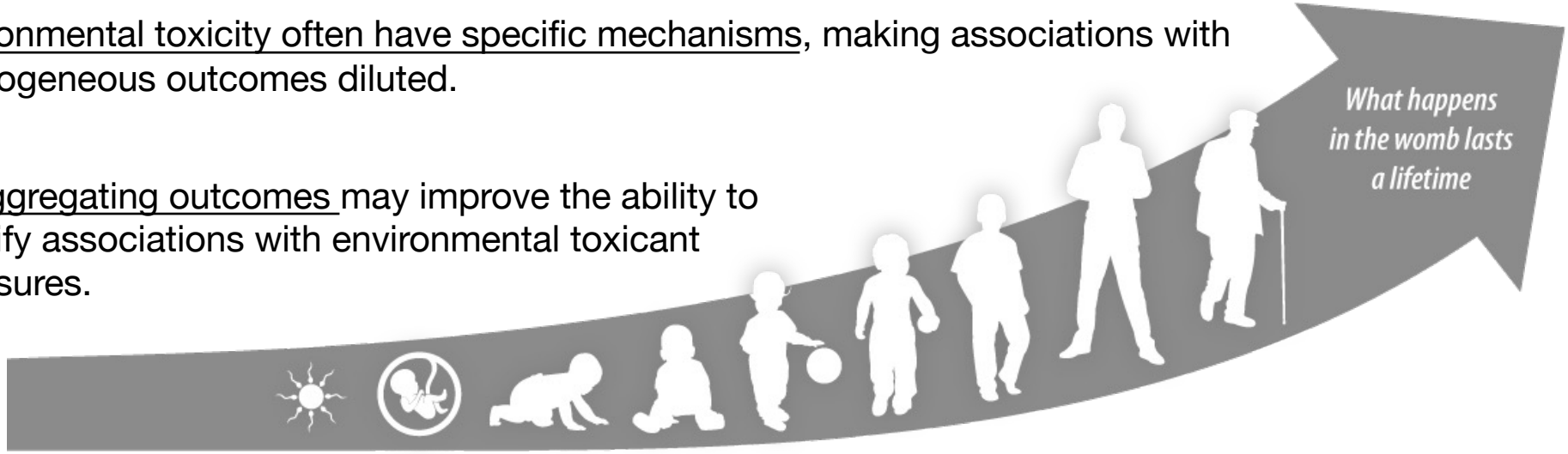
PRIORITY 1: DISAGGREGATING HETEROGENEOUS OUTCOMES

Fetal development is a critical period of susceptibility to environmental impacts. Birth outcomes associated with later-life disease include preterm birth and low birth weight.

These outcome definitions are crude approximations of timing of delivery and fetal growth, and they capture heterogeneous etiologies of disease.

Environmental toxicity often have specific mechanisms, making associations with heterogeneous outcomes diluted.

Disaggregating outcomes may improve the ability to identify associations with environmental toxicant exposures.



PRIORITY 2: NEW RESEARCH TO ADDRESS NEW EXPOSURES

Profiles of environmental chemical exposures change dramatically over time with the identification of toxic compounds and efforts made to replace them.

Exposure to replacement chemicals is increasing as others are phased out.

We cannot solely rely on historic data collection in human populations to answer questions about new exposures.

PRENATAL PHTHALATE EXPOSURE AS AN EXAMPLE

<u>Disaggregating heterogeneous outcomes</u>

Phthalate exposure and preterm birth

- Findings among spontaneous preterm births
- Findings from a pooled study of 16 US cohorts

Phthalate exposure and fetal to early childhood growth

- Findings from longitudinal growth data from 20 weeks gestation to 6 years of age

<u>Exposure to replacement chemicals</u>

The paradigm of phthalate replacements

PHTHALATE EXPOSURE AND PRETERM BIRTH

- There is a large literature on these associations with mixed findings
- The major limitation to this body of literature is the # of preterm births in each study

PREVIOUS WORK ON PHTHALATES AND PRETERM BIRTH

	Odds Ratio (95% CI) of preterm birth
MEP	1.11 (0.93, 1.32)
MBP	**1.27 (0.99, 1.63)**
MiBP	0.98 (0.72, 1.34)
MBzP	1.09 (0.86, 1.38)
ΣDEHP	**1.33 (1.04, 1.70**
MCPP	1.19 (0.95, 1.49)

LIFECODES, 2006-2008

- N=130 cases of preterm birth, N=352 controls
- Phthalate metabolites measures from 3 visits

DEHP metabolites and MBP associated with preterm birth

Ferguson et al. 2014, *JAMA Pediatrics*

PRETERM BIRTH IS A HETEROGENOUS OUTCOME

SPONTANEOUS

Clinical presentation

- preterm premature rupture of membranes
- spontaneous preterm labor

Placental histology

- inflammation

PLACENTAL

Clinical presentation

- intrauterine growth restriction
- preeclampsia

Placental histology

- poor placentation

LIFECODES, 2006-2008

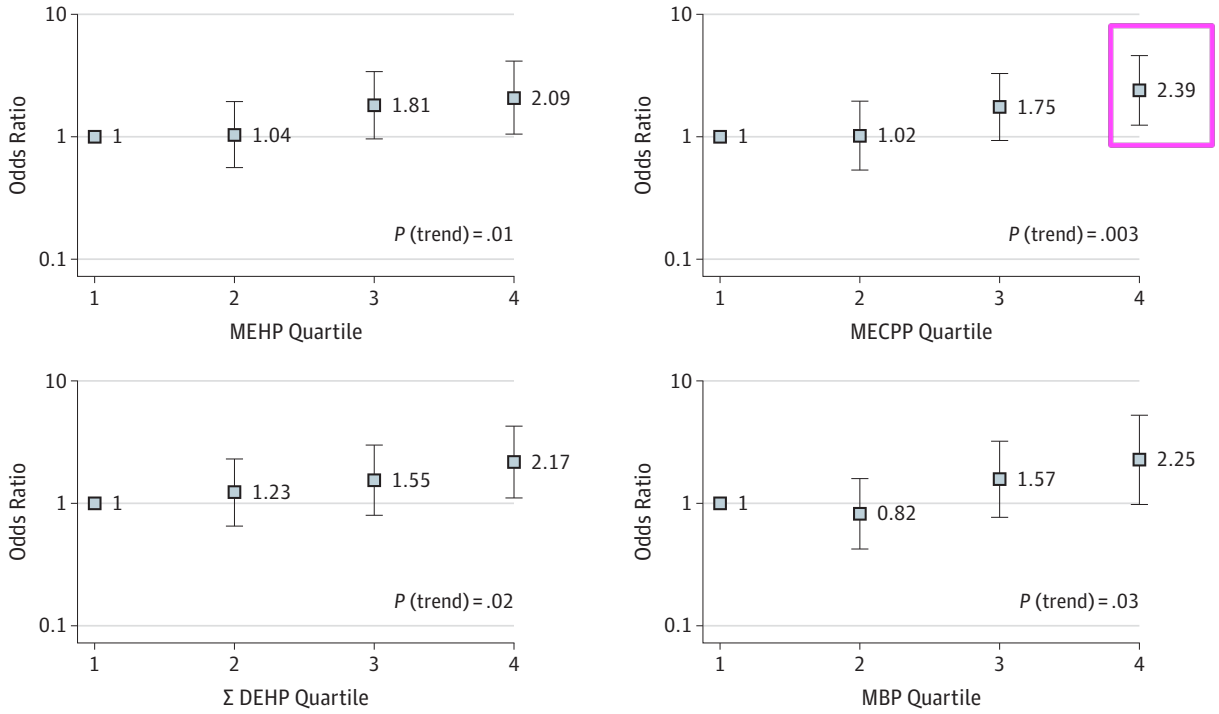
- N=130 cases of preterm birth, N=352 controls
- Phenotyping preterm based on presentation:
  - Spontaneous (n=56)
  - Placental (n=35)
  - Neither (n=39)

McElrath et al. 2008, *American Journal of Epidemiology*

PHTHALATE EXPOSURE AND OVERALL PRETERM BIRTH

DEHP metabolites and MBP associated with overall preterm birth

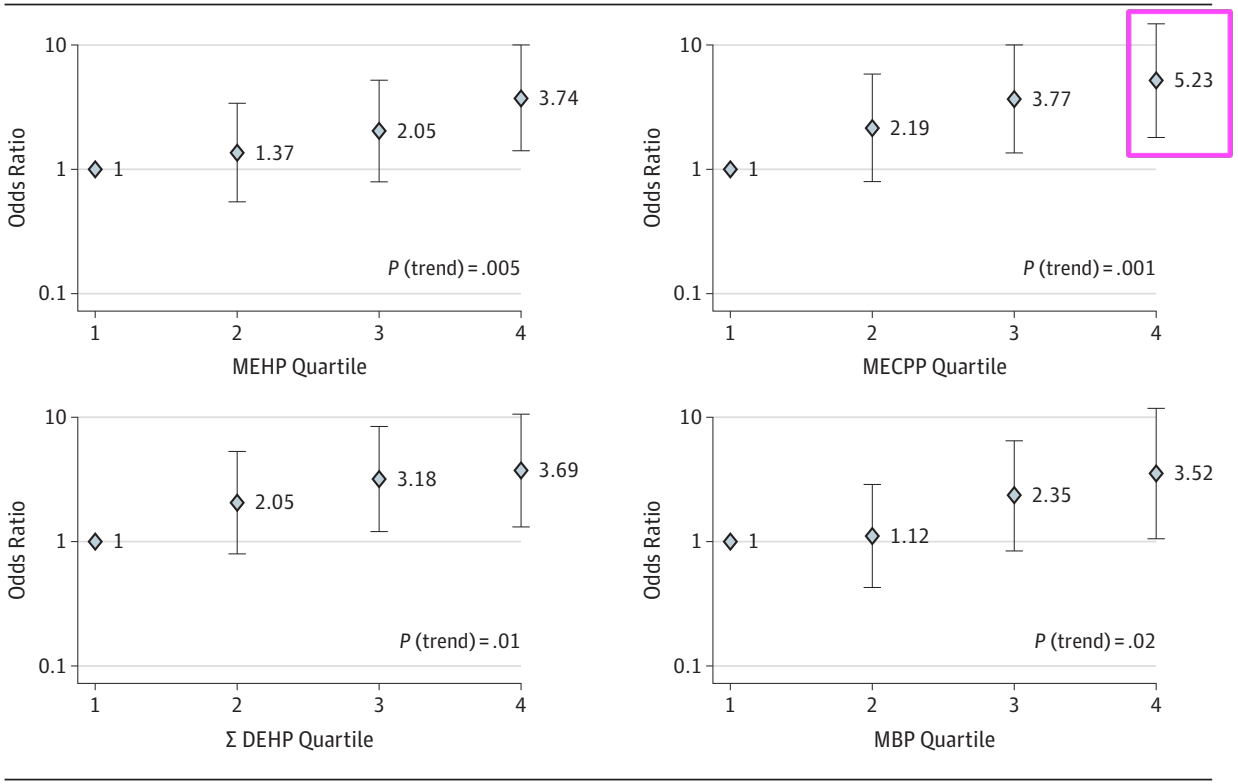
Figure 1. Odds of Preterm Birth and 95% CI Levels by Quartile of Average Phthalate Metabolite Level Measured During Pregnancy



Ferguson et al. 2014, *JAMA Pediatrics*

PHTHALATE EXPOSURE AND SPONTANEOUS PRETERM BIRTH

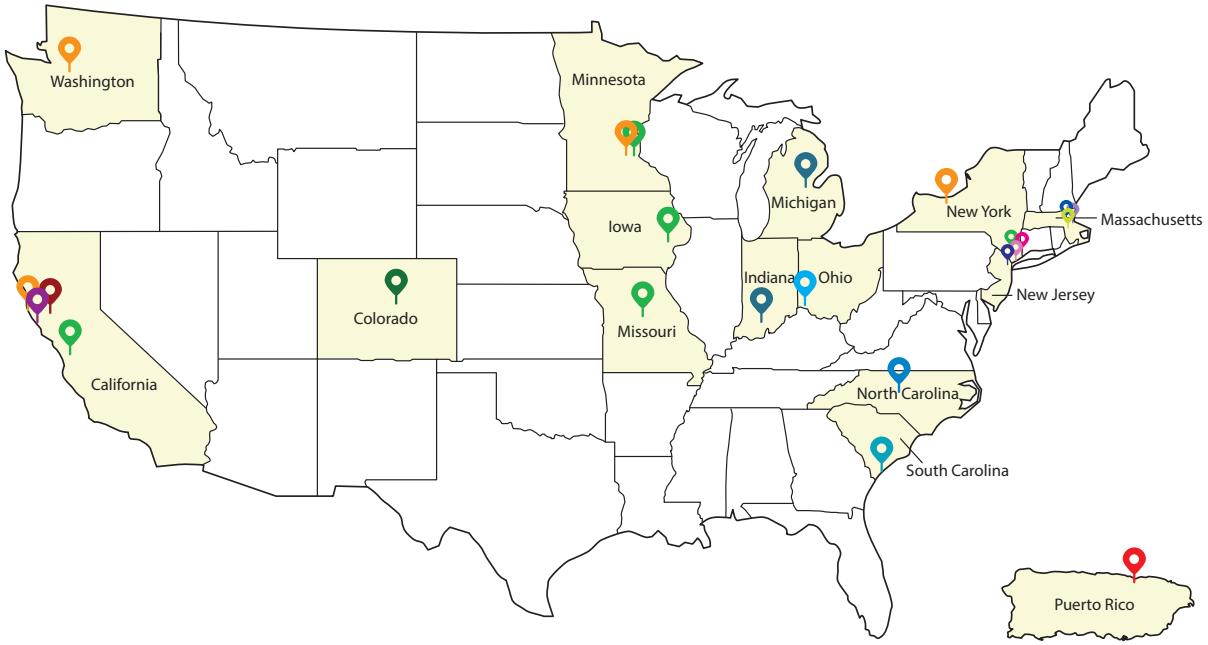
Figure 2. Odds of Spontaneous Preterm Birth and 95% CI Levels by Quartile of Average Phthalate Metabolite Level Measured During Pregnancy



Greater effect estimates observed for spontaneous preterm birth alone

Ferguson et al. 2014, *JAMA Pediatrics*

POOLED STUDY OF PHTHALATE EXPOSURE AND PRETERM BIRTH

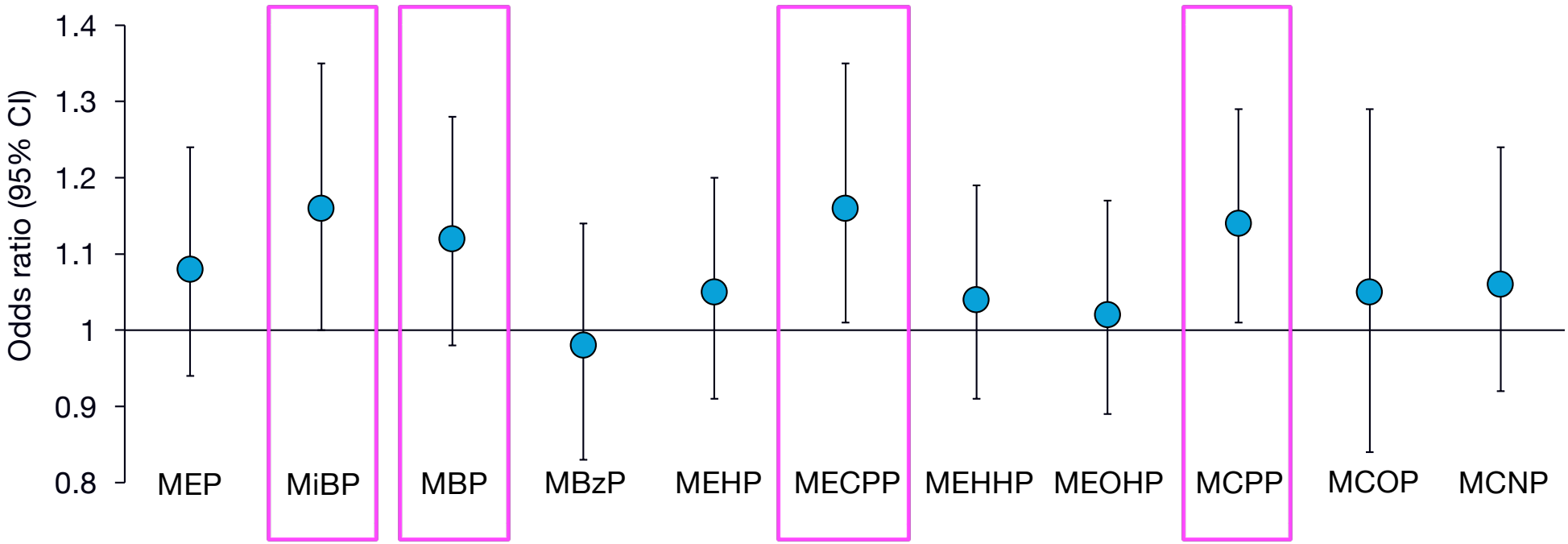


PROTECT	San Juan, Puerto Rico	CCCEH	New York City, NY	SFF	New York City, NY
TIDES	Seattle, WA	HOME	Cincinnati, OH	SFF	Iowa City, IA
TIDES	Rochester, NY	EARTH	Boston, MA	RDS	Charleston, SC
TIDES	Minneapolis, MN	MSSM	New York City, NY	HEBC	Boston, MA
TIDES	San Francisco, CA	SFF	Los Angeles, CA	MARBLES	Davis, CA
LIFECODES	Boston, MA	SFF	Minneapolis, MN	EPS	Durham, NC
Healthy Start	Denver, CO	SFF	Columbia, MO	MMIP	Ann Arbor, MI
CHAMACOS	Salinas, CA			Rutgers	Rutgers, NJ

- Pooled data from all US studies with prenatal measurements of one or more urinary phthalate metabolites
- 16 cohorts
- N=6043 births
  - N=538 preterm

Welch et al. 2022, *JAMA Pediatrics*

POOLED STUDY OF PHTHALATE EXPOSURE AND PRETERM BIRTH



The phthalate metabolites MiBP, MBP, MECPP, and MCPP were associated with increased odds of preterm birth in adjusted models

Welch et al. 2022, *JAMA Pediatrics*

PHTHALATE EXPOSURE AND PRETERM BIRTH

- TAKEAWAY: Exposure to several phthalates is associated with preterm birth, but associations were greater in magnitude with spontaneous preterm births
- CHALLENGES: Combining data across multiple studies when this level of clinical detail is rarely available, or creating studies with sufficient sample size to overcome this heterogeneity

PHTHALATES AND FETAL TO EARLY CHILDHOOD GROWTH

- Similarly, a large literature on these associations with mixed findings
- Major limitations include:
    - Use of birthweight as a proxy for intrauterine growth
    - Use of child weight when specific compartments may undergo differential impact from exposure
    - Restriction to outcome assessment at a limited number of timepoints, incompletely capture the trajectory of fetal to early to childhood growth

FETAL AND EARLY CHILDHOOD GROWTH IS HETEROGENEOUS

Catch-up growth in childhood and death from coronary heart disease: longitudinal study

J G Eriksson, T Forsén, J Tuomilehto, P D Winter, C Osmond, D J P Barker

Table 3 Hazard ratios for death from coronary heart disease according to ponderal index at birth and body mass index at age 11 years, adjusted for length of gestation

	Body mass index* (kg/m^2) (No of deaths)			
Ponderal index (kg/m^3)	**⩽15.5**	**–16.5**	**–17.5**	**>17.5**
⩽25	2.7 (21)	3.3 (26)	3.7 (19)	5.3 (14)
–27	1.5 (14)	3.2 (40)	4.0 (35)	2.7 (14)
–29	2.2 (17)	1.6 (18)	1.8 (19)	3.2 (21)
>29	1.0 (4)	1.7 (11)	1.5 (12)	1.9 (12)

*Cut off points are approximately quartiles.

Few environmental epidemiology studies examine associations with a longitudinal trajectory of catchup growth

PHTHALATES AND FETAL TO EARLY CHILDHOOD GROWTH

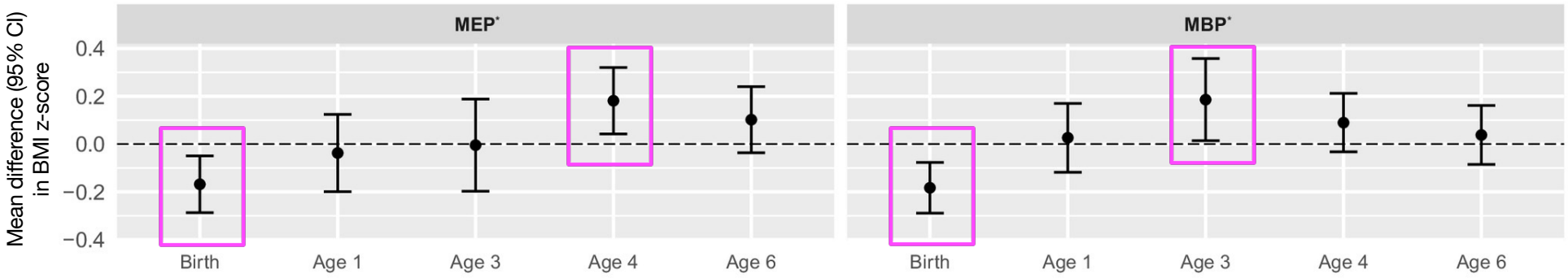
The Infant Development and the Environment Study (TIDES)

- Recruitment from 2010-2012 at 4 US sites
- N=780 participants
- Follow-up to age 6
- Measures of weight (EFW, weight) from in utero to age 6
- Measures of adiposity (weight-for-length, BMI) from birth to age 6

Hypothesis: Longitudinal trajectories of adipose accumulation can capture an adverse metabolic phenotype that is missed by cross-sectional measures of weight or BMI

Ferguson et al. 2022, *Environ Health Perspect*

PHTHALATES AND FETAL TO EARLY CHILDHOOD GROWTH

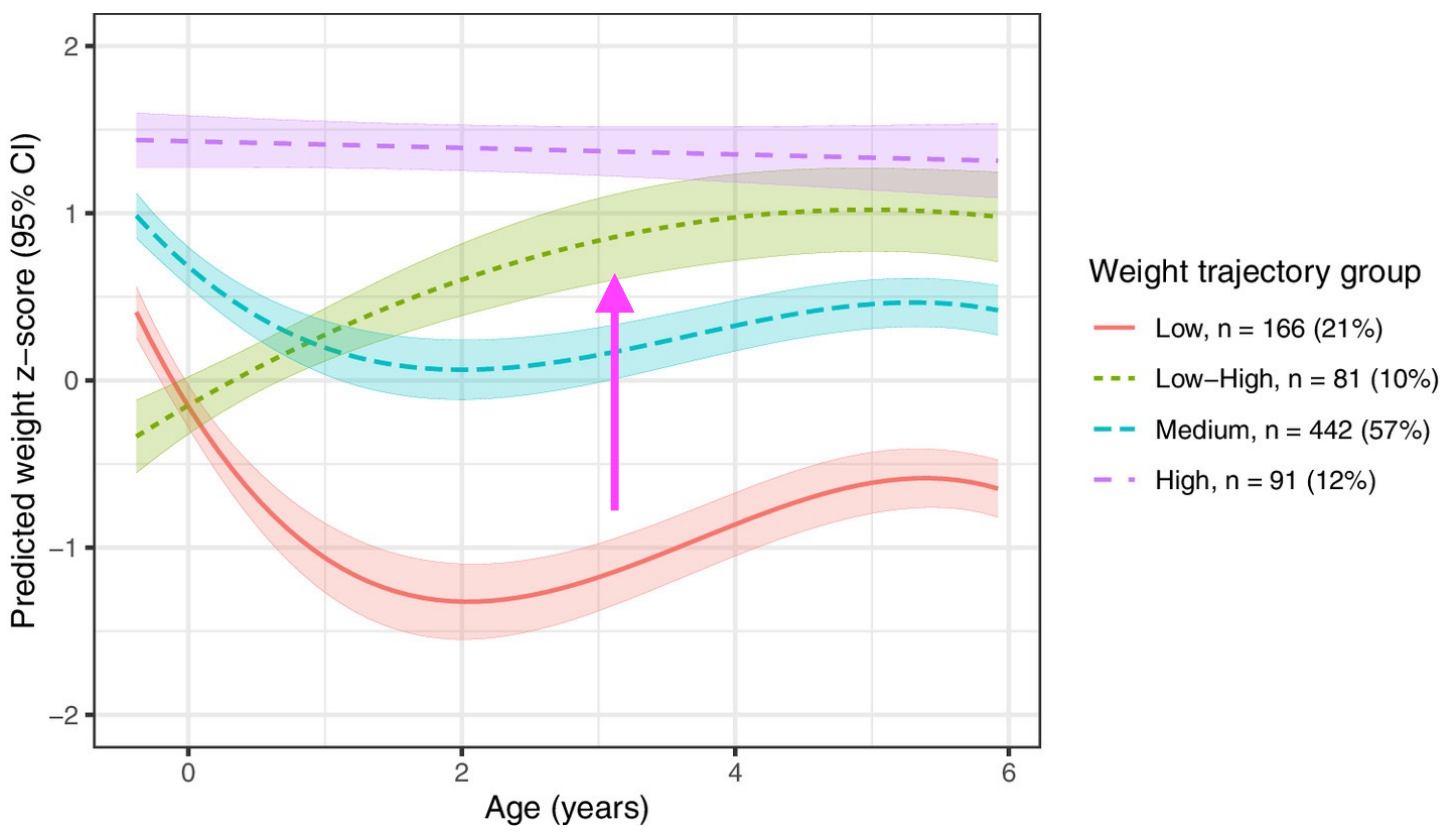


FINDINGS

- In longitudinal models, MEP and MBP metabolites were associated with decreased adiposity at birth but increased adiposity in childhood
- Inconsistencies in findings across time points in childhood could be due to attrition
- The most striking findings were for adiposity rather than weight

Ferguson et al. 2022, *Environ Health Perspect*

PHTHALATES AND FETAL TO EARLY CHILDHOOD GROWTH



Trajectories of weight capture a low-high weight gain phenotype

Ferguson et al. 2022, *Environ Health Perspect*

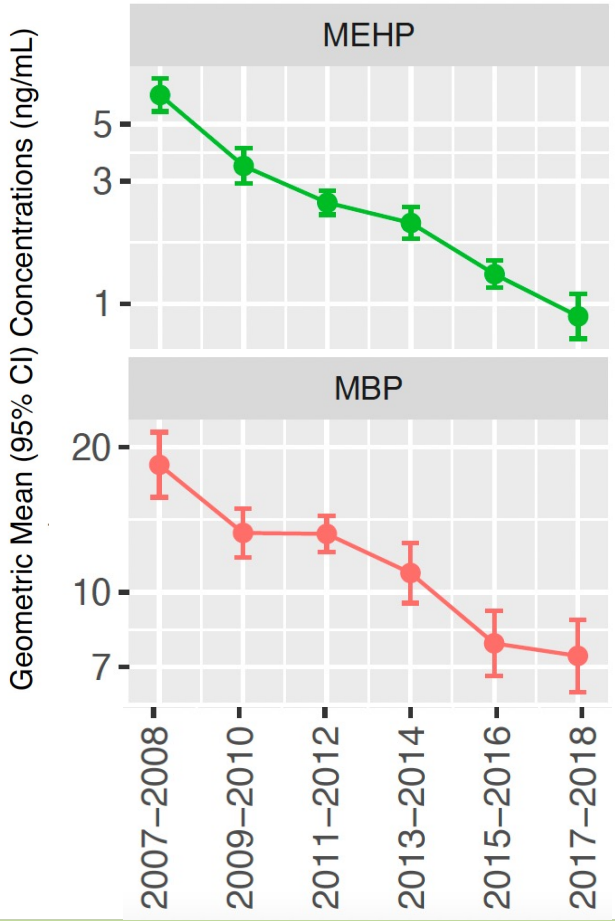
PHTHALATES AND FETAL TO EARLY CHILDHOOD GROWTH

- TAKEAWAY: Exposure to several phthalates may be associated with decreased adiposity at birth and higher adiposity in childhood
- CHALLENGE: Capturing complete longitudinal data from pregnancy through childhood on a sample size that is large enough to identify smaller groups

EXPOSURE TO REPLACEMENT CHEMICALS

- Of the phthalate metabolites examined in these studies, many are decreasing in the US population over time, while replacements are increasing
- Historic cohorts are not capturing the mixture of phthalates we are exposed to today

ATTENTION TO REPLACEMENT CHEMICALS IS NEEDED



- Previous work using NHANES has illustrated decreasing exposure to DEHP and other phthalates but increases in the phthalates used to replace them

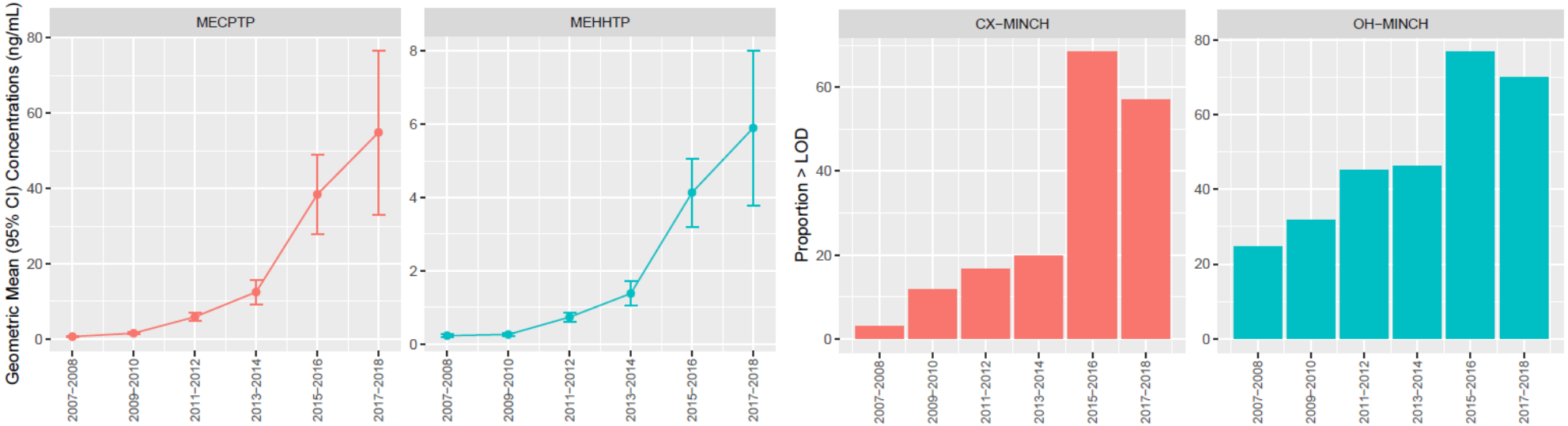
- In the LIFECODES study from 2007-2018 (N~900) we demonstrate decreasing exposure to *all* phthalate metabolites in pregnant participants

unpublished findings; Zota et al. 2014, *Environ Health Perspect*

ATTENTION TO REPLACEMENT CHEMICALS IS NEEDED

- However, exposure to phthalate replacements may be a growing concern

- Among the same LIFECODES participants, terephthalate metabolites as well as detection of metabolites from the phthalate replacement DINCH increased dramatically from 2007-2018



unpublished findings

EXPOSURE TO REPLACEMENT CHEMICALS

- TAKEAWAY: Exposure to most phthalates is decreasing in the US; however, exposure to phthalate replacements is increasing dramatically
- CHALLENGE: We need to study pregnant people who experience these exposures, which do not exist in our older cohorts

SUMMARY

Disaggregating heterogeneous outcomes

- Capturing detailed information on pregnancy and child health outcomes in a standardized manner can facilitate subtyping of disease for improved detection of toxicity and understanding of mechanism.
- This applies to many other child health outcomes not described today, such as measures of executive function as opposed to IQ

Exposure to replacement chemicals

- Exposure profiles are changing dramatically over time. Other examples include changes in:
    - Pesticide use
    - Flame retardants
    - Per- and polyfluoroalkyl substances (PFAS)
- New recruitment is needed to understand the consequences of new exposures

THANK YOU!

TRAINEES

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