PRENATAL EXPOSURE TO PHTHALATES, BISPHENOL, AND ORGANOPHOSPHATE PESTICIDE MIXTURES AND FETAL GROWTH

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OVERVIEW

My overarching research objective is to improve the understanding of how the environment impacts pregnancy and childhood health.

ENVIRONMENT ⟶ **MECHANISMS** ⟶ **PREGNANCY** ⟶ **CHILD HEALTH**

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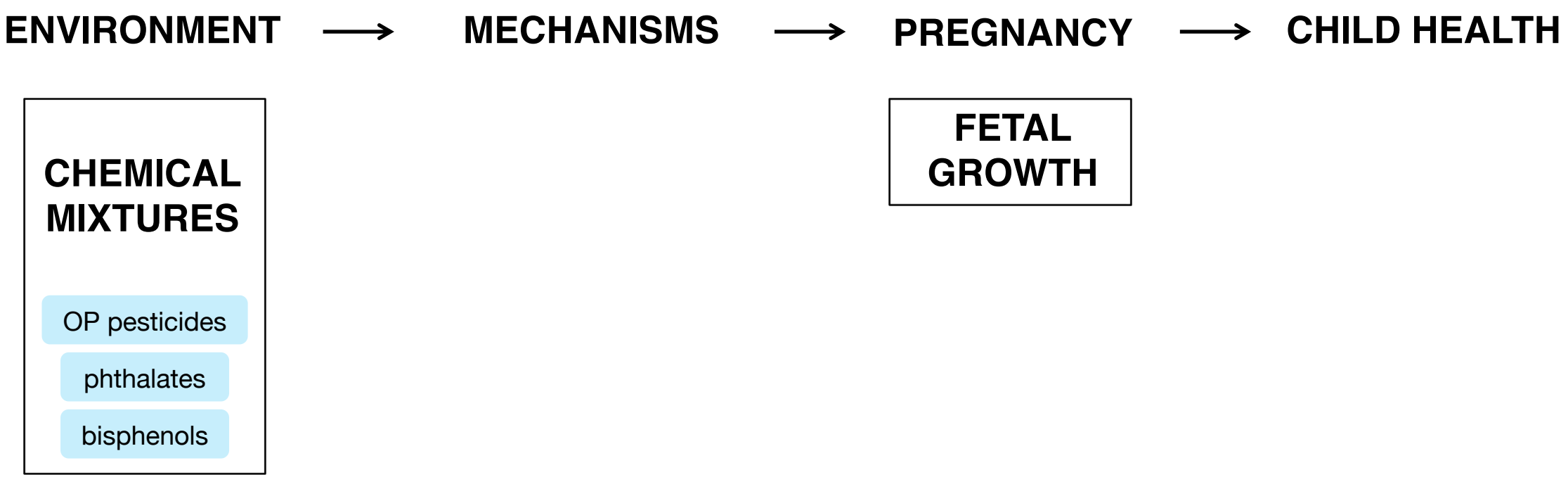

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CHEMICAL MIXTURES

- OP pesticides
- phthalates
- bisphenols

1. **Introduction to environmental chemical exposures**
2. **Why examining the mixture is important**
3. **How we examine the mixture**

ORGANOPHOSPHATE PESTICIDE EXPOSURE

SOURCES

Diet is main concern (fruits and vegetables)

METABOLISM

Broken down into non-specific dialkyl phosphate metabolites (DAPs)

Excreted in urine rapidly (~24 hours)

HEALTH EFFECTS

Neurotoxic potential through acetylcholinesterase inhibition

PHTHALATE EXPOSURE

SOURCES

Personal care products
Vinyl plastics
Food and beverage packaging

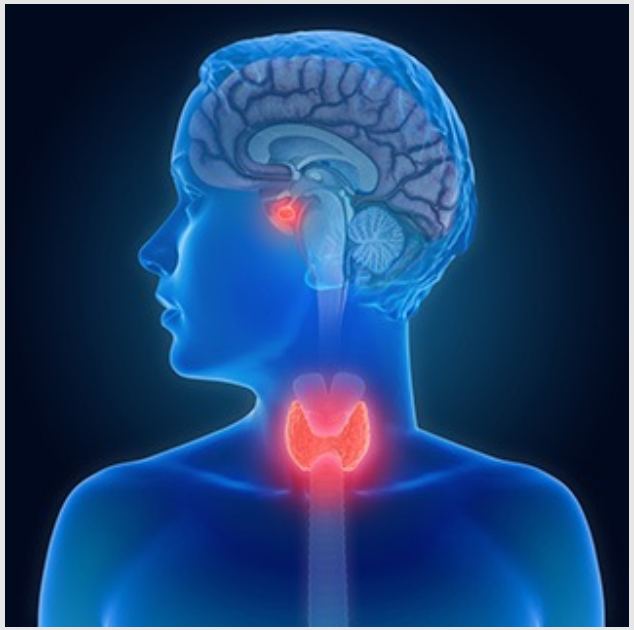
METABOLISM

Broken down into monoester metabolites

Excreted in urine rapidly (~24-48 hours)

HEALTH EFFECTS

Endocrine disruption
Neurodevelopmental outcomes



BISPHENOL EXPOSURE

SOURCES

Hard plastic
Thermal receipts
Can linings

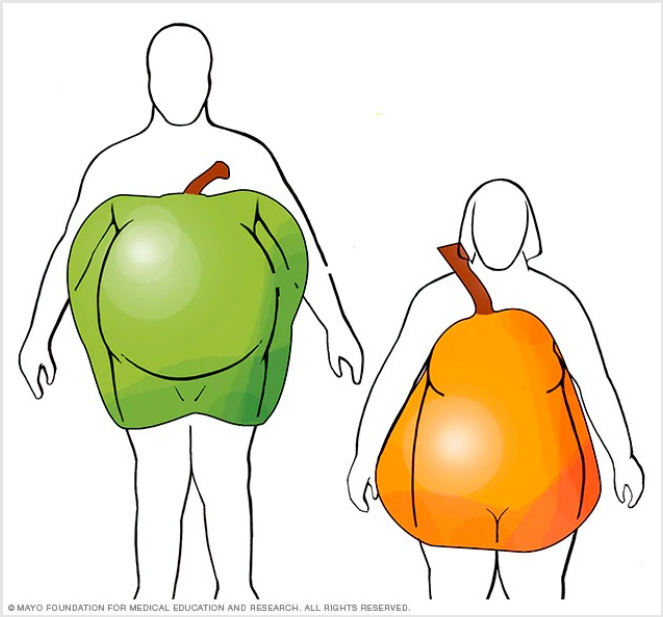
METABOLISM

Glucuronidated

Excreted in urine rapidly (~24 hours)

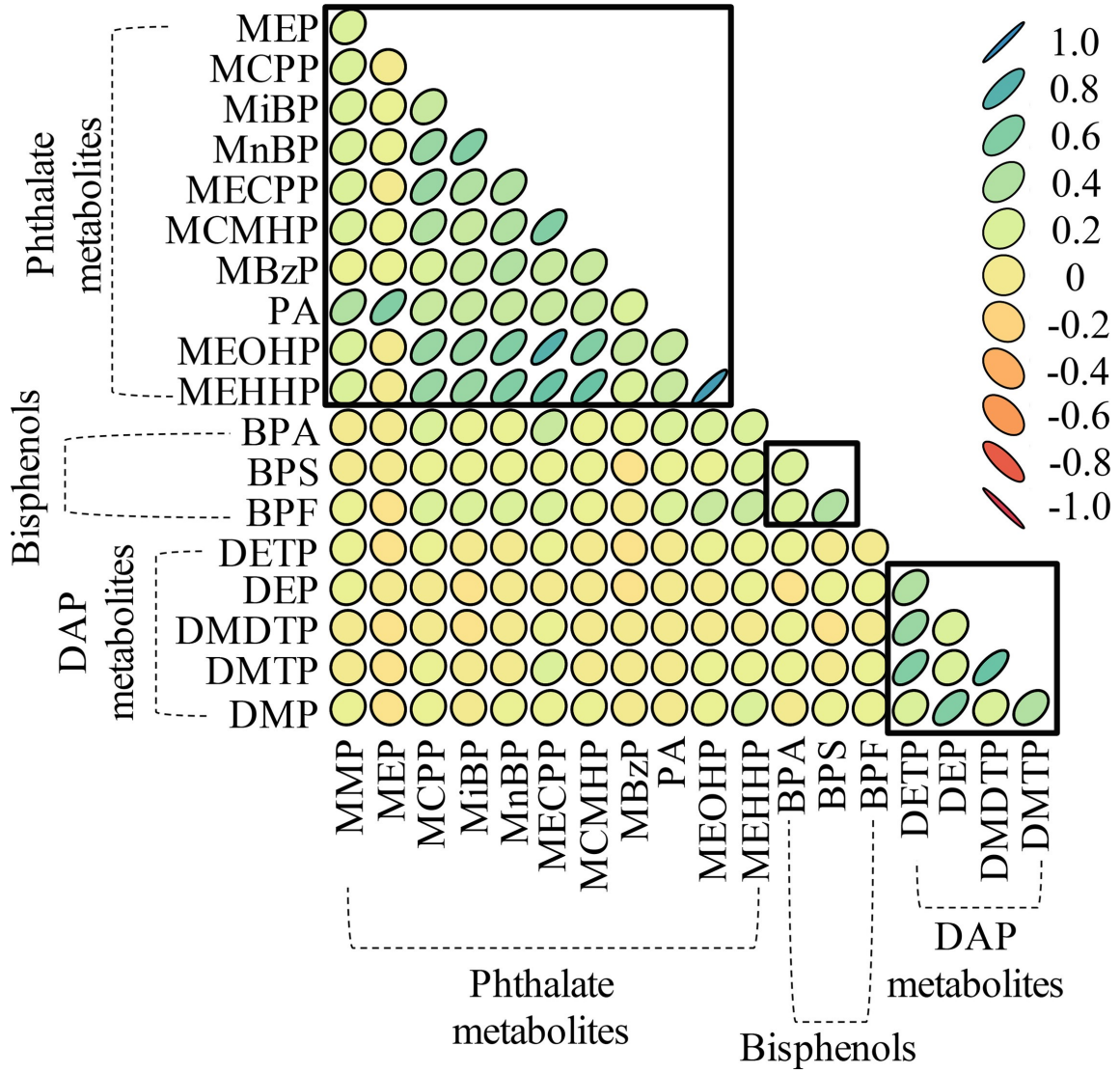
HEALTH EFFECTS

Hormone disruption
Metabolic dysfunction



WHAT ABOUT THE MIXTURE?

- **<u>These chemical exposures are correlated.</u>**
- Highest correlations within chemical classes
- Some correlations across classes also observed (particularly bisphenols and phthalates)



van den Dries et al., 2021, *EHP*

WHAT ABOUT THE MIXTURE?

- There are several questions that we can ask:
  1. Which compound is the most toxic?
  2. What is the impact of an *a priori* identified group of chemicals?
  3. What is the interactive effect?
  4. What is the pattern of exposure in our population?
  5. **What is the overall effect of the chemical mixture?**

Braun et al. 2016, *EHP*

Joubert et al. 2022, *IJERPH*

WHAT ABOUT THE MIXTURE?

- **<u>The joint effect of the mixture may be more realistic than individual effect estimates.</u>**

- Changing behaviors or policies to avoid exposure to a class of chemicals (rather than a single chemical) may be a more reasonable approach

Joubert et al. 2022, *IJERPH*

HOW DO WE ESTIMATE THE JOINT EFFECT?

- In an effort led by collaborator Alex Keil, we developed a novel approach: **quantile g computation**
- Easy interpretation: the change in outcome per quantile increase in all exposures in the mixture
- Easy (and fast) implementation: qgcomp package in R
- Allows for non-linearity and non-additivity of the effects of individual exposure and the mixture as a whole

Keil et al. 2020, *EHP*

Joubert et al. 2022, *IJERPH*

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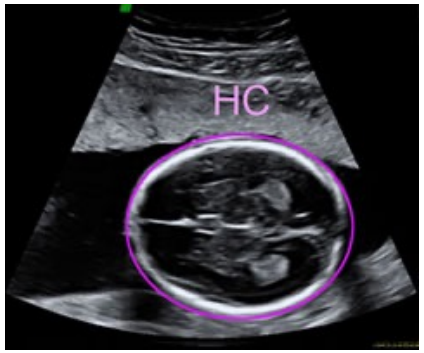
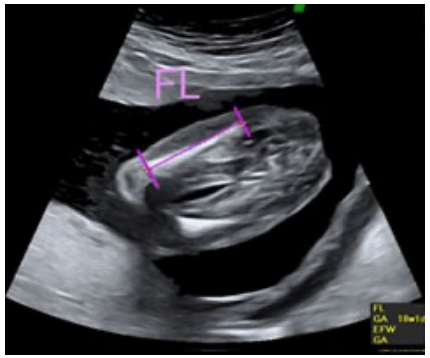
FETAL GROWTH

1. **Advantages of utilizing ultrasound measures**

ULTRASOUND MEASURES OF FETAL GROWTH





- Improve on outcome assessment by:
  1. Allow detection of deviations from normality occurring during gestation (not just at delivery)
  2. Investigation of rates of change in growth, rather than a snapshot of size
  3. Assessment of specific growth measures in addition to weight
     - Femur length as an indicator of skeletal growth
     - Head circumference to reflect brain development

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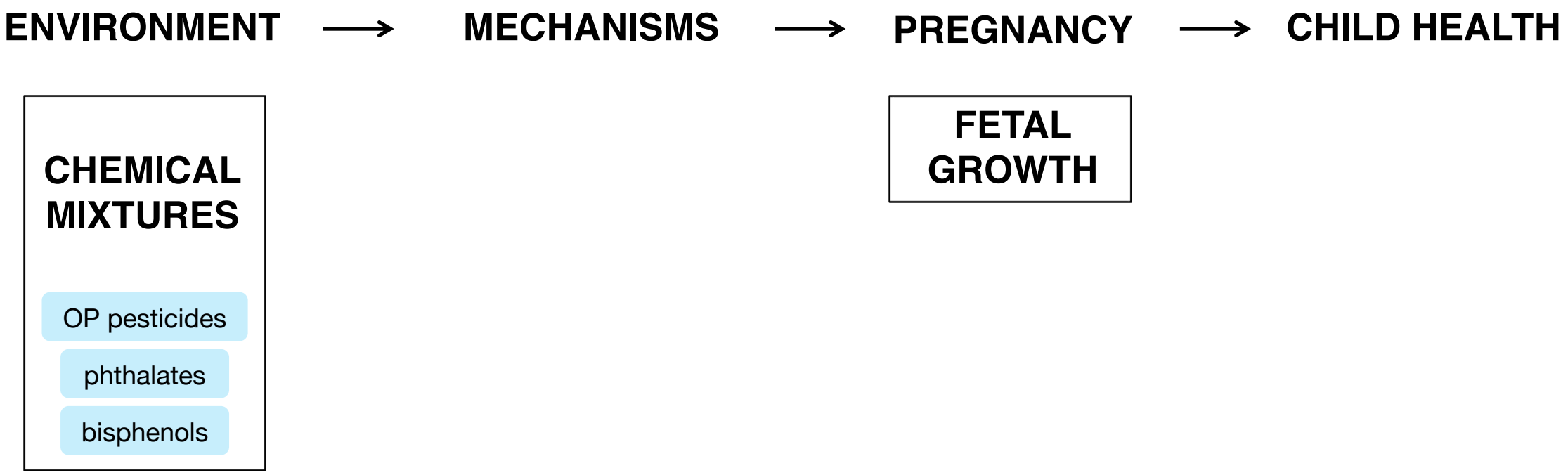
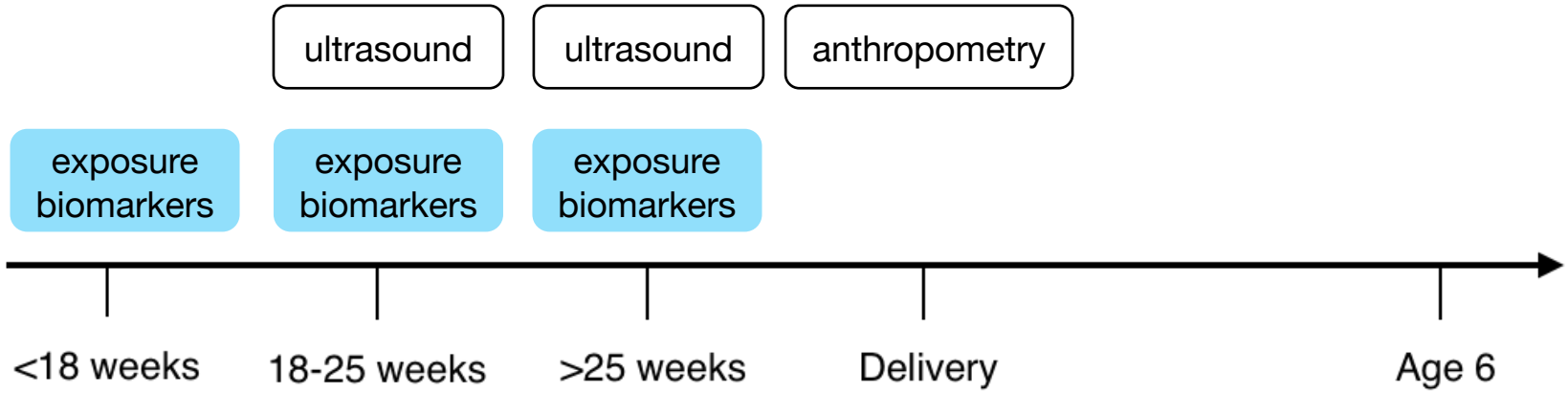


GENERATION R STUDY



- Prospective birth cohort in Rotterdam, The Netherlands
- PI: Vincent Jaddoe, Erasmus Medical Center
- Primary objective: identify early environmental and genetic determinants of development
- Recruitment 2002-2006
- **N = 784** for present analysis

Koojman et al. 2017, *Eur J Epidemiol*

SAMPLE CHARACTERISTICS

Age
~31 y

51%
Male

Weight
~140 lbs

90%
have
partner

55% High
Education

N=784

58%
Dutch

van den Dries et al., 2021, *EHP*

METHODS

- **EXPOSURE BIOMARKERS**
  - 6 dialkyl phosphates
  - 18 phthalate metabolites
  - 8 bisphenols

Funding obtained by Leonardo Trasande and analysis performed by Kurunthachalam Kannan (NYU Grossman School of Medicine)

- **OUTCOMES**
  - Standard deviation scores (SDS) of measures based on internal standard
    - Ultrasound measures of head circumference, femur length, estimated fetal weight
    - Delivery measures of head circumference, length, and weight

van den Dries et al., 2021, *EHP*

METHODS

- **STATISTICAL ANALYSIS**
  - Repeated exposure measurements were standardized to urinary creatinine and averaged (hereafter, pregnancy average)
  - Quartiles of exposure were created for each biomarker with sufficient detection (>80% of measurements above LOD)
  - Fetal growth measurements examined separately by study visit
  - Non-linearity assessed by adding quadratic terms for exposure and comparing model AIC
  - **Primary models: Change in outcome per quartile increase in pregnancy-average of all exposures within the mixture**
    - Models adjusted for fetal sex, maternal age, pre-pregnancy weight, height, education, income, marital status, parity, smoking, alcohol use, and folic acid use

van den Dries et al., 2021, *EHP*

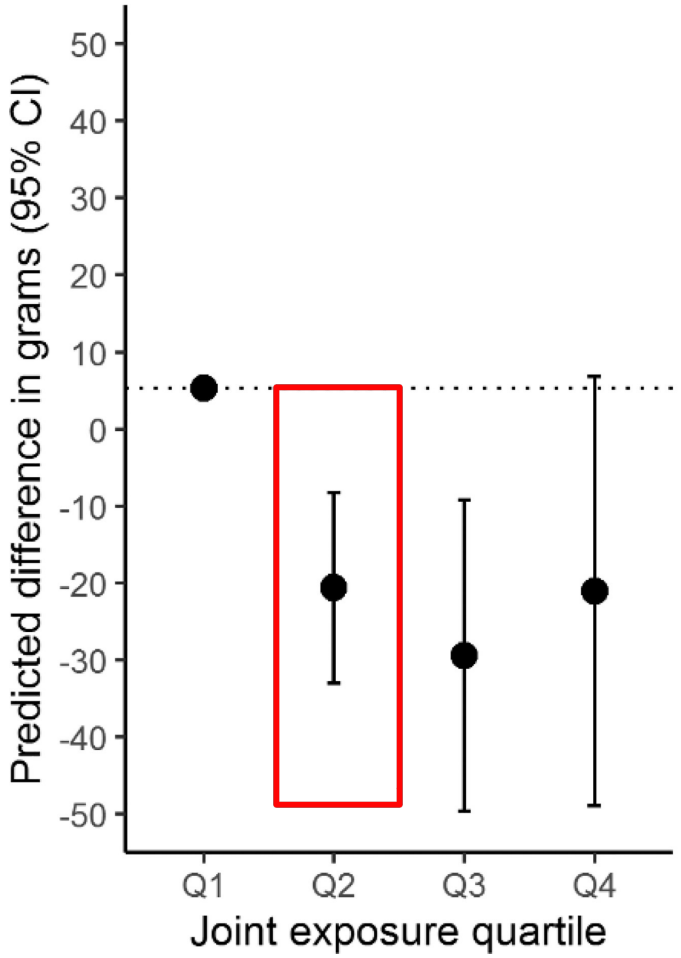
RESULTS AND TAKEAWAYS

1. Pregnancy exposure to the mixture was associated with decreased estimated fetal weight (EFW), even with low levels

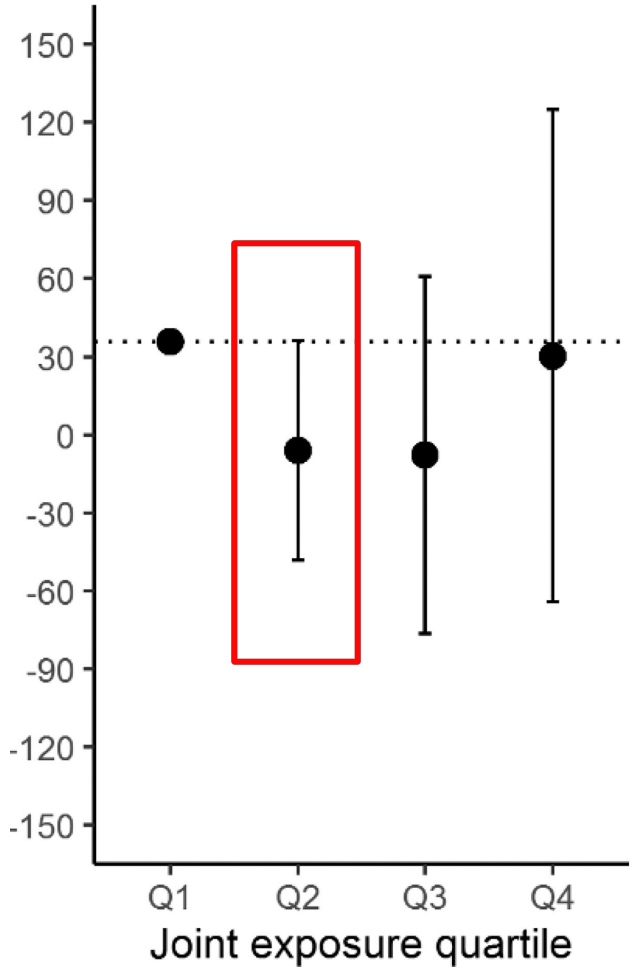
van den Dries et al., 2021, *EHP*

EXPOSURE MIXTURE AND EFW

Estimated fetal weight at 20 weeks



Estimated fetal weight at 30 weeks



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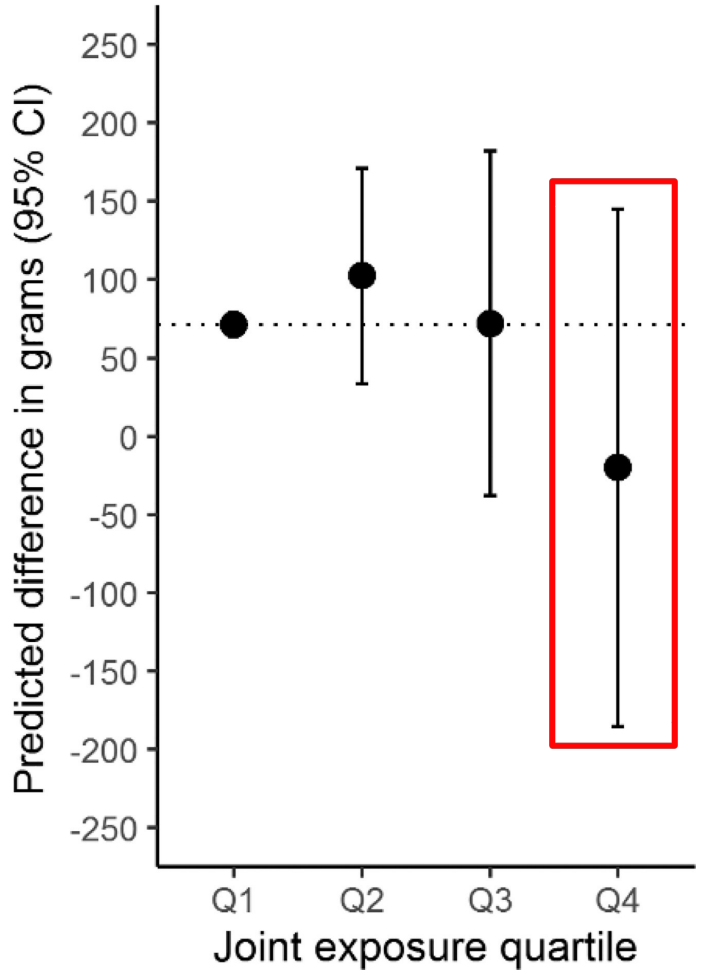
EXPOSURE MIXTURE AND BIRTH WEIGHT

Birth weight



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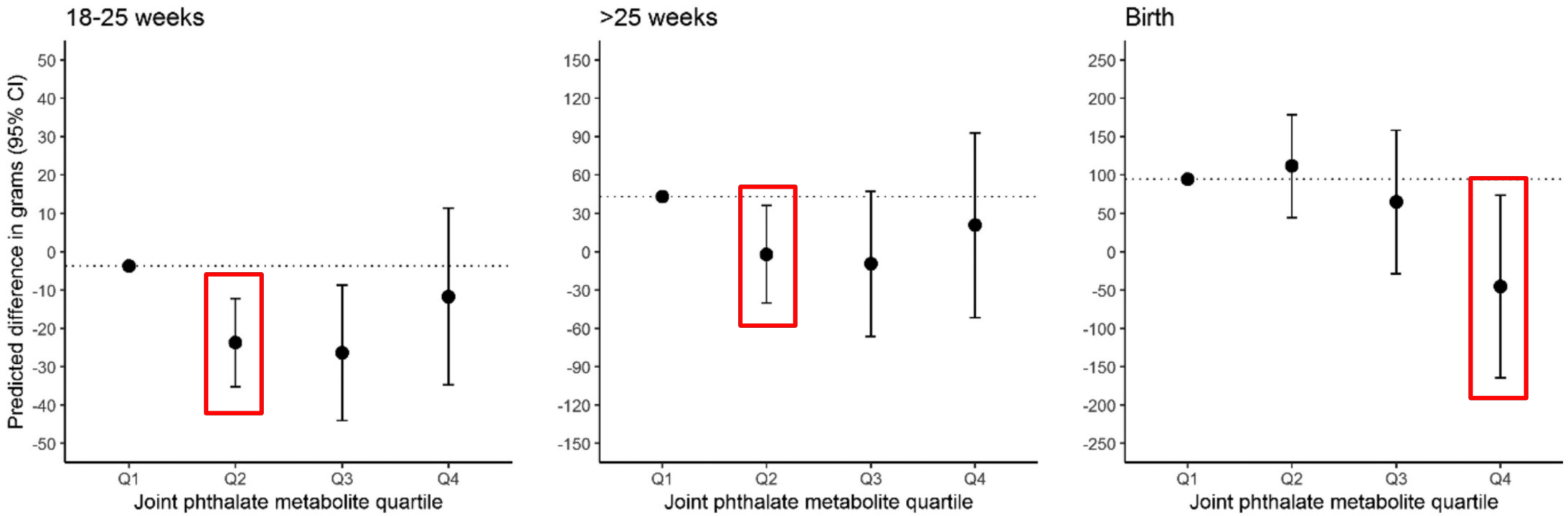
van den Dries et al., 2021, *EHP*

PHTHALATE MIXTURE AND FETAL GROWTH



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4. Associations with EFW appeared to be driven by **femur length**; no associations were observed between the overall mixture and head circumference

van den Dries et al., 2021, *EHP*

OVERALL CONCLUSIONS

- Exposure mixtures
  - Examining the mixture (at least within class) may be more relevant for public health than examining chemicals one at a time
- Fetal growth
  - Investigating growth longitudinally allows us to see effects that are important, but not visible, when examining birth weight alone

PUBLIC HEALTH IMPACT

- Intervention studies could reduce exposure to multiple chemicals simultaneously and improve fetal health
  - Decreasing consumption of packaged and processed foods
  - Using personal care products that are phthalate and phenol free
  - Reducing household dust
  - Consuming organic foods

Braun and Sears 2021, *EHP* (invited commentary)

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