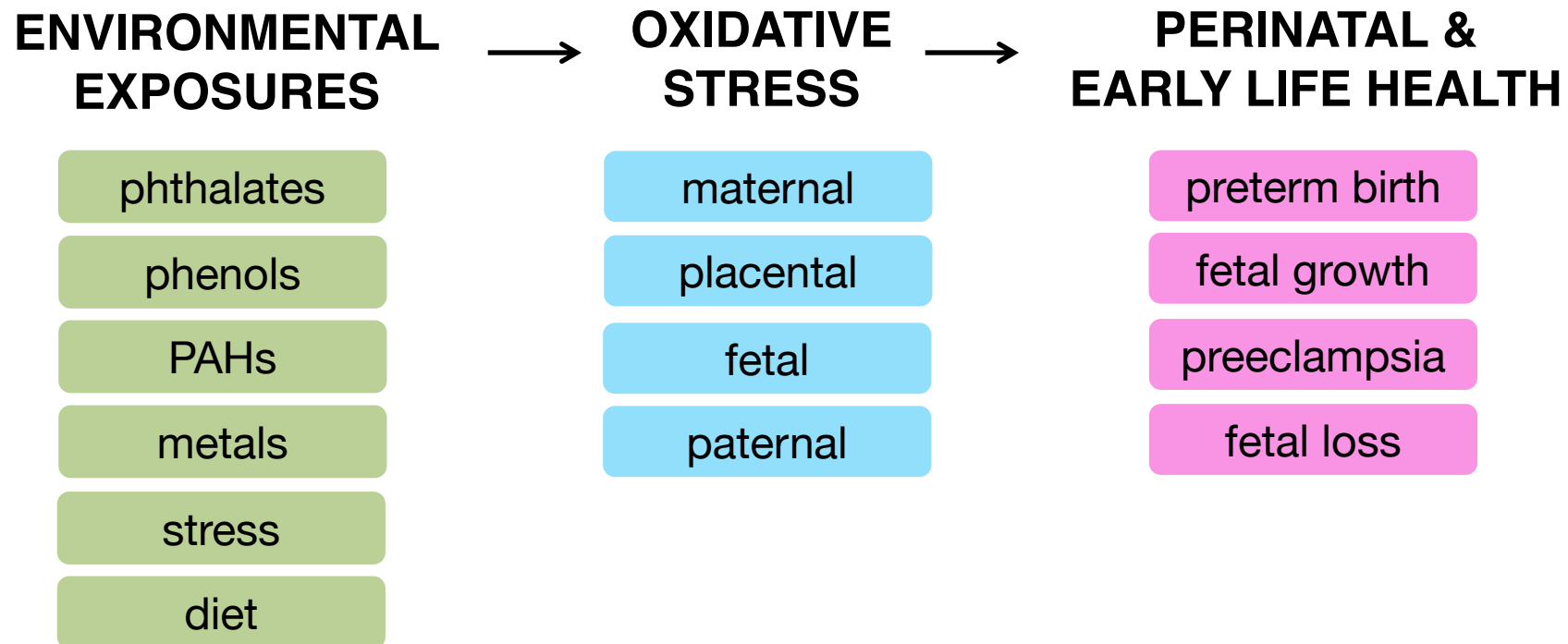


# ENVIRONMENTAL CHEMICALS AND PRETERM BIRTH: EMERGING THREATS AND PRIORITIES FOR FUTURE RESEARCH

Kelly K. Ferguson  
Tenure track investigator  
Epidemiology Branch  
National Institute of Environmental Health Sciences

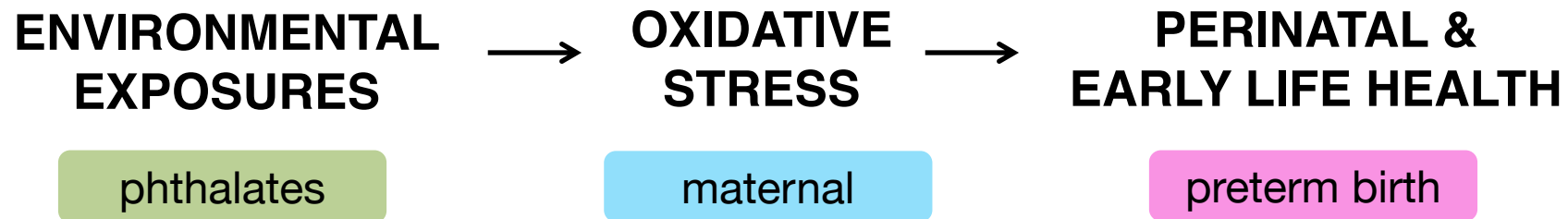
# OVERVIEW

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



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# PRETERM BIRTH

- Defined as delivery before 37 weeks gestation
- Affects roughly 10 percent of pregnancies
- Most important risk factor for neonatal mortality
- Associated with neonatal morbidities and high healthcare costs
- **Public health priority**

## ENVIRONMENTAL CHEMICALS

Stay Safe During Pregnancy

Every pregnant woman in America is exposed to at least 43 different toxic chemicals.



Many chemicals can pass from a pregnant woman to her fetus.

Prenatal exposure to certain chemicals is associated with:

- Stillbirth
- Miscarriage
- Birth defects
- Childhood cancers
- Impaired brain development in children

Toxic chemicals can have long-lasting reproductive health effects.



Reduce your exposure to environmental chemicals before and during pregnancy:

- Limit processed foods
- Use BPA-free products
- Limit foods high in animal fat
- Avoid pesticides and solvents
- Wash fresh fruits and vegetables
- Avoid fish with high mercury levels

# PHTHALATE EXPOSURE

## Environmental exposure sources

Personal care products  
Vinyl plastics  
Food and beverage



## Absorption and metabolism

Ingestion  
Dermal absorption  
Inhalation

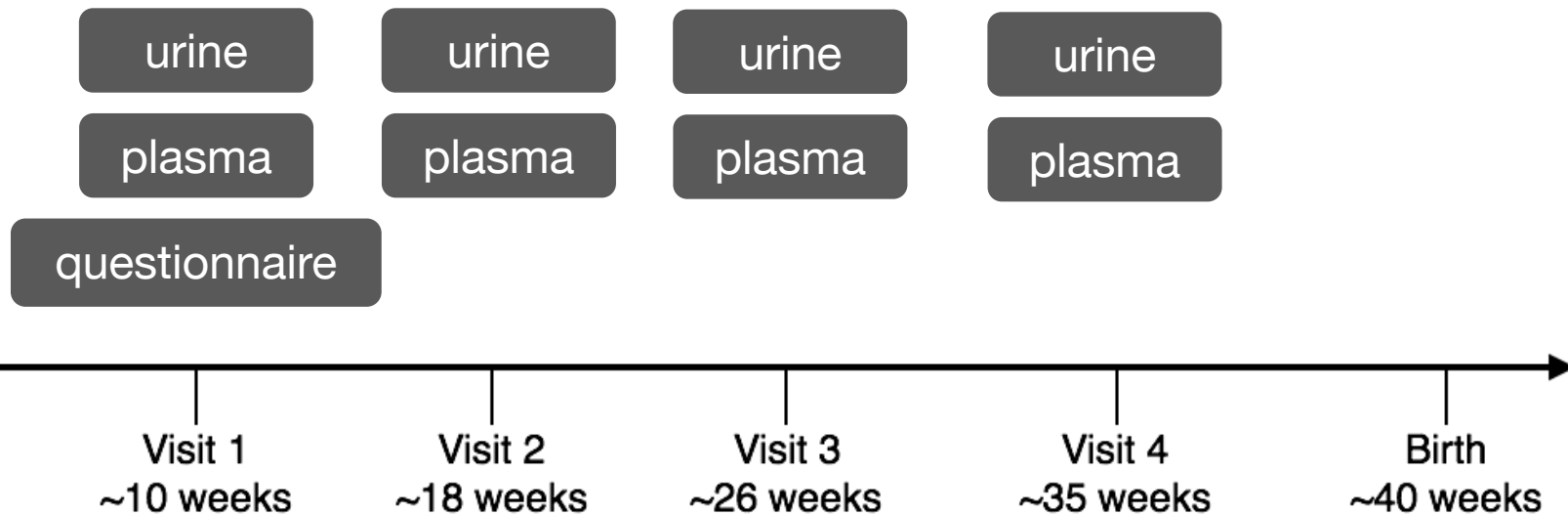


## Associated health outcomes

Hormone disruption  
Infant development  
Birth outcomes



# LIFECODES BIRTH COHORT



- Conducted at Brigham and Women's Hospital
- PI: Dr. Thomas McElrath
- Ongoing recruitment since 2006 (N~4000)
- Key features:
  - Early recruitment
  - Repeated sampling
  - Validation of pregnancy outcomes

# PRETERM BIRTH IN LIFECODES

## SPONTANEOUS

### Presentation

- preterm premature rupture of membranes
- spontaneous preterm labor

### Placental histology

- inflammation

## PLACENTAL

### Presentation

- intrauterine growth restriction
- preeclampsia

### Placental histology

- poor placentation

## CASE-CONTROL STUDY OF PRETERM BIRTH

- 2006-2008
- 130 cases (<37 weeks gestation)
- 352 controls
- Phenotyping preterm based on presentation:
  - Spontaneous (n=56)
  - Placental (n=35)
  - Neither (n=39)

# PHTHALATE EXPOSURE

- ▣ Phthalates metabolites measured in urine from each of four study visits
- ▣ Total (free+glucuronidated) levels measured via mass spectrometry
- ▣ Specific gravity used to adjust for urine dilution



NSF International

## High molecular weight phthalates

$\Sigma$ DEHP

MCPP



## Low molecular weight phthalates

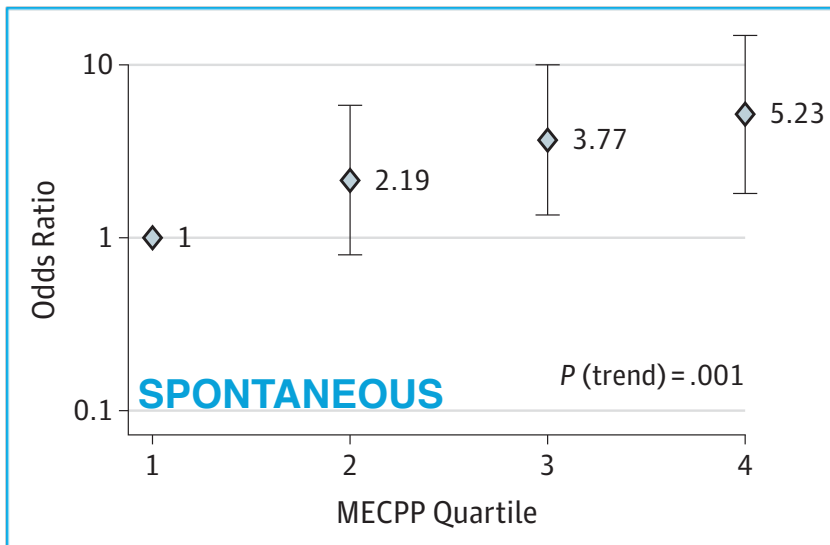
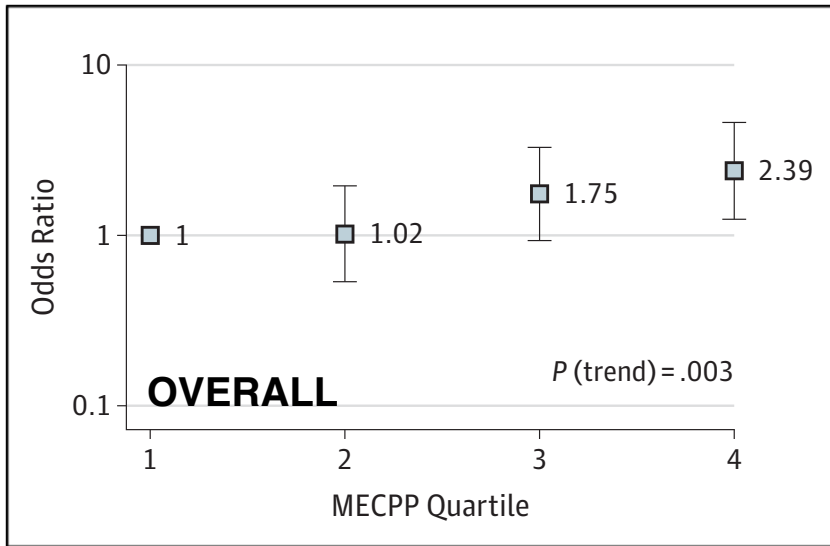
MBP

MEP

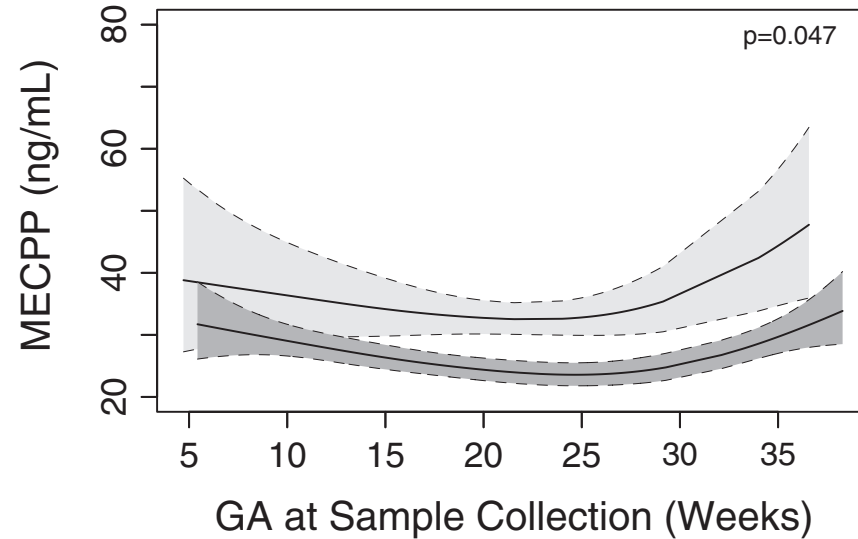




# PHTHALATE EXPOSURE AND PRETERM BIRTH



## Urinary phthalate levels by gestational age at sample collection



- Cases of spontaneous PTB in light gray
- Controls in dark gray
- Greatest differences later in gestation

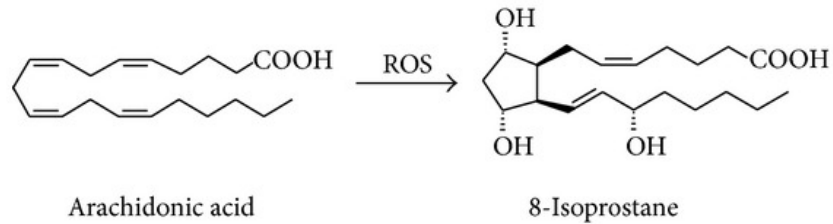
Ferguson et al. 2014, *Environ Int*

phenotyping  
preterm birth

windows of  
vulnerability

# WHAT ABOUT MECHANISM?

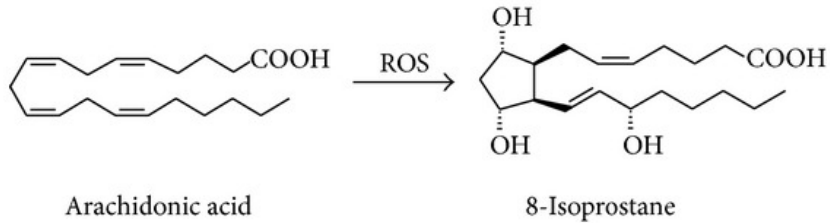
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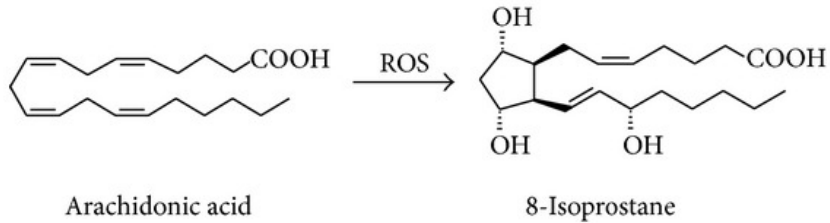
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**Table 4.** Percent difference (95% CIs) in oxidative stress biomarker in association with IQR increase in phthalate metabolite level.

Metabolite	IQR <sup>a</sup>	8-OHdG		8-Isoprostane	
		% difference (95% CI)	p-Value	% difference (95% CI)	p-Value
MEHP	16.6 µg/L	2.74 (-0.47, 6.05)	0.09	14.1 (8.06, 20.5)	< 0.001
MEHHP	56.9 µg/L	8.40 (4.93, 12.0)	< 0.001	15.8 (9.53, 22.4)	< 0.001
MEOHP	29.4 µg/L	7.34 (4.01, 10.8)	< 0.001	15.9 (9.87, 22.3)	< 0.001
MECPP	80.5 µg/L	6.53 (2.96, 10.2)	< 0.001	23.0 (16.0, 30.4)	< 0.001
ΣDEHP	0.63 µmol/L	6.67 (3.23, 10.2)	< 0.001	19.1 (12.7, 25.9)	< 0.001
MBzP	12.5 µg/L	20.7 (15.6, 26.1)	< 0.001	42.7 (31.8, 54.4)	< 0.001
MBP	24.8 µg/L	18.1 (13.5, 22.9)	< 0.001	42.0 (32.0, 52.7)	< 0.001
MiBP	11.3 µg/L	30.3 (24.4, 36.5)	< 0.001	56.4 (43.9, 69.9)	< 0.001
MEP	355 µg/L	11.5 (7.32, 15.9)	< 0.001	19.7 (11.8, 28.2)	< 0.001
MCPP	2.98 µg/L	7.23 (3.83, 10.7)	< 0.001	20.2 (13.7, 27.1)	< 0.001

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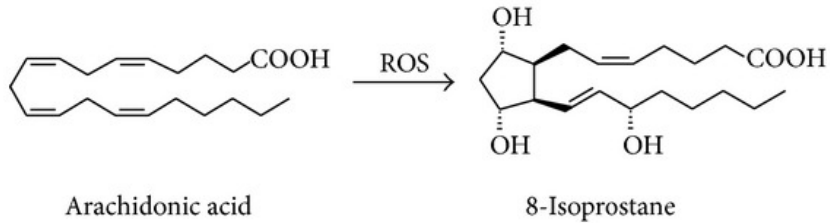
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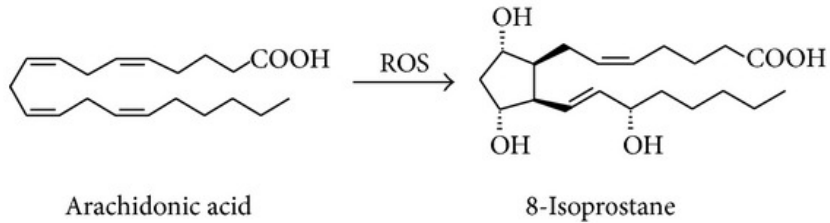
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Preterm birth in association with interquartile range increase in geometric average (visits 1-3) urinary oxidative stress biomarkers

Variable	Model 1 <sup>a</sup>			Model 2 <sup>b</sup>		
	Control cases, n	Odds ratio (95% confidence interval)	P value	Control cases, n	Odds ratio (95% confidence interval)	P value
Overall preterm birth						
8-OHdG	129,349	0.19 (0.11–0.34)	< .001	126,331	0.19 (0.10–0.34)	< .001
8-Isoprostane	129,349	2.17 (1.48–3.20)	< .001	126,331	2.22 (1.47–3.36)	< .001
Spontaneous preterm birth						
8-OHdG	56,349	0.21 (0.10–0.42)	< .001	56,331	0.18 (0.09–0.40)	< .001
8-Isoprostane	56,349	4.25 (2.21–8.15)	< .001	56,331	6.25 (2.86–13.7)	< .001
Placental preterm birth						
8-OHdG	35,349	0.17 (0.07–0.41)	< .001	33,331	0.11 (0.04–0.32)	< .001
8-Isoprostane	35,349	1.45 (0.79–2.66)	.24	33,331	0.94 (0.52–1.70)	.84

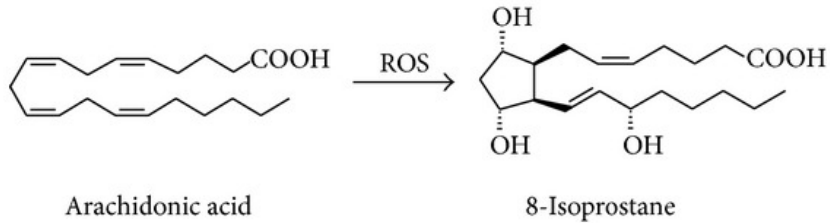
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Ferguson. Oxidative stress and preterm birth. *Am J Obstet Gynecol* 2015.

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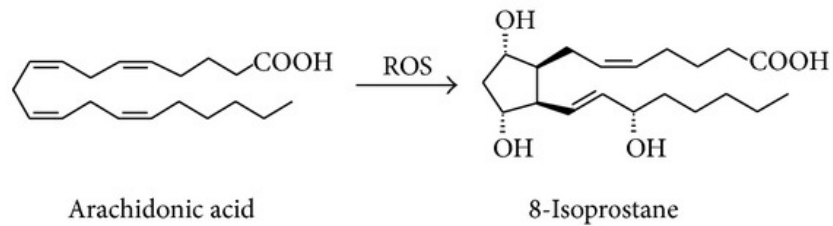
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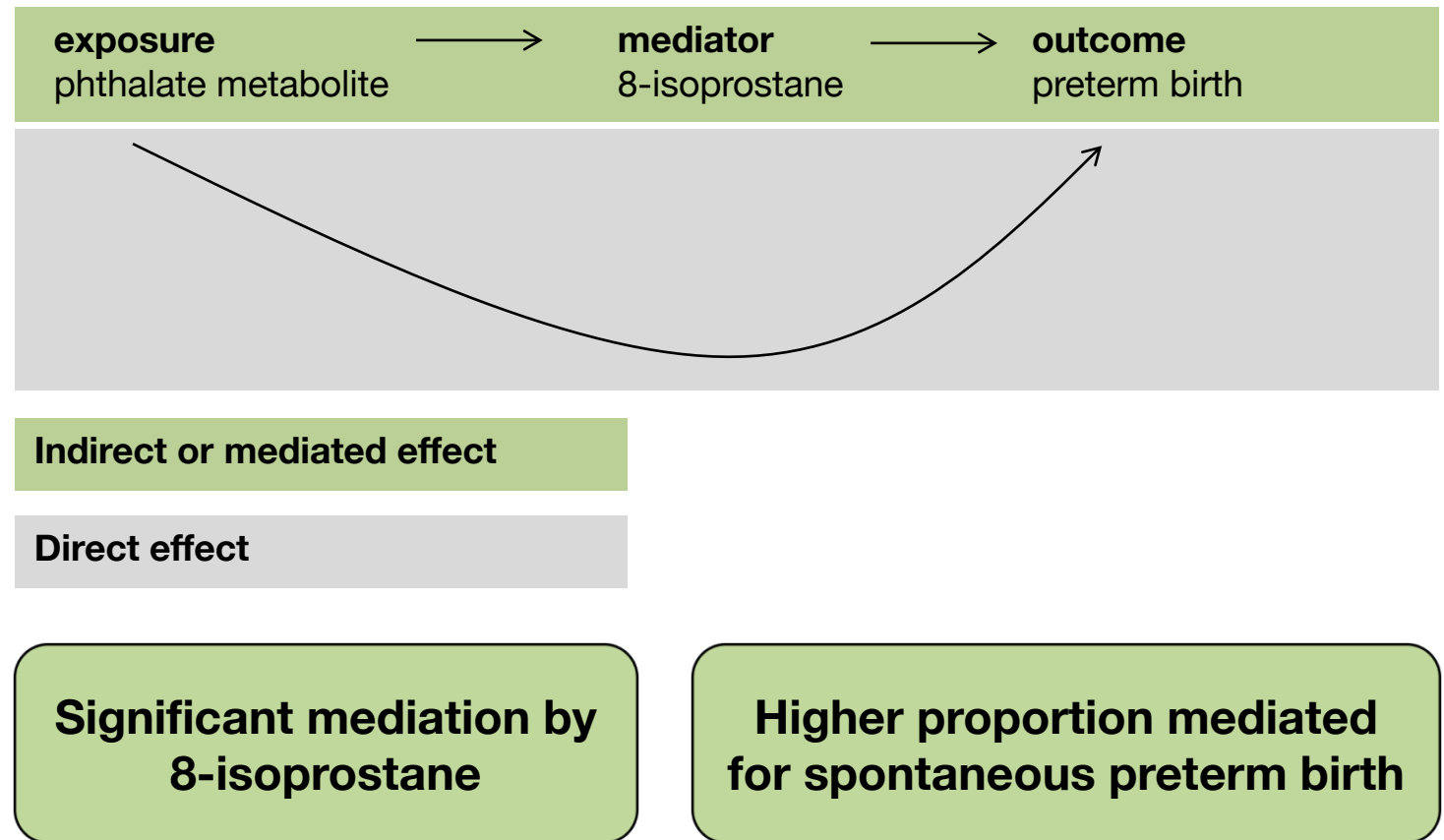
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## MEDIATION FRAMEWORK



Ferguson et al. 2016, *EHP*



# WHAT'S NEXT?



What about maternal exposure to mixtures?

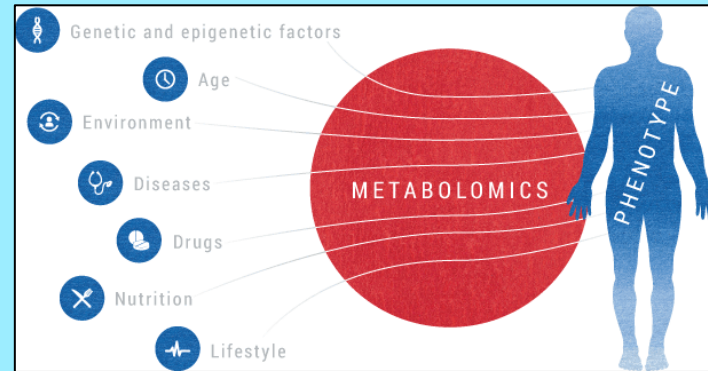


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Can we disaggregate other birth outcomes in environmental epidemiology?

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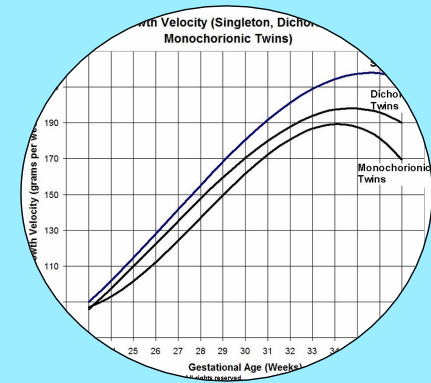
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# ACKNOWLEDGEMENTS

## COLLABORATORS

John Meeker

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David Cantonwine

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