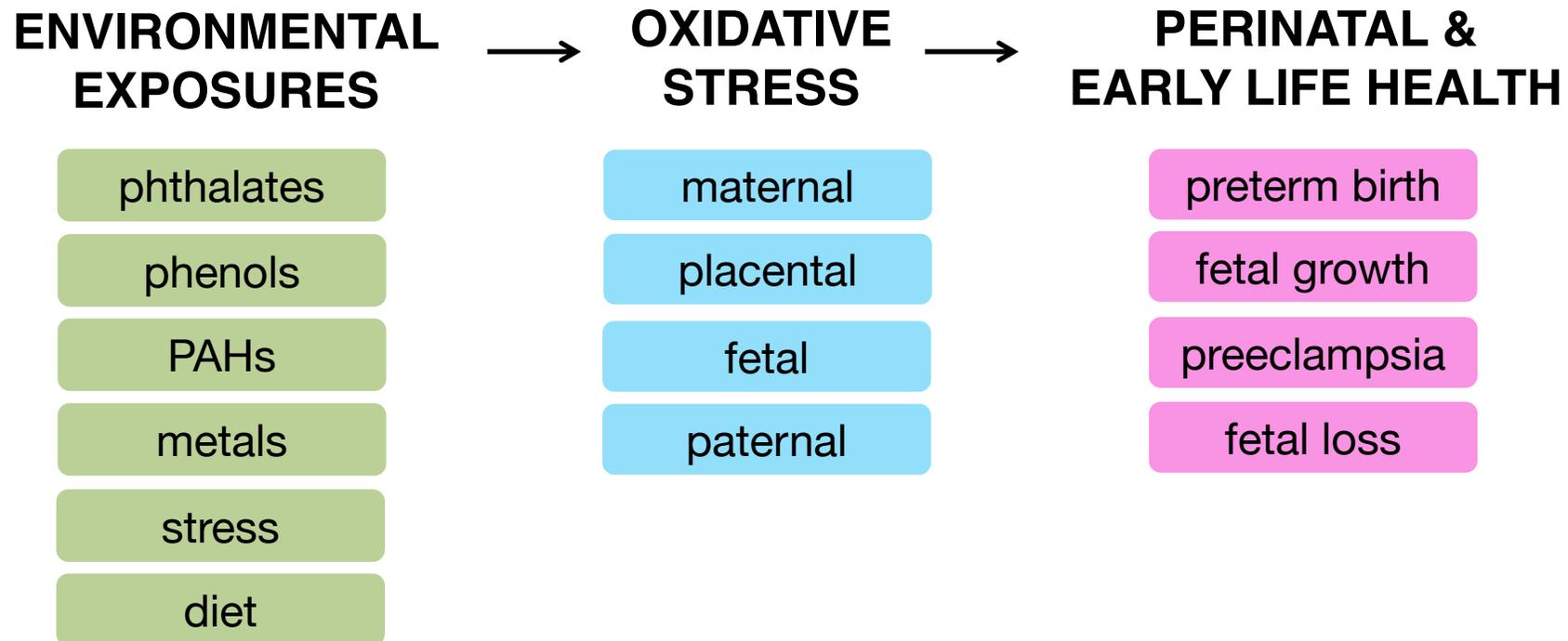


ENVIRONMENTAL CHEMICALS AND PRETERM BIRTH: EMERGING THREATS AND PRIORITIES FOR FUTURE RESEARCH

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

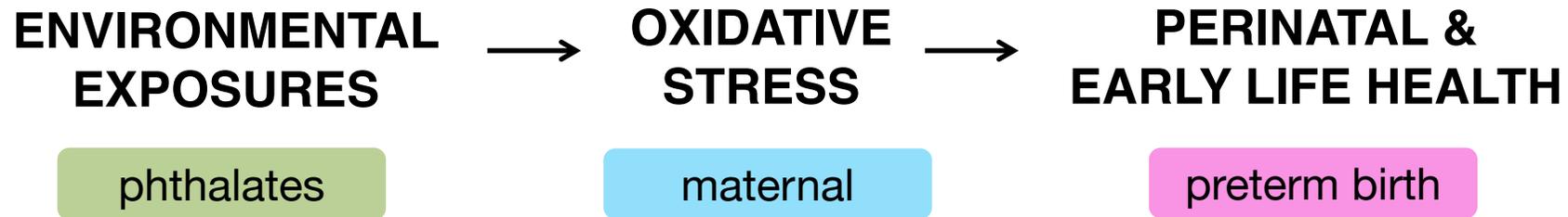
OVERVIEW

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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

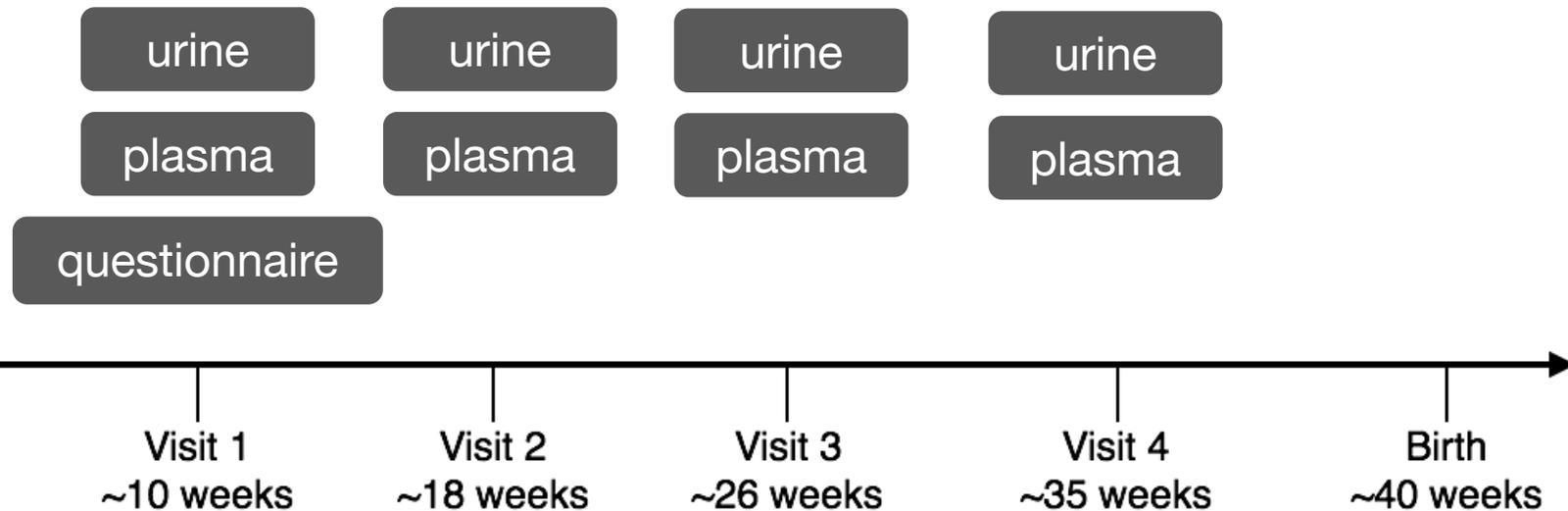


Associated health outcomes

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

Σ DEHP

MCPP



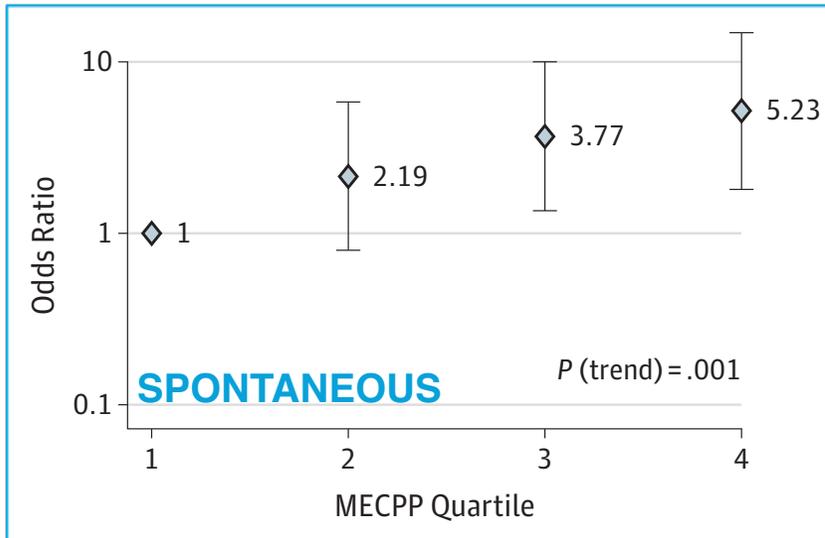
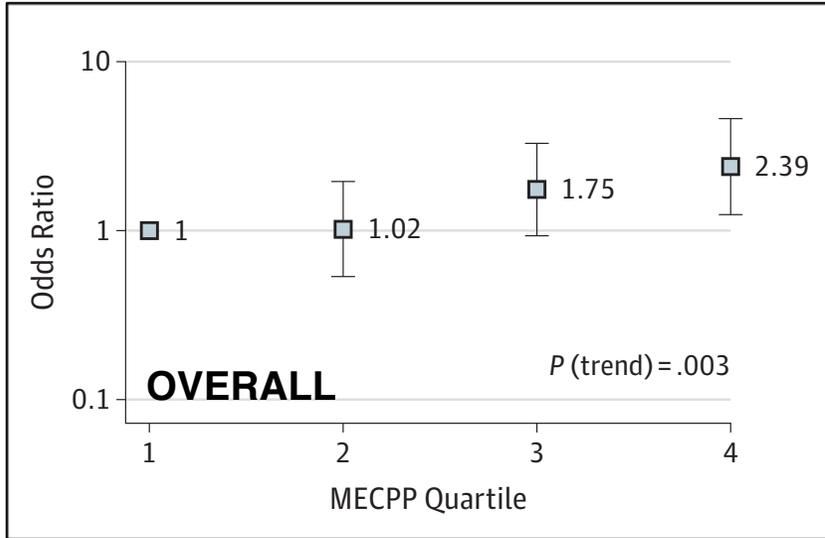
Low molecular weight phthalates

MBP

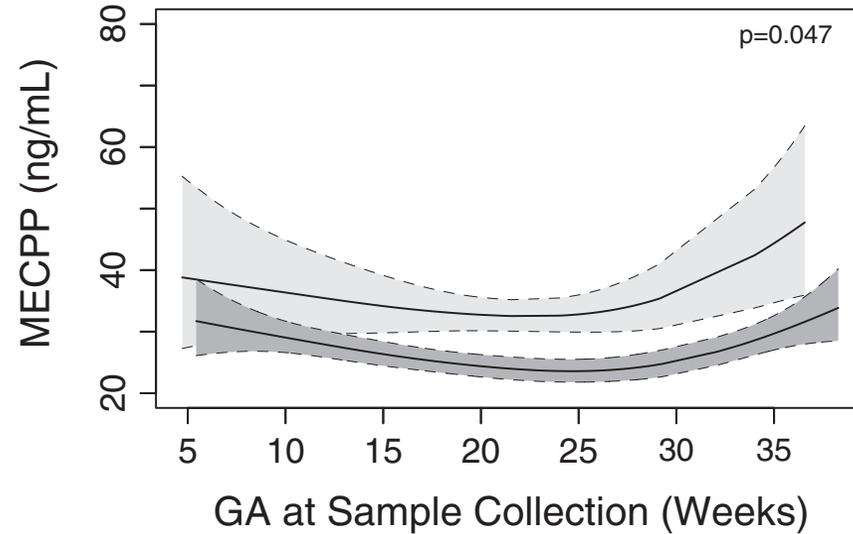
MEP



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

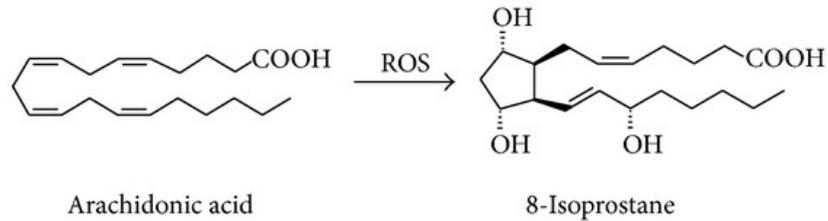
Ferguson et al. 2014, *Environ Int*

phenotyping
preterm birth

windows of
vulnerability

WHAT ABOUT MECHANISM?

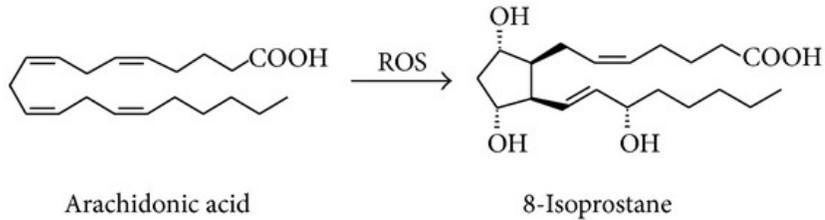
8-ISOPROSTANE



- Established by the Biomarkers of Oxidative Stress Study (NIEHS) as best biomarker of oxidative stress
- Sensitive, specific, and consistent
- Easy to measure in stored urine samples

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Urinary Phthalate Metabolites and Biomarkers of Oxidative Stress in Pregnant Women: A Repeated Measures Analysis

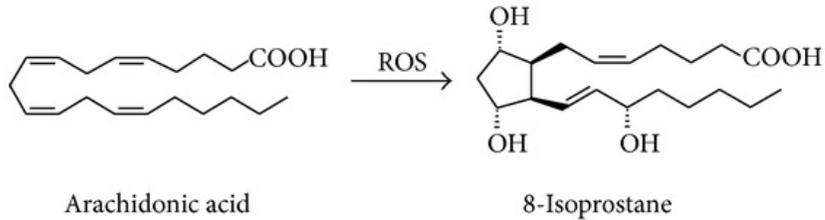
Kelly K. Ferguson,¹ Thomas F. McElrath,² Yin-Hsiu Chen,³ Bhramar Mukherjee,³ and John D. Meeker¹

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

Metabolite	IQR ^a	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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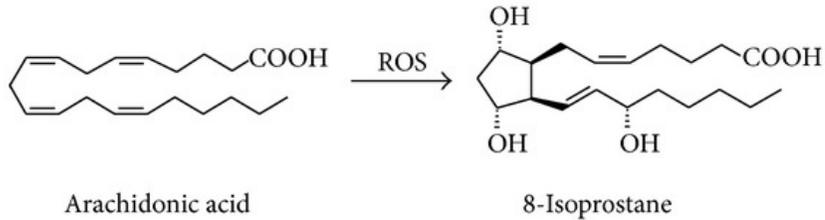
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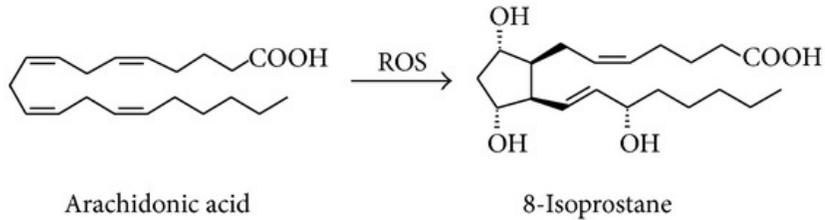
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TABLE 2

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

Variable	Model 1 ^a			Model 2 ^b		
	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

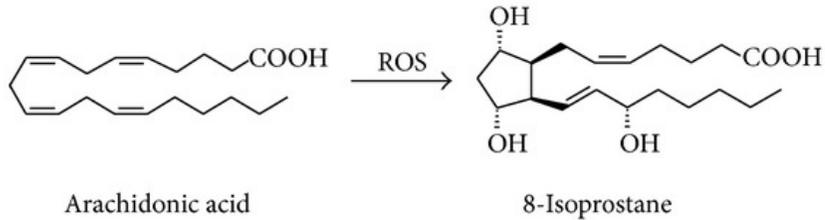
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Ferguson. Oxidative stress and preterm birth. *Am J Obstet Gynecol* 2015.

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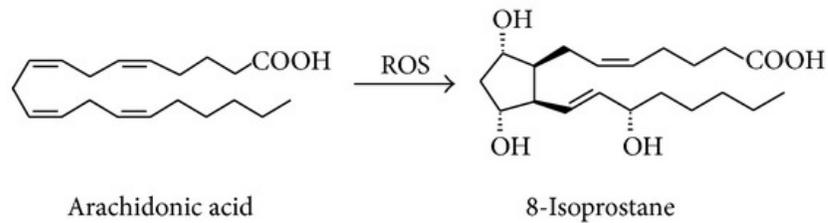
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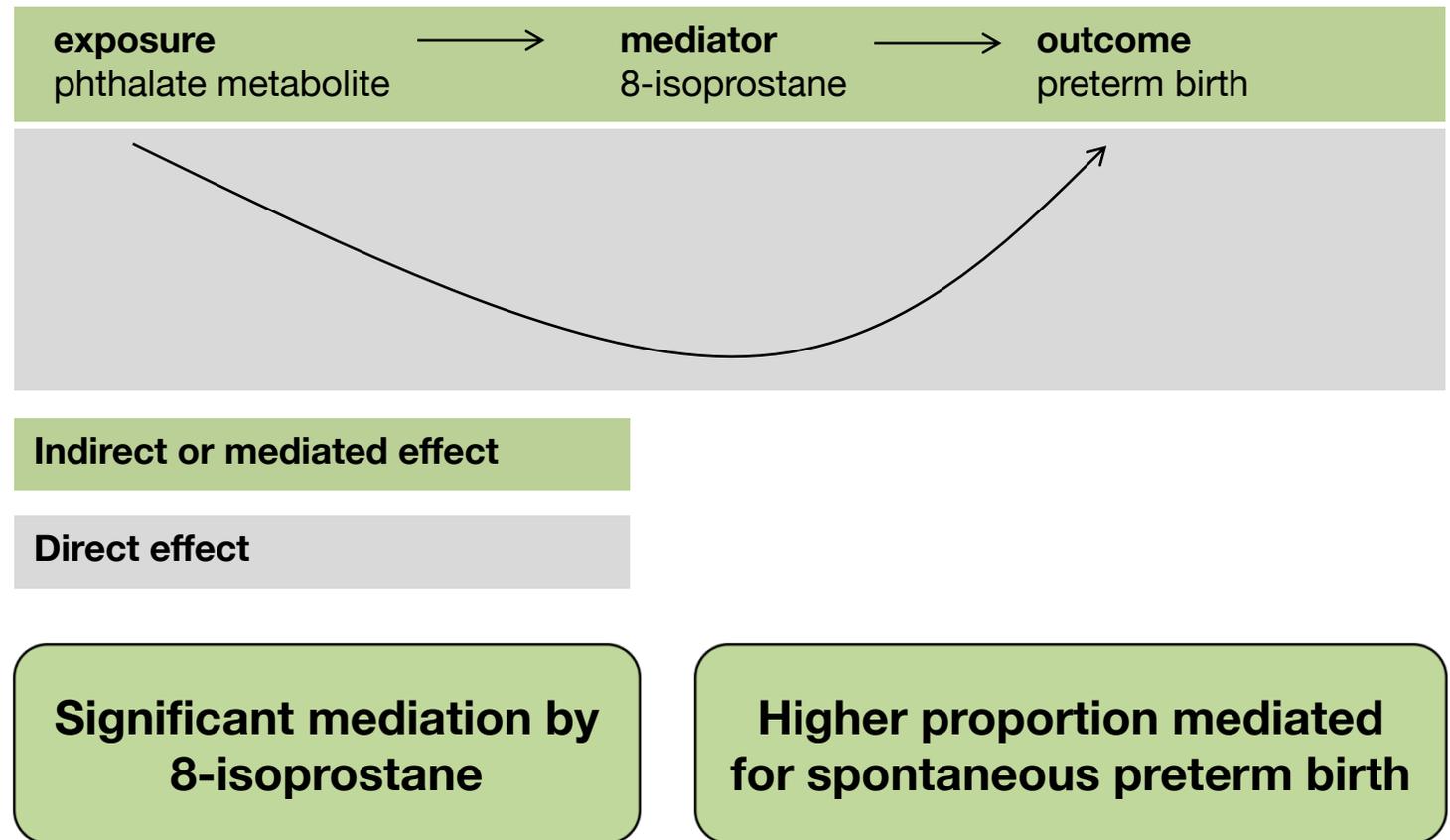
MEDIATION BY OXIDATIVE STRESS

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MEDIATION FRAMEWORK



Ferguson et al. 2016, *EHP*

WHAT'S NEXT?



What about maternal exposure to mixtures?

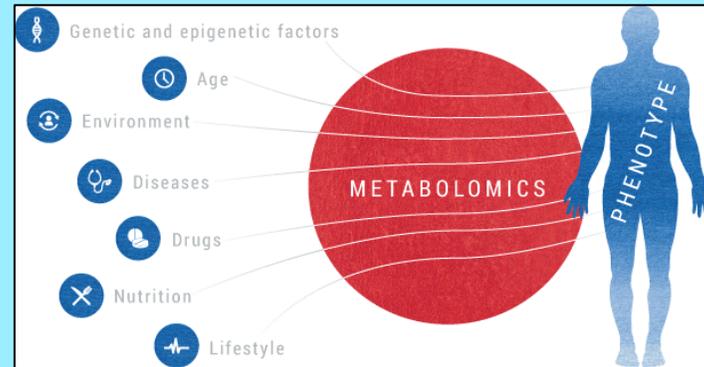


What do the oxidative stress markers mean?

Can we disaggregate other birth outcomes in environmental epidemiology?

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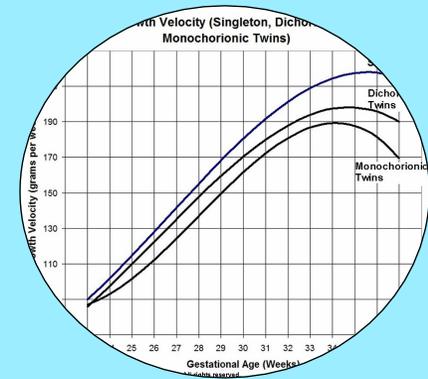
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ACKNOWLEDGEMENTS

COLLABORATORS

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Thomas McElrath

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