Endocrine disruptors and hormones in pregnancy

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YESS Webinar

Tuesday, May 7, 2024

Scan for article

Today’s presentation

- Background & research gaps
  - Replacement chemicals
  - EDC mixtures
  - Non-linearities
  - Fetal sex
- Objectives
- Methods
- Results
- Conclusions & future directions

Pregnancy as part of the life cycle

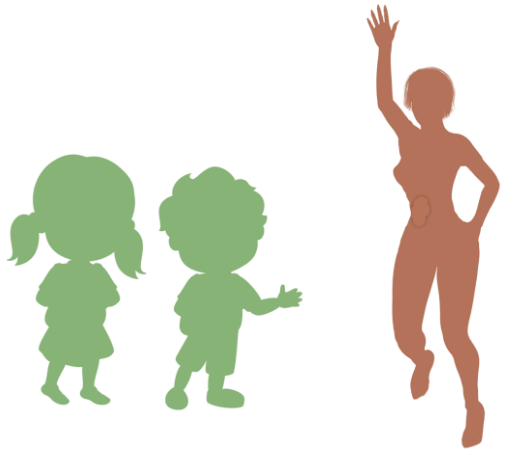
Pregnancy is important because:

1. **Produces babies**
2. **Happens to the pregnant individual**

Perturbations during pregnancy can have lasting consequences for maternal and child health

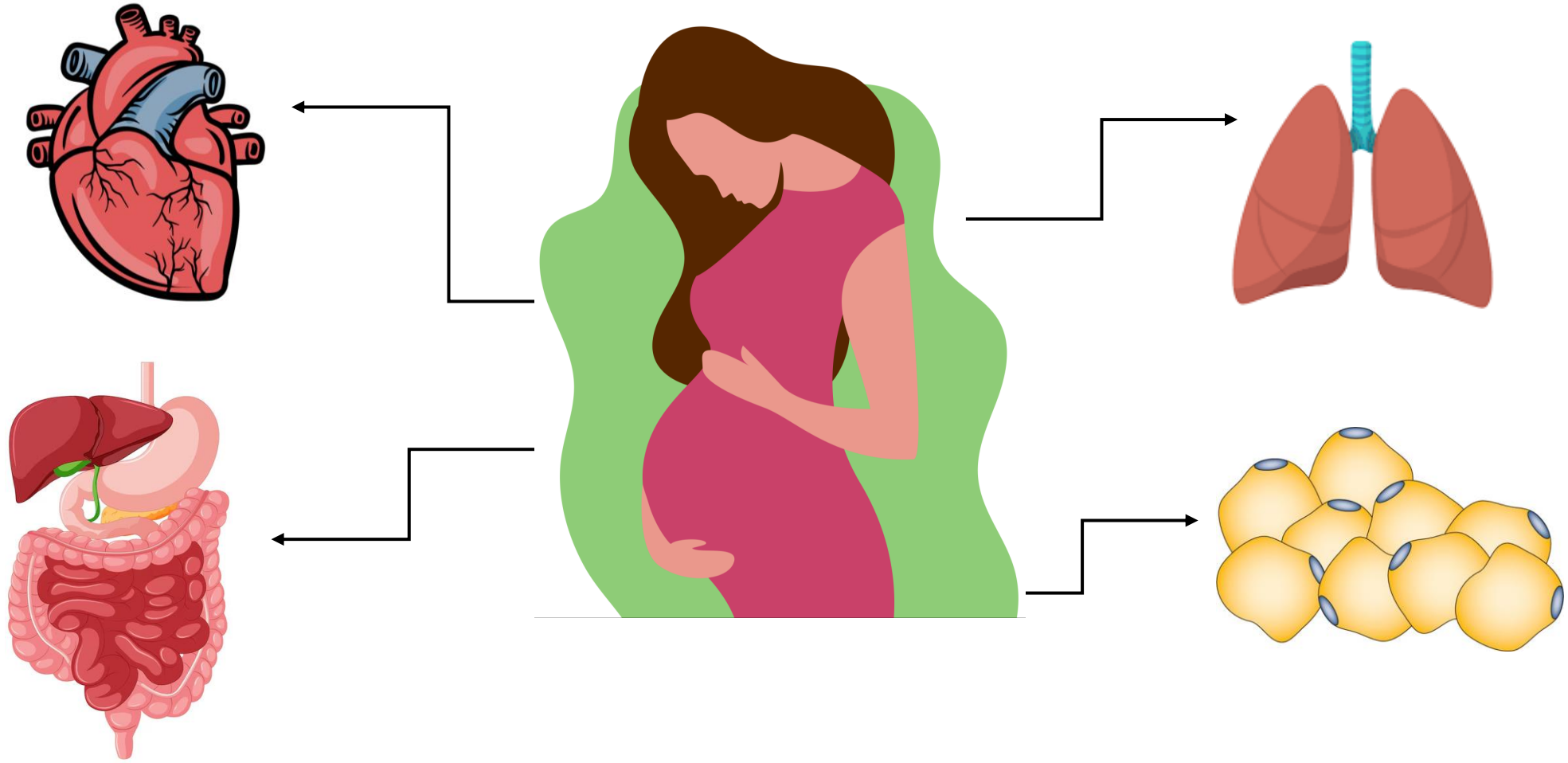
Pregnancy hypertensive disorders
Gestational diabetes
Inappropriate weight gain
Pre-term birth

Cardiometabolic disease
Osteoporosis
Reproductive dysfunction
Cognitive dysfunction
Aging, cancer



Gluckman *et al*., *The epigenome and developmental origins of health and disease*, 2016; Dessanayake *et al*., *Cardiology in Review*, 2020; Haggerty, Upson, Pacyga *et al*., *Reproduction*, 2021.

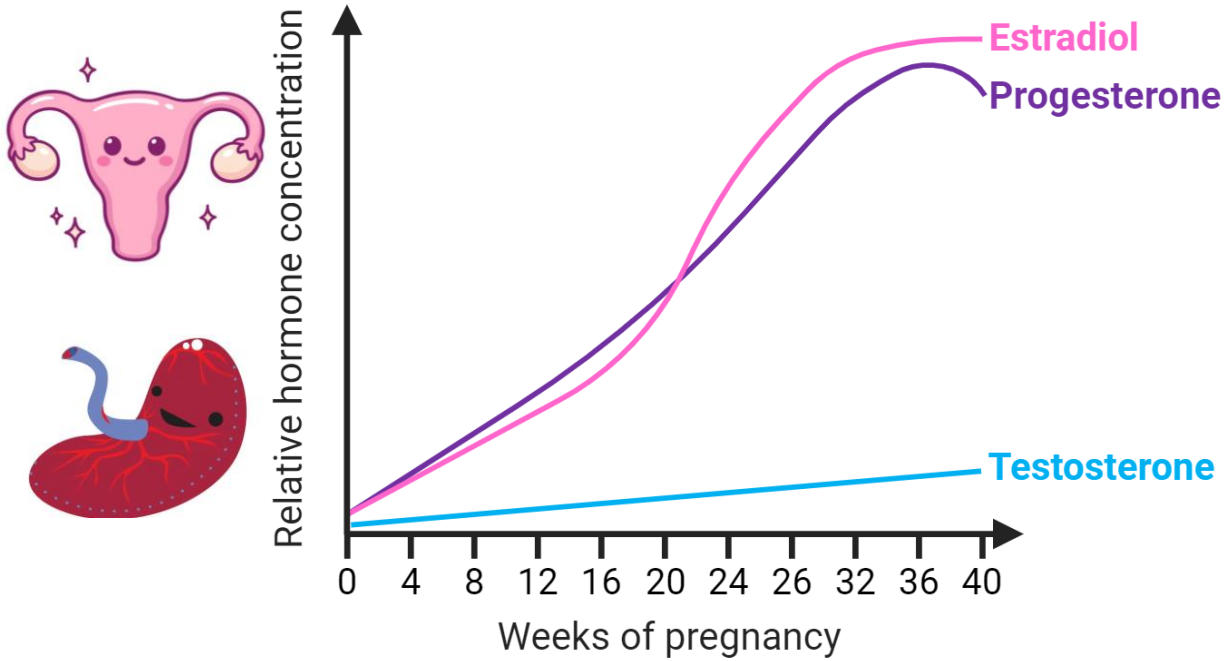
Pregnancy involves many physiological changes



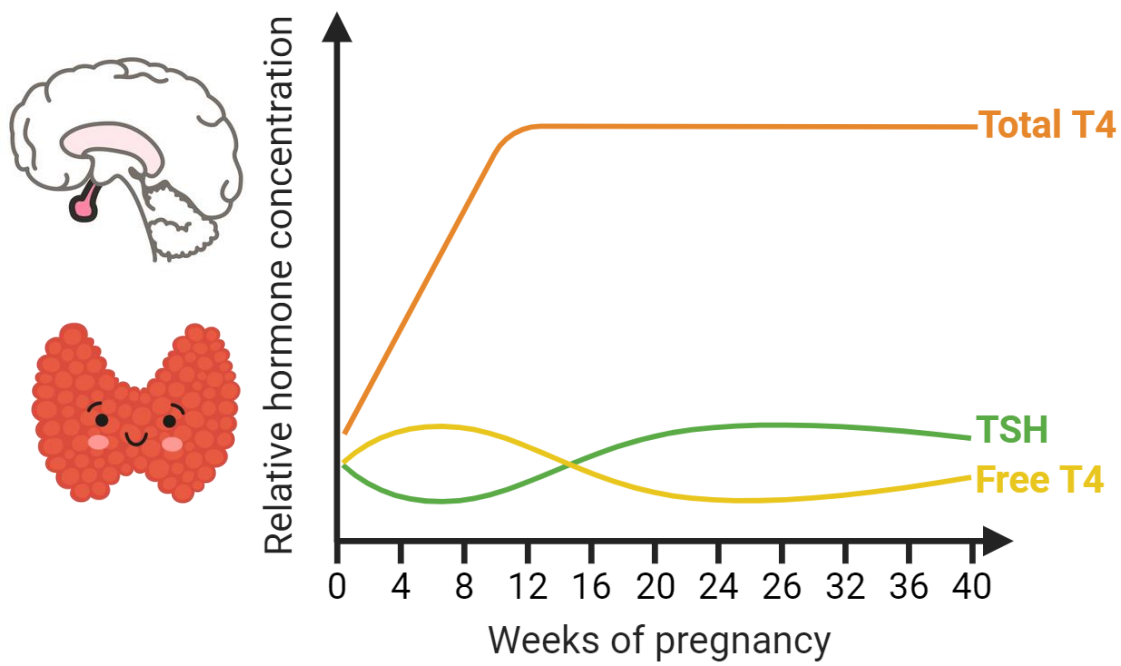
Costatine, *Frontiers in Pharmacology*, 2014; Hacker and Moore's *Essentials of Obstetrics & Gynecology*, 2016.

Adaptations in hormones support pregnancy

Sex-steroid hormones



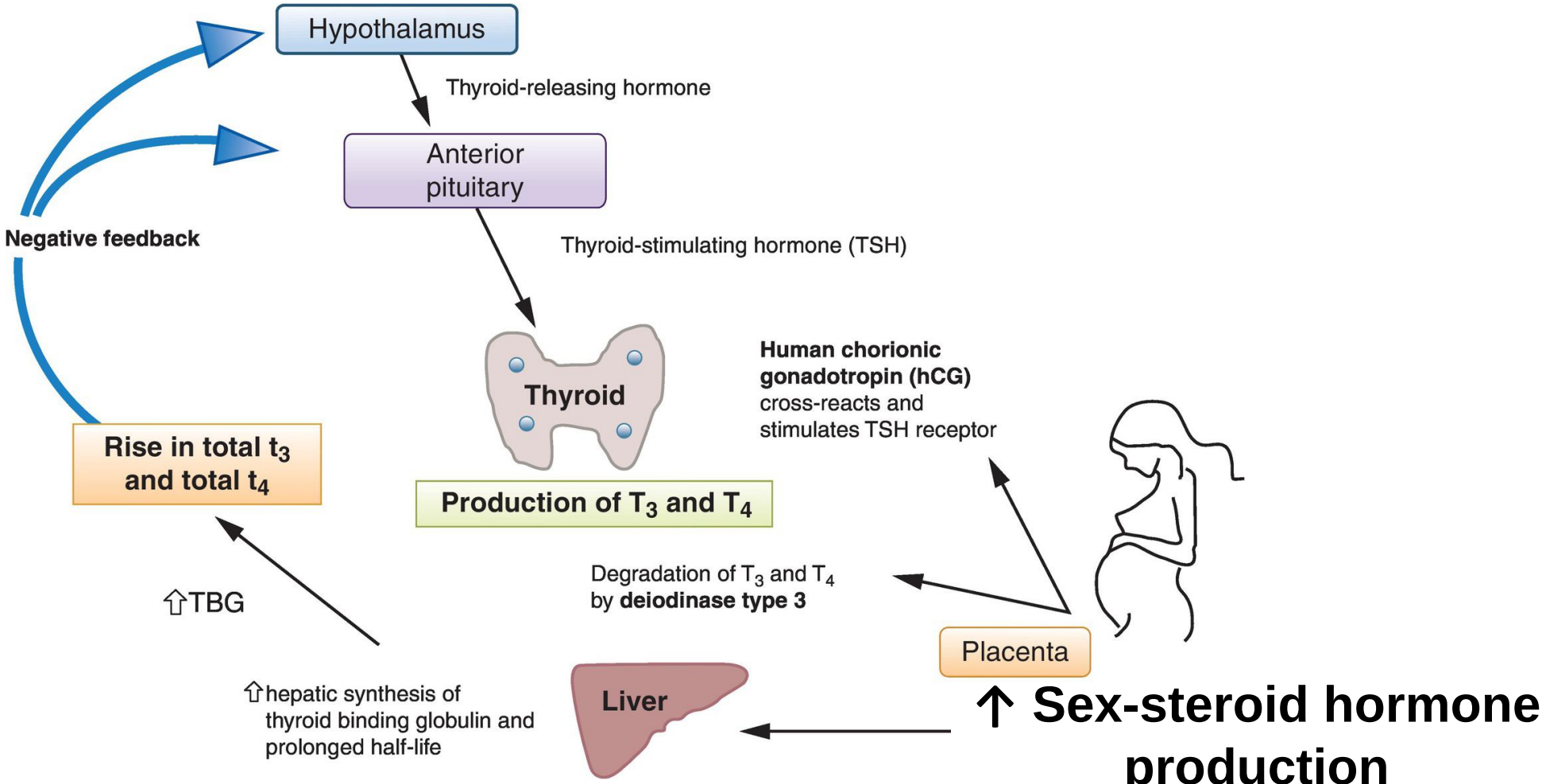
Thyroid hormones



Implantation | **Placental angiogenesis** | **Immune adaptation** | **Metabolic adaptation** | **Parturition**

Hacker & Moore's *Essentials of Obstetrics and Gynecology*, 2010; Silve et al., *Biol. Reprod.*, 2018.

Sex-steroid and thyroid hormones are part of a coordinated system



Hacker & Moore's *Essentials of Obstetrics and Gynecology*, 2010; Jarvis and Nelson-Piercy *High-Risk Pregnancy*, 2017.

Altered hormone levels are associated with adverse pregnancy and birth outcomes

Infertility | **Miscarriage** | **Gestational hypertension** | **Pre-term birth** | **Low birthweight**

Hacker & Moore's *Essentials of Obstetrics and Gynecology*, 2010; Silve et al., *Biol. Reprod.*, 2018.

Almost all pregnant women are exposed to chemicals found in common consumer products

Phthalates

DEHP

DEP

Phenols

Bisphenol A

Methylparaben

Benzophenone-3

Dichlorophenols

Woodruff et al., *Environmental Health Perspectives*., 2011; CDC Biomonitoring Data, 2022; National Biomonitoring Program, 2017; Mortensen et al., *Environmental Research*., 2014; Janjua et al., *International Journal Andrology*., 2008; Moos et al., *Archives in Toxicology*., 2006; Gingrich et al., *Chemosphere*., 2019.

Phthalates and phenols are associated with adverse pregnancy and birth outcomes

Gestational Hypertension

Gestational Diabetes

Caesarean section

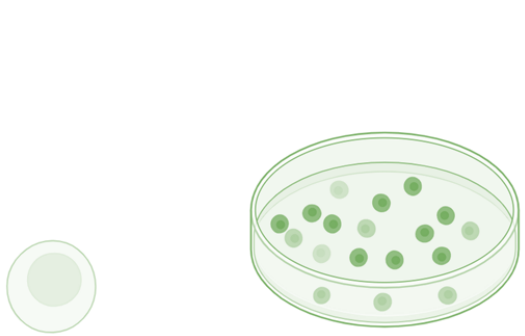
Pre-term birth

Toft et al., *Environmental Health Perspectives*, 2012; Adibi et al., *American Journal of Epidemiology*, 2009; Ferguson et al., JAMA Pediatrics, 2014; Philippat et al., *Environmental Health Perspectives*, 2017; Ipapo et al., *Environmental Research*, 2017; Gascon et al., *Journal of Allergy Clinical Immunology*, 2015; Harley et al., *Pediatric Research*, 2017.

Phthalates and phenols are endocrine disrupting chemicals (EDCs)

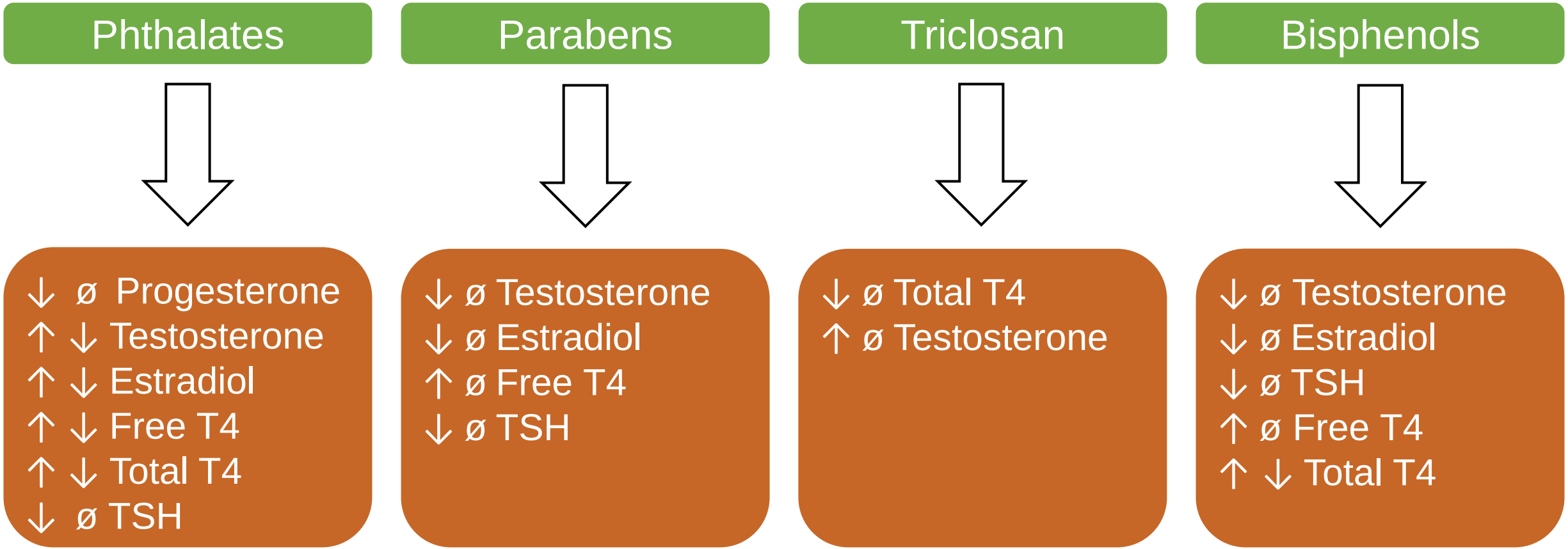
Receptors
Enzymes

Tissues
Circulating levels



Aker et al., *Environ Research*, 2016; Wang et al., *Toxicology*, 2017; Strakovsky & Schantz, *Toxicol Sci*., 2018; Warner *et al*., *Reprod Toxicol*., 2021; Pacyga, DC et al., *Environ. Int*., 2021; CDC National Biomonitoring.

Epidemiological studies have identified associations of single EDCs with maternal pregnancy hormones



Sathyanarayana *et al. Reproduction*, 2014; Johns *et al. Reprod Biol Endocrinol*, 2015; Sathyanarayana *et al. J Clin Endocrinol Metab*, 2017; Cathey *et al*., 2019; Banker *et al*., 2020; Aker et al., *Environmental Health*., 2019; Kolatorova et al., *Environmental Research*, 2018; Banker et al., *Journal of Clinical Endocrinology and Metabolism*, 2021.

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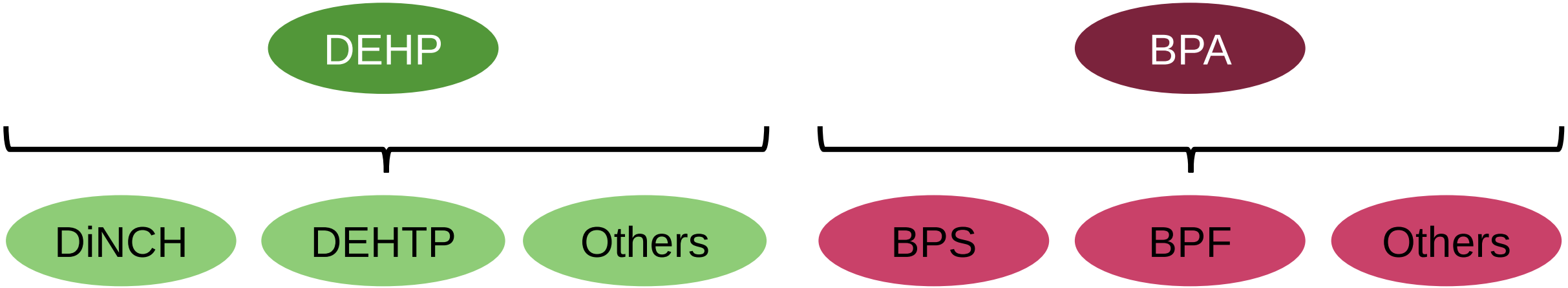
Pregnant women are becoming increasingly exposed to newer chemical replacements



Regrettable substitution:

When a chemical with unknown hazard is used to replace a chemical identified as problematic

Maertens *et al*., *ACS Sustainable Chem. Eng.*, 2021; Bui *et al*., *Sci Total Environ*., 2016; Lemke *et al*., *Int J Hyg Environ Health*, 2021.

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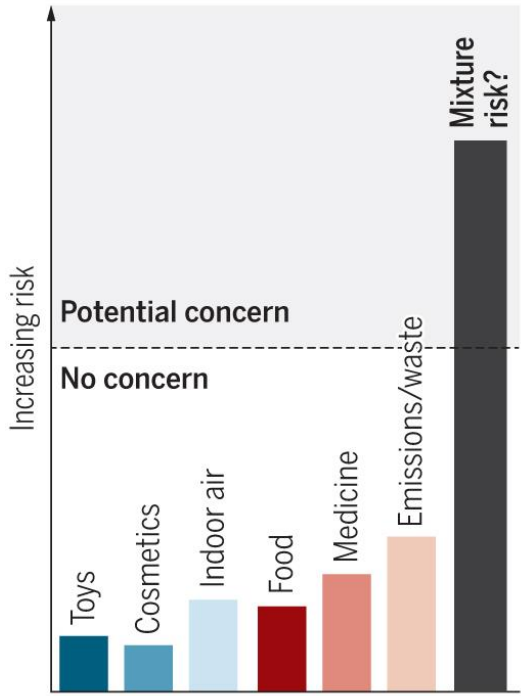
Pregnant women are exposed to chemicals as mixtures



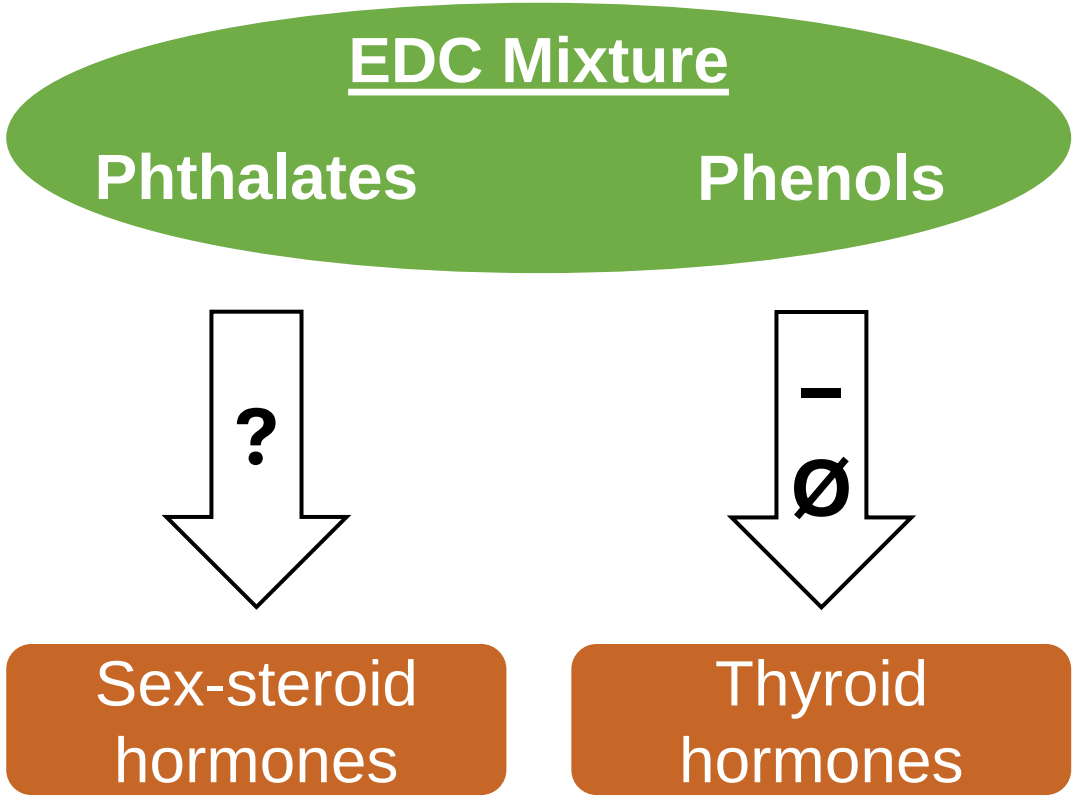
Regulatory gaps
Humans and the environment are exposed to myriad chemicals from many different sources, but little is known about their combined risk.

Science
AAAS

Cumulative effect	**“Bad actors”**
Could be larger than individual effects	**Individual co-exposures contributing to cumulative effect**

Andreas Kortenkamp and Michael Faust *Science* 2018;361:224-226

Limited studies have assessed associations of an EDC mixture with pregnancy hormones



Limitations:

- Single class mixtures
- No replacements

Romano et al. *Int J Hyg Environ Health,* 2018; Souter et al. *EHP,* 2020; Huang et al. *Environ Sci Pollut Res Int*, 2022; Yang et al. *Ecotoxicol Envion Saf*, 2022; Sarzo et al. *Environ Pollut*, 2022; Nakiwala et al., *EHP*, 2022.

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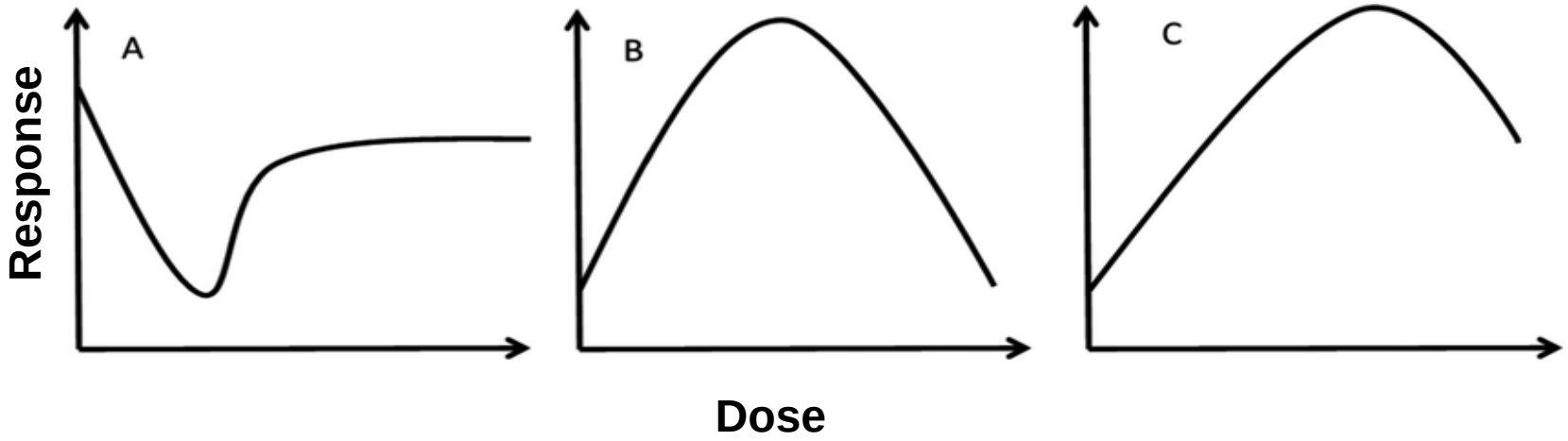
Experimental studies have demonstrated non-linear dose-response effects of EDCs



Examples in mice:

- BPA with reproduction (fertility, behaviors, expression of embryo receptors)
- DEHP with aromatase activity, cholesterol levels, and pubertal timing

Possible causes:

- Cytotoxicity, receptor down-regulation, and endocrine feedback loops

Vandenberg et al., *Endocrine Reviews* 2012.

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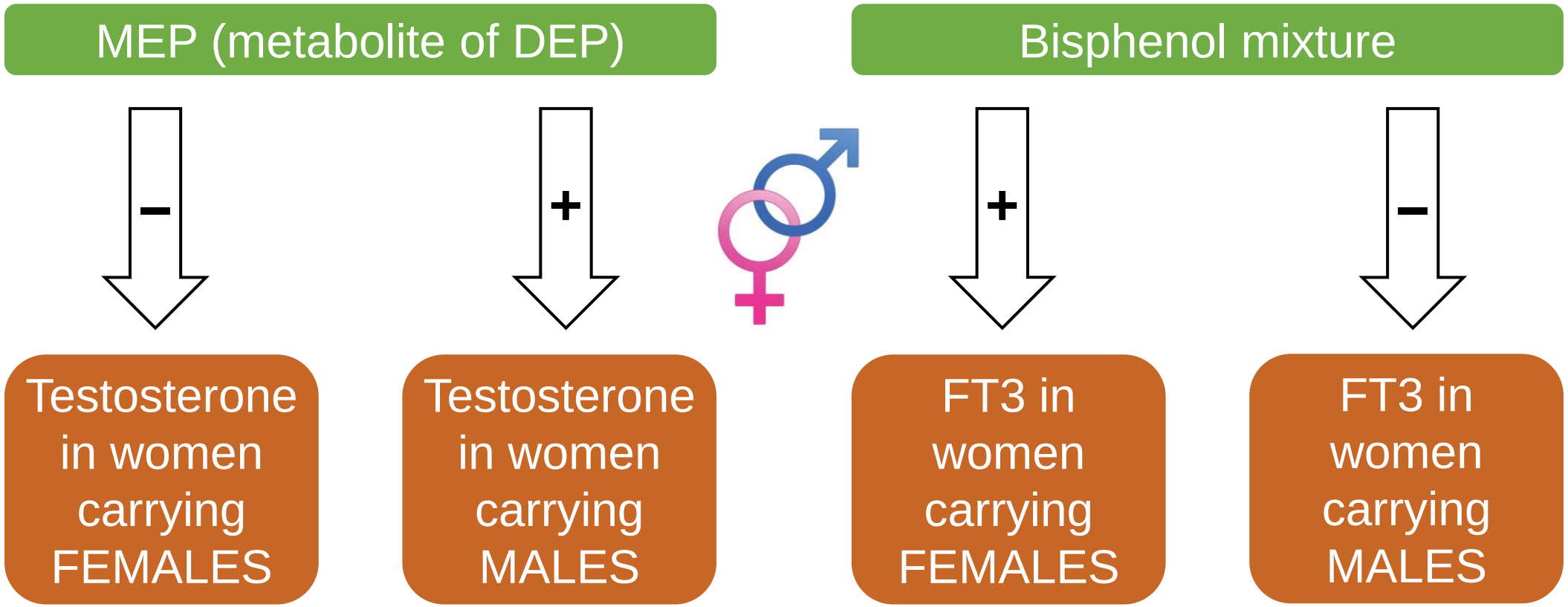
Associations of EDCs with hormones may differ by fetal sex



Sathyanarayana et al. *Reproduction*, 2014; Aker et al., *Environmental Health*., 2019; Huang et al., *Environ Sci Pollut Res Int*, 2022.

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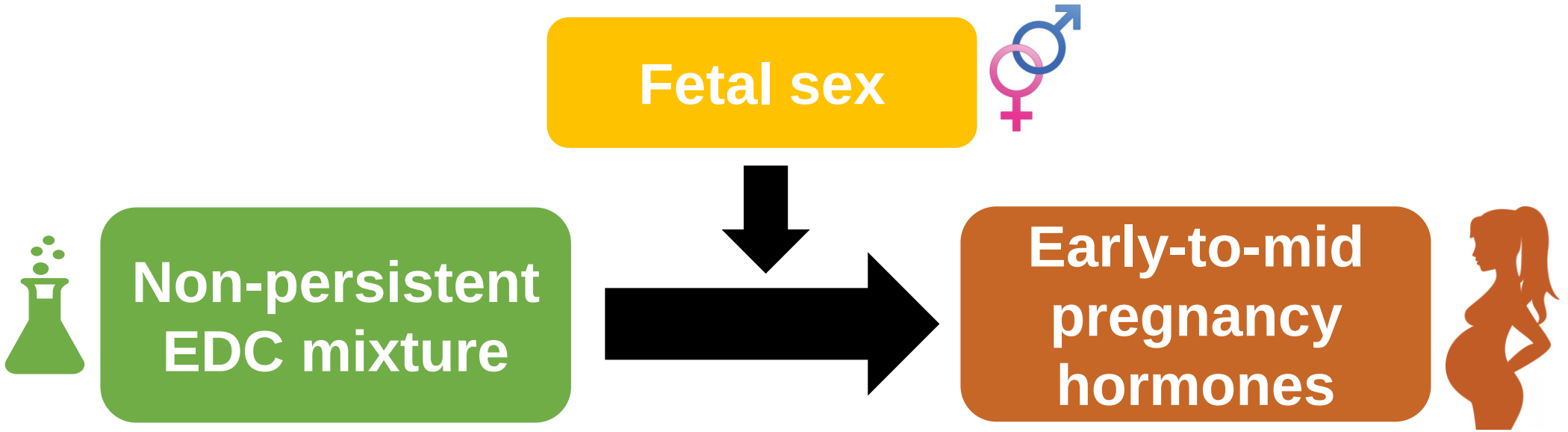
Objectives



Objective 1: Overall mixture association

Objective 2: Individual contributors

Objective 3: Non-linearities

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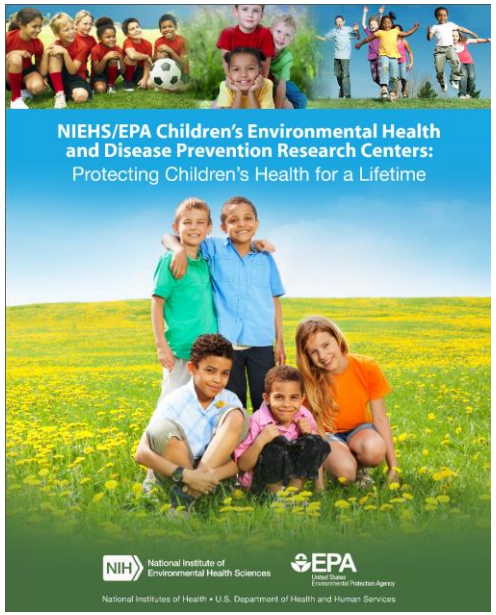
NIEHS/EPA Children's Environmental Health Research Centers



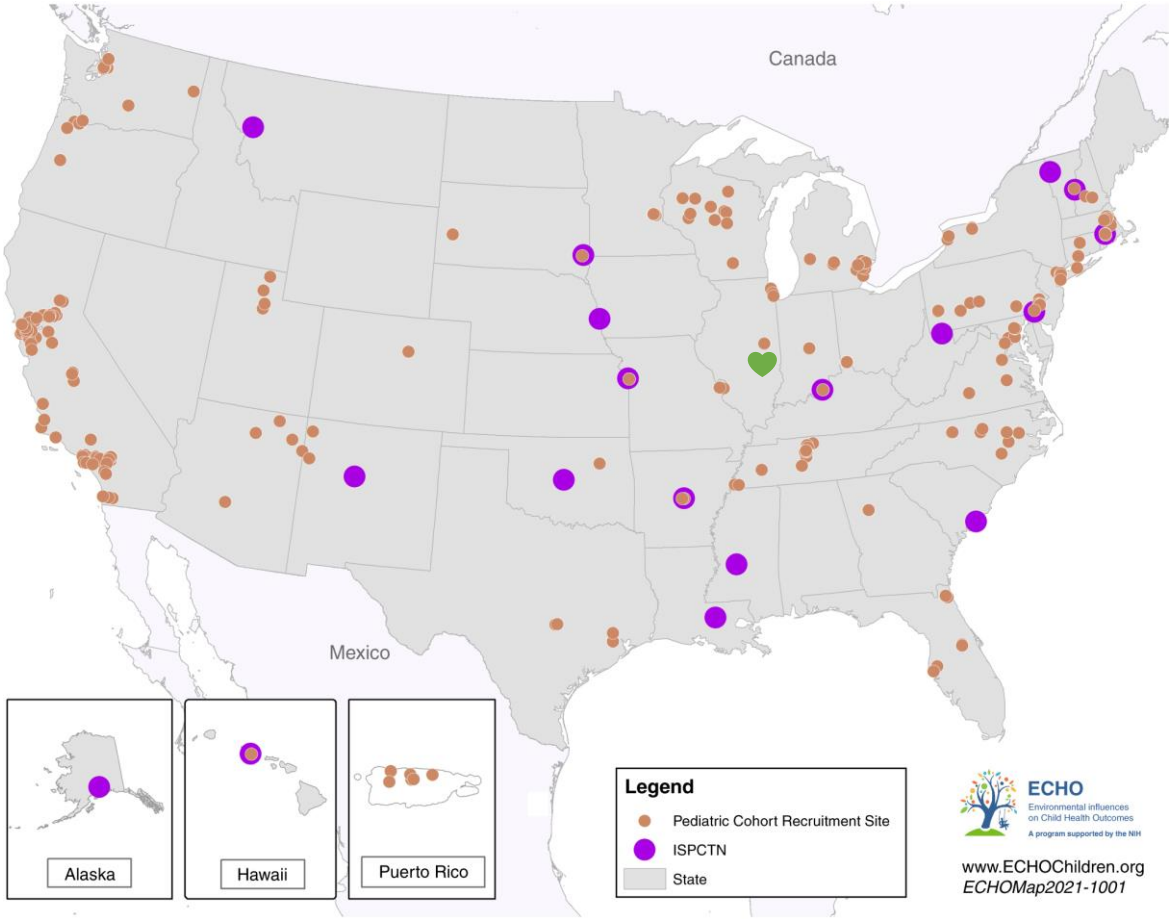
Role of the environment in:

- Birth outcomes
- Cognition (ADD/ADHD, autism, IQ)
- Asthma, immunity
- Obesity and diabetes
- Childhood cancers
- Reproductive outcomes

Exposures of interest:

- Air pollutants
- Trace metals
- Pesticides
- Endocrine disruptors

Environmental influences on Child Health Outcomes



Role of the environment in:

- Upper and lower airway
- Obesity
- Pre-, peri-, and postnatal outcomes
- Neurodevelopment

Exposures of interest:

- Everything is an exposure

ECHO
Environmental influences on Child Health Outcomes
A research program supported by the National Institutes of Health

Romano et al., *Pediatric Research*., 2021. Map is from Cycle 1 of ECHO.

Illinois Kids Development Study (I-KIDS)

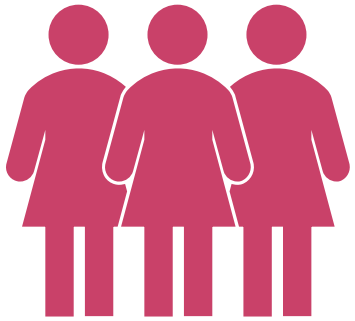
- Prospective pregnancy and birth cohort in Champaign-Urbana, IL
- Enrolling pregnant women between 2013 and 2020
- Women and their children are followed from early pregnancy through childhood
- Women must be in a low-risk, singleton pregnancy, speak English, live within 30 minutes of UIUC, and not planning on moving
- For this study, we used information from **302 women**

IKIDS

ECHO
Environmental influences on Child Health Outcomes

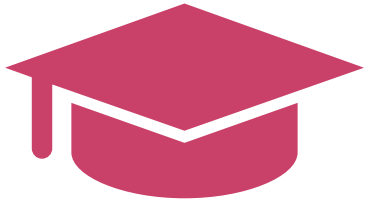
A research program supported by the National Institutes of Health

Characteristics of I-KIDS women

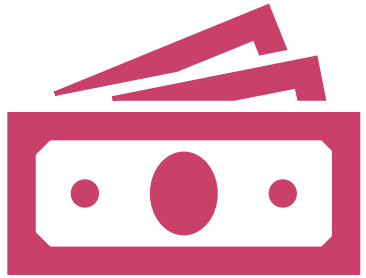


≥30 years old (59%)
N-H White (80%)

Employed (86%)

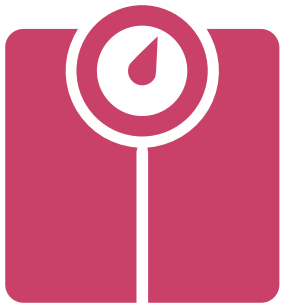


College educated (81%)

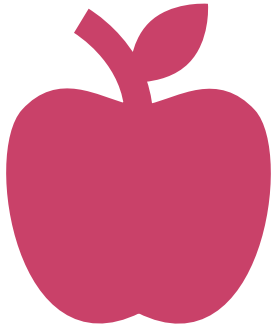


≥$60,000 (71%)

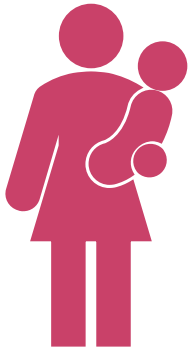
Non-smokers in the 1st trimester (96%)



Under/normal weight BMI (54%)



AHEI-2010 median: 55.8 (min: 28.1, max: 82.8)



No prior births (51%)

Pacyga and Haggerty et al., *Environment International*., 2022.

Outcome: Plasma hormone concentrations in early second trimester

13 weeks → **17 weeks** → **23 weeks** → **28 weeks** → **34 weeks** → **Birth**

- Women fasted 10-12 hours prior to blood draw
- 30-35 mL of blood drawn by certified phlebotomist
- Blood samples processed and stored at -80°C
- ELISA, University of Michigan Diabetes Research Center

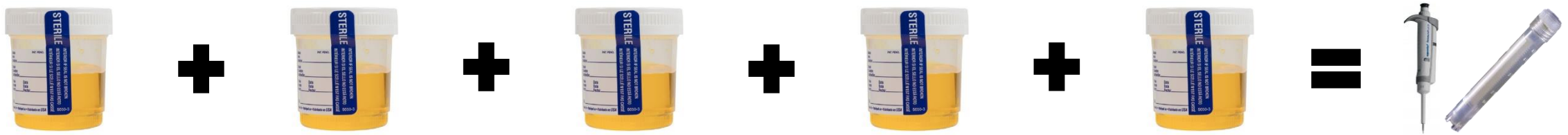
Sex-steroid hormones
Progesterone
Testosterone
Estradiol

Thyroid hormones
Total thyroxine (T4)
Free thyroxine (T4)
Thyroid stimulating hormone (TSH)

Ryva BA *et al.*, *Environment International*, 2024.

Exposure: EDC concentrations measured in pools of 5 first morning urines collected across pregnancy

13 weeks → **17 weeks** → **23 weeks** → **28 weeks** → **34 weeks** → **Birth**



Pooled Sample

Shin et al., *Environment International*, 2019; Vernet et al., *Epidemiology*, 2019.

Exposure: 31 urinary biomarkers measured in pooled urine reflect exposure to 22 EDCs

Phthalates								Replacements	
∑DEHP	**∑DiNP**	**DiDP**	**DOP**	**BBzP**	**DEP**	**∑DBP**	**∑DiBP**	**∑DiNCH**	**∑DEHTP**
MEHP MEHHP MEOHP MECPP	MCOP MiNP MONP	MCNP	MCPP	MBzP	MEP	MBP MHBP	MiBP MHiBP	MHiNCH MCOCH	MEHHTP MECPTP

Pooled Sample

Phenols			Other
Bisphenols	**Parabens**	**Others**	
Bisphenol A Bisphenol S Bisphenol F	Butylparaben Ethylparaben Methylparaben Propylparaben	Benzophenone-3 (BP-3) Triclosan (TCS) 2,4 dichlorophenol (2,4-DCP) 2,5 dichlorophenol (2,5-DCP)	Triclocarban

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Most women in I-KIDS had measurable levels of EDCs

- Most EDC biomarkers were measurable in >90% of the pooled urine samples
  - Butylparaben, bisphenol F, and triclocarban were below the lower limit of detection in >30% of pooled urine samples
- Urinary EDC concentrations in I-KIDS were similar to same aged women in the National Health and Nutrition Examination Survey (NHANES), except:

Biomarker	I-KIDS Median	NHANES Median
MEP (DEP metabolite)	25.0 ng/mL	34.4 ng/mL
MEHHTP (DEHTP metabolite)	8.7 ng/mL	6.0 ng/mL
MECPTP (DEHTP metabolite)	60.5 ng/mL	20.7 ng/mL

Pacyga et al., *Environment International*, 2022.

Using statistical mixtures methods to model our maternal EDC mixture

Important to select statistical mixtures methods based on the goals of the study!

Weighted Quantile Sum (WQS) Regression

Objective 1: Overall mixture association

Objective 2: Individual contributors

Objective 3: Non-linearities

Bayesian Kernel Machine Regression (BKMR)

Joubert BR *et al.*, *IJERPH* 2022. Image on the right courtesy of Marianthi-Anna Kioumourtzoglou.

19 EDC biomarkers were modeled in the mixture

Phthalates								Replacements	
∑DEHP	∑DiNP	DiDP	DOP	BBzP	DEP	∑DBP	∑DiBP	∑DiNCH	∑DEHTP
MEHP MEHHP MEOHP MECPP	MCOP MiNP MONP	MCNP	MCPP	MBzP	MEP	MBP MHBP	MiBP MHiBP	MHiNCH MCOCH	MEHHTP MECPTP

Pooled Sample

Phenols			Other
Bisphenols	**Parabens**	**Others**	
Bisphenol A Bisphenol S ~~Bisphenol F~~	~~Butylparaben~~ Ethylparaben Methylparaben Propylparaben	Benzophenone-3 (BP-3) Triclosan (TCS) 2,4 dichlorophenol (2,4-DCP) 2,5 dichlorophenol (2,5-DCP)	~~Triclocarban~~

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CENTERS FOR DISEASE CONTROL AND PREVENTION

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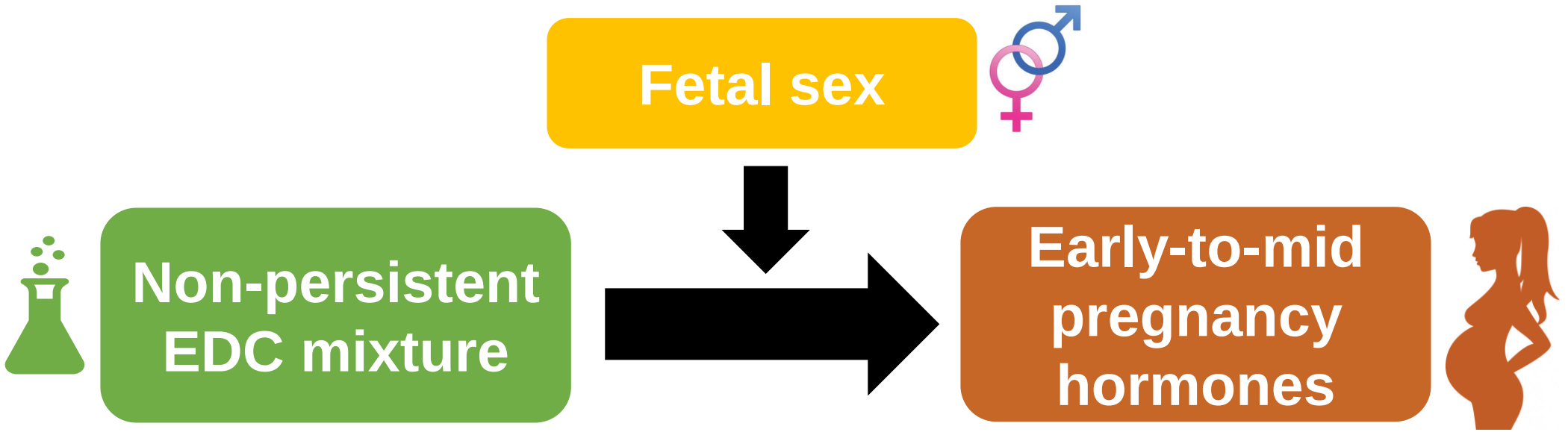

Objective 1: Overall mixture association

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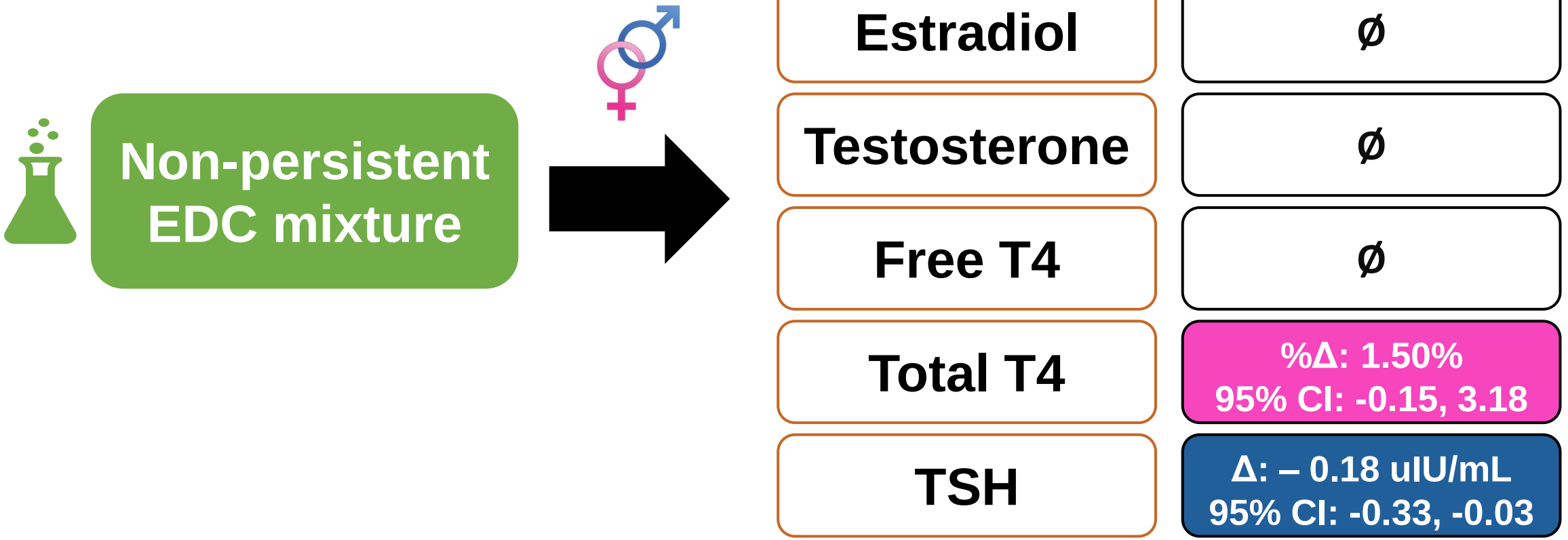
In all women, the EDC mixture was associated with lower testosterone and TSH using WQS regression models

Non-persistent EDC mixture

Progesterone	**ø**
Estradiol	**ø**
Testosterone	**%Δ: – 5.65% 95% CI: -9.79, -1.28**
Free T4	**ø**
Total T4	**ø**
TSH	**Δ: − 0.09 µIU/mL 95% CI: −0.20, 0.00**

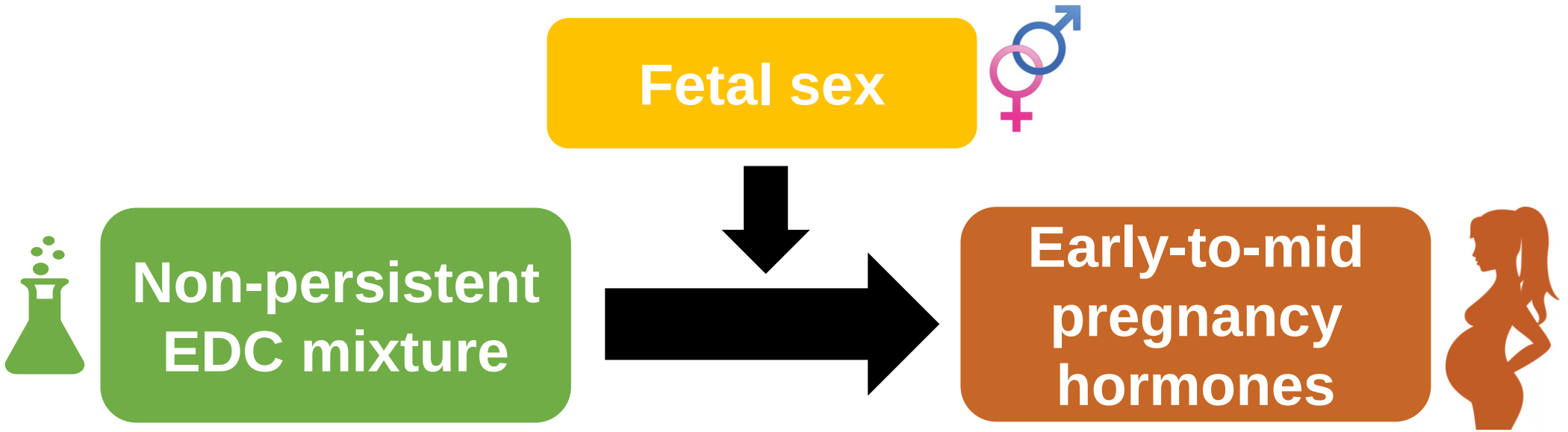
Ryva BA *et al.*, *Environment International*, 2024. Weighted Quantile Sum (WQS) regression models accounted for age, race/ethnicity, education, smoking, diet quality, perceived stress, parity, pre-pregnancy body mass index, and gestational age at blood collection. Both positively and negatively constrained WQS models were evaluated.

Associations of the EDC mixture with total T4 and TSH were fetal sex-specific in WQS regression models



Ryva BA *et al.*, *Environment International*, 2024. Weighted Quantile Sum (WQS) regression models accounted for age, race/ethnicity, education, smoking, diet quality, perceived stress, parity, pre-pregnancy body mass index, and gestational age at blood collection. Both positively and negatively constrained WQS models were evaluated.

Objectives



Objective 1: Overall mixture association

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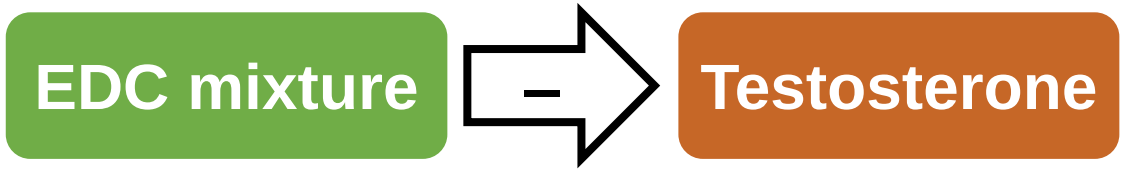
Triclosan, propylparaben, and dichlorophenols were responsible for associations with testosterone

All women



<u>"Bad actors" in mixture (weight, %)</u>

1. Triclosan (14%)
2. Propylparaben (13%)
3. 2,5-dichlorophenol (12%)
4. Bisphenol S (11%)
5. 2,4-dichlorophenol (8%)
6. ΣDEHTP (7%)

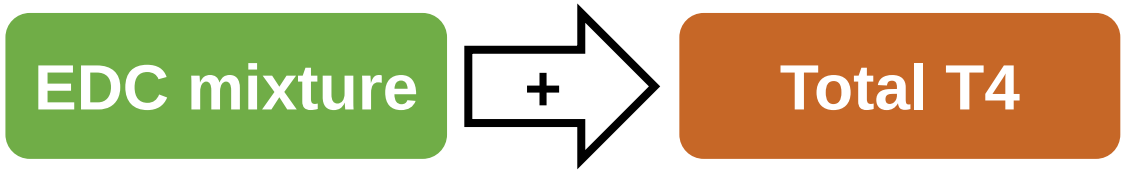
<u>Single chemical models (%Δ (95% CI))</u>

1. 2,4-dichlorophenol: -1.11 (-2.03, -0.17)
2. 2,5-dichlorophenol: -0.62 (-1.18, -0.06)
3. Propylparaben: -0.40 (-0.87, 0.07)
4. Triclosan: -0.37 (-0.86, 0.12)

Ryva BA *et al.*, *Environment International*, 2024. Weighted Quantile Sum (WQS) regression models accounted for age, race/ethnicity, education, smoking, diet quality, perceived stress, parity, pre-pregnancy body mass index, and gestational age at blood collection. Both positively and negatively constrained WQS models were evaluated.

MBzP and 2,5-dichlorophenol were responsible for associations with total T4 in women carrying females

Women carrying females



“Bad actors” in mixture (weight, %)

1. MBzP (14%)
2. 2,5-dichlorophenol (10%)
3. Propylparaben (10%)
4. 2,4-dichlorophenol (8%)
5. Benzophenone-3 (8%)
6. Bisphenol S (7%)

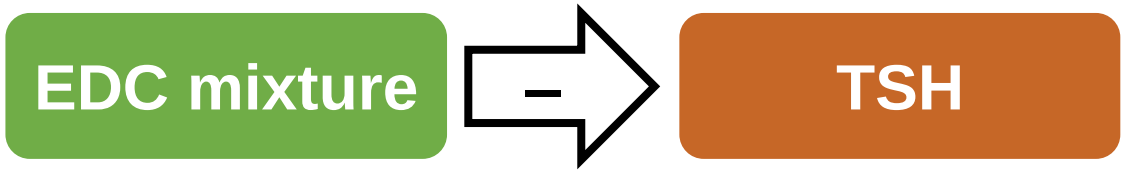
Single chemical models (%Δ (95% CI))

1. MBzP: 0.36 (0.12, 0.60)
2. 2,5-dichlorophenol: 0.27 (0.04, 0.49)

Ryva BA *et al.*, *Environment International*, 2024. Weighted Quantile Sum (WQS) regression models accounted for age, race/ethnicity, education, smoking, diet quality, perceived stress, parity, pre-pregnancy body mass index, and gestational age at blood collection. Both positively and negatively constrained WQS models were evaluated.

Ethylparaben was responsible for associations with TSH in women carrying males

Women carrying males



“Bad actors” in mixture (weight, %)

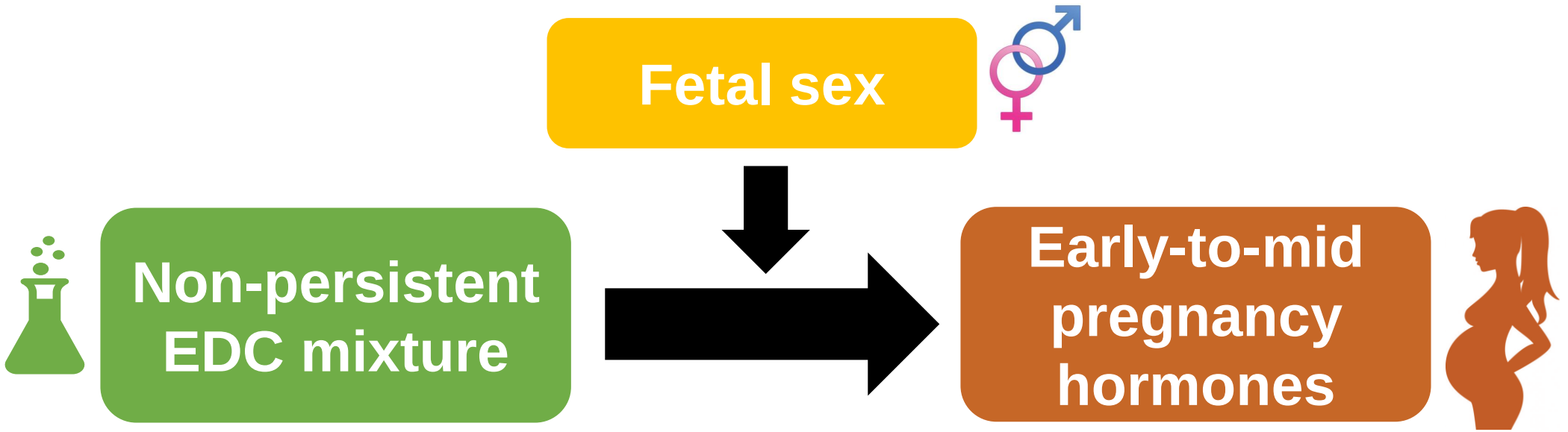
1. 2,5-dichlorophenol (17%)
2. Ethylparaben (12%)
3. Bisphenol A (7%)
4. MEP (7%)
5. ΣDiNP (7%)
6. MCNP (6%)
7. Triclosan (6%)

Single chemical models (uIU/mL Δ (95% CI))

1. Ethylparaben: -0.01 (-0.02, 0.00)
2. MBzP: 0.02 (0.00, 0.04)
3. ΣDBP: 0.04 (0.01, 0.07)

Ryva BA *et al.*, *Environment International*, 2024. Weighted Quantile Sum (WQS) regression models accounted for age, race/ethnicity, education, smoking, diet quality, perceived stress, parity, pre-pregnancy body mass index, and gestational age at blood collection. Both positively and negatively constrained WQS models were evaluated.

Objectives

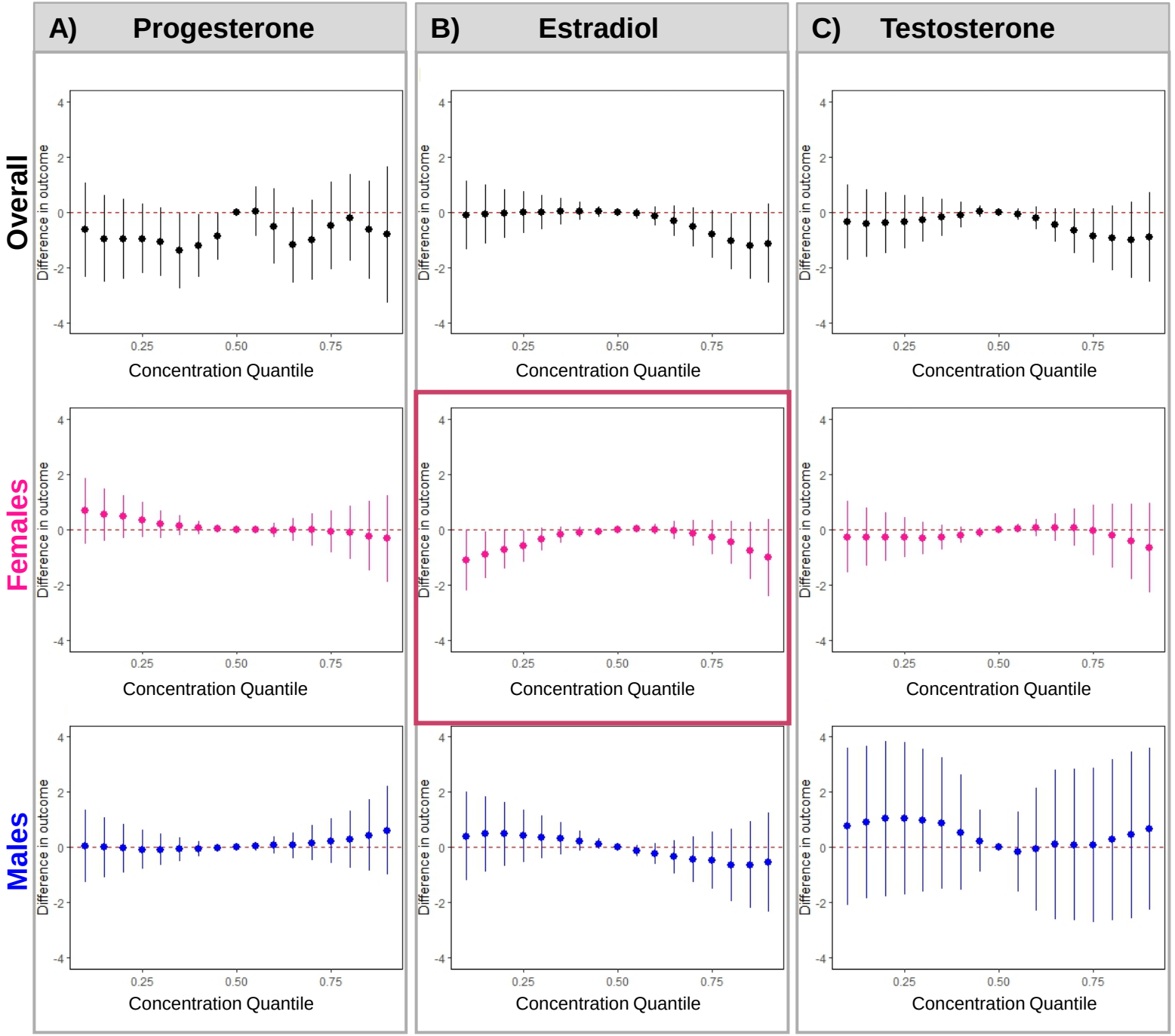


Objective 1: Overall mixture association

Objective 2: Individual contributors

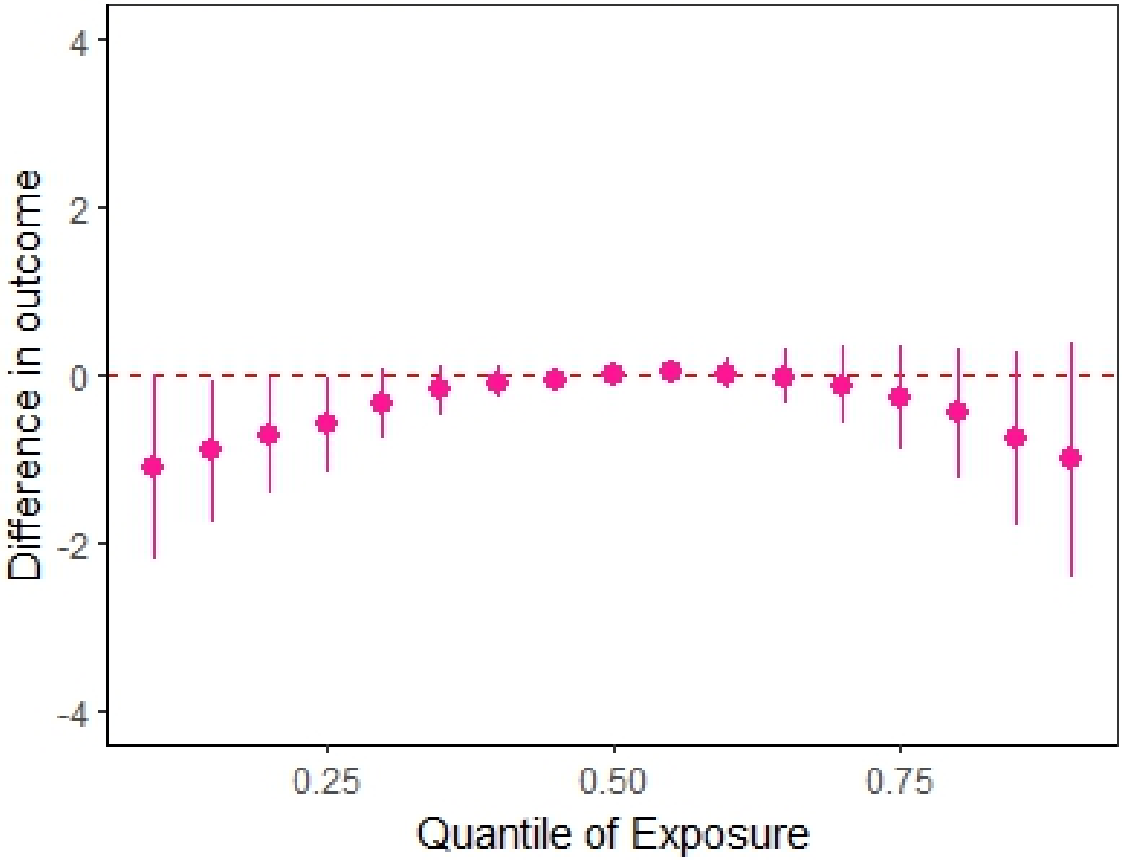
Objective 3: Non-linearities

BKMR only identified a non-linear association between the EDC mixture and estradiol



Ryva BA *et al.*, *Environment International*, 2024.

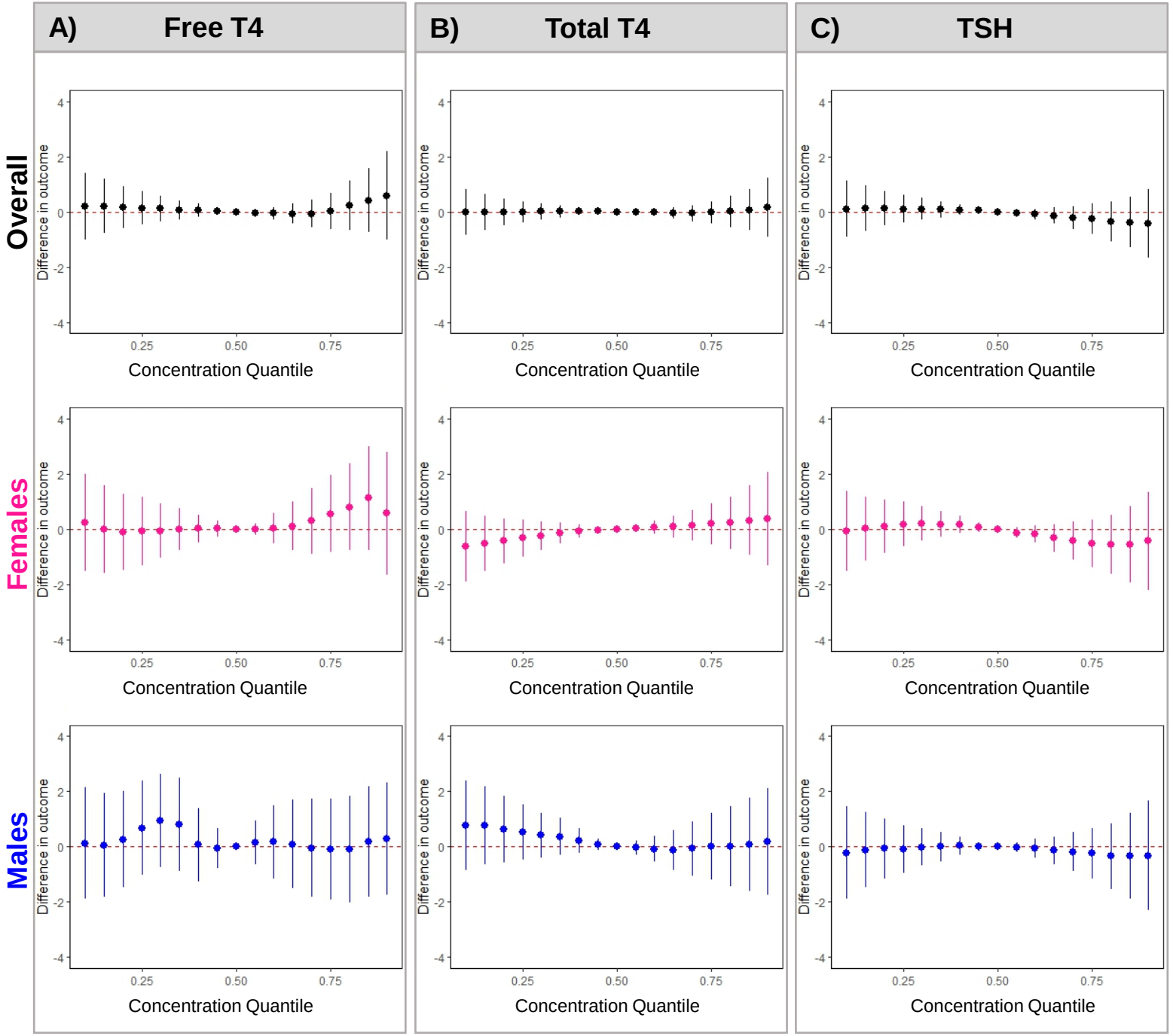
Using BKMR, the EDC mixture was non-linearly associated with estradiol in women carrying females



- Exhibits a non-monotonic exposure-response relationship where the mixture is negatively associated with estradiol at lower and higher levels of exposure
- Future experimental studies are needed to understand the exact mechanisms responsible
- Relationship driven by bisphenol A and propylparaben

Ryva BA *et al*., *Environment International*, 2024.

BKMR did not identify any non-linear associations of the EDC mixture with thyroid hormones



Ryva BA *et al.*, *Environment International*, 2024.

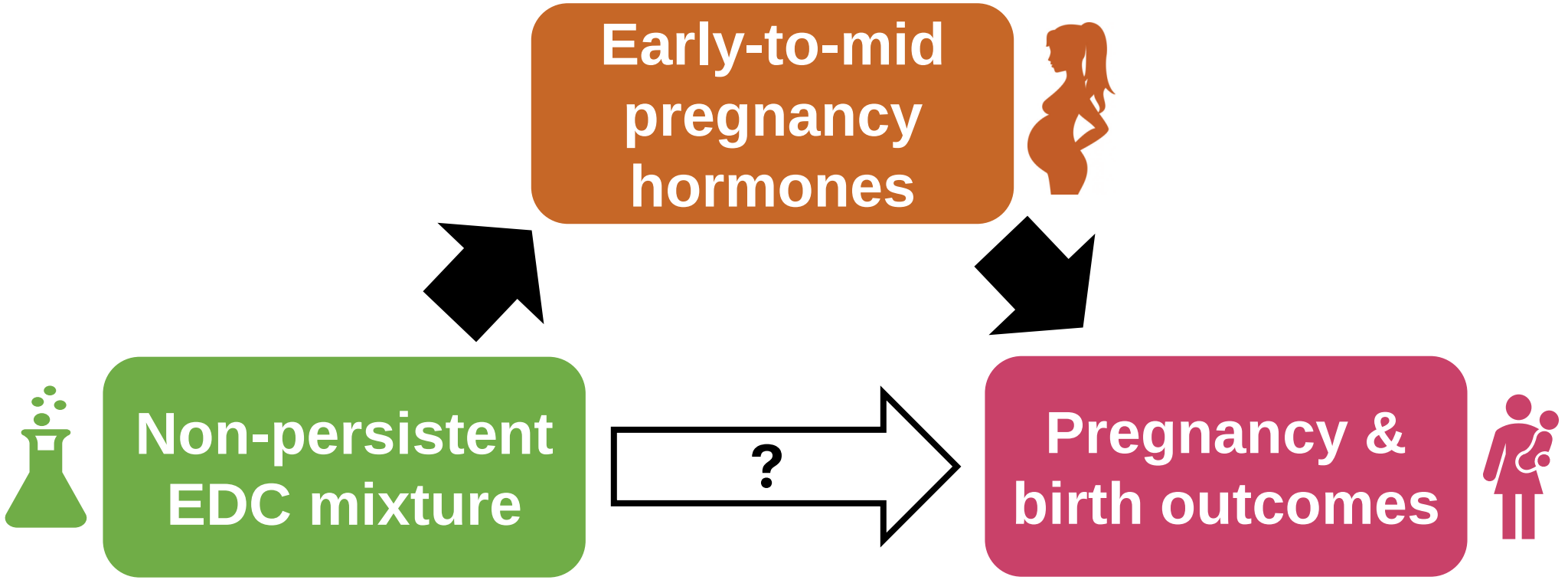
Today’s presentation

- Background & research gaps
  - Replacement chemicals
  - EDC mixtures
  - Non-linearities
  - Fetal sex
- Objectives
- Methods
- Results
- Conclusions & future directions

Conclusions

- The EDC mixture was associated with altered maternal sex-steroid and thyroid hormone levels
- Provides further insights about hormone disrupting potential of select EDCs in pregnancy
- Mixture findings indicate that some associations may be non-linear
- Future studies should investigate how these associations relate to pregnancy outcomes

Future directions: Associations of the EDC mixture with pregnancy and birth outcomes



Methyl and propyl parabens were associated with smaller birth size in female newborns

ELSEVIER

Environmental Research
Volume 214, Part 3, November 2022, 114078

Maternal diet quality moderates associations between parabens and birth outcomes

Diana C. Pacyga [a b], Nicole M. Talge [c], Joseph C. Gardiner [c], Antonia M. Calafat [d], Susan L. Schantz [e f], Rita S. Strakovsky [a b]

Methyl & propyl parabens

Fetal sex ♀

Birth weight
Body length

Phthalate/replacement mixture was associated with lower weight gain in women carrying females

ELSEVIER

Science of The Total Environment
Volume 855, 10 January 2023, 158788

Associations of individual and cumulative urinary phthalate and replacement biomarkers with gestational weight gain through late pregnancy

Diana C. Pacyga [a b], Marisa A. Patti [c], George D. Papandonatos [d], Diana K. Haggerty [a], Antonia M. Calafat [e], Joseph C. Gardiner [f], Joseph M. Braun [c], Susan L. Schantz [g h], Rita S. Strakovsky [a b]

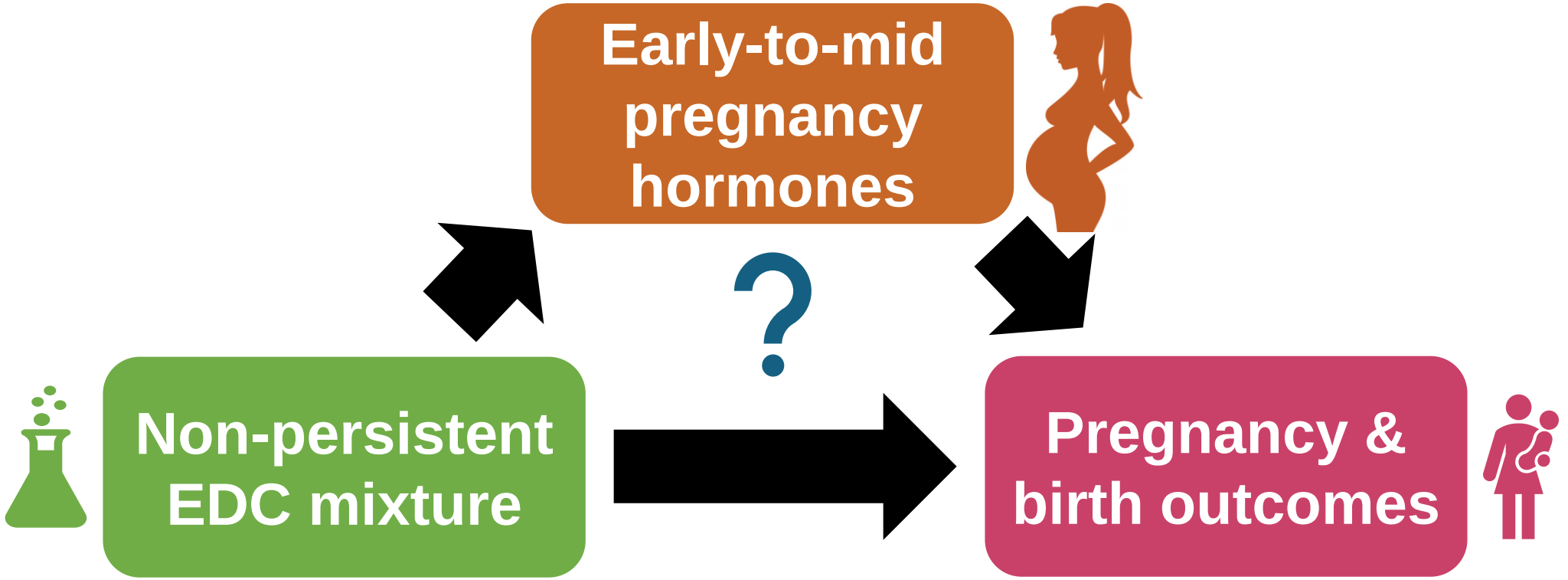
Phthalate & replacement mixture

Driven by DEHP

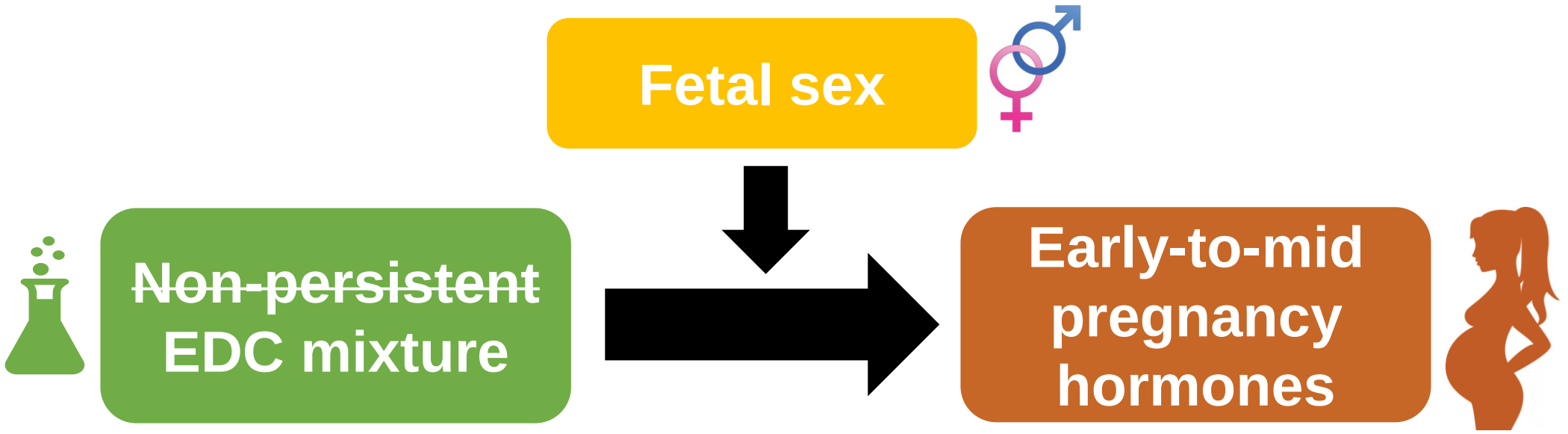
Fetal sex ♀

Gestational weight gain

Future directions: EDCs with pregnancy and birth outcomes – can hormonal disruption explain this?



Future directions: What about other chemicals to which pregnant women are ubiquitously exposed?



Individual PFAS, not their mixture, were associated with altered maternal sex-steroid hormone levels

International Journal of Hygiene and Environmental Health
Volume 259, June 2024, 114380

Associations of per- and polyfluoroalkyl substances with maternal early second trimester sex-steroid hormones

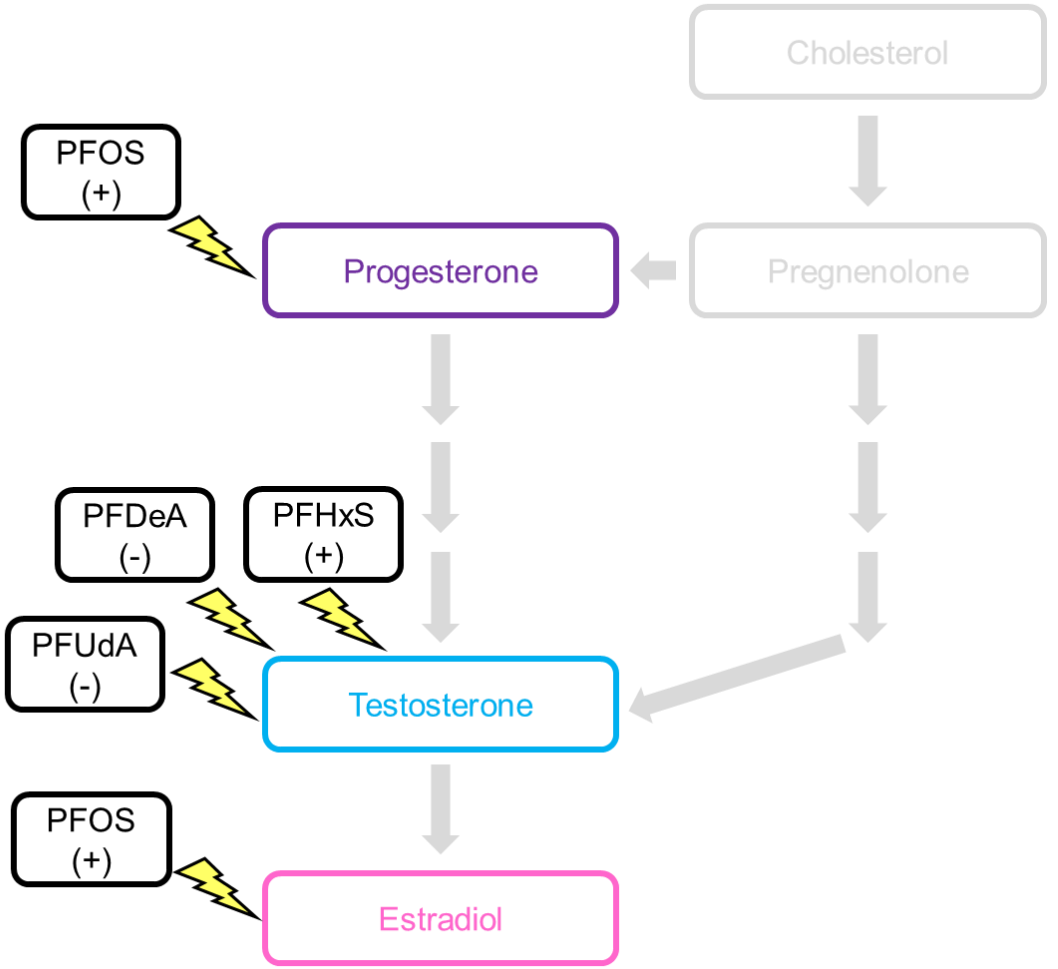
Diana C. Pacyga [a b c], George D. Papandonatos [d], Libeth Rosas [e], Jason Whalen [f], Sabrina Smith [g], June-Soo Park [g h], Joseph C. Gardiner [i], Joseph M. Braun [j], Susan L. Schantz [e k], Rita S. Strakovsky [a b]

Is prenatal PFAS exposure associated with altered maternal mid-pregnancy sex steroid hormone levels?

✓ PFAS Individually

🚫 PFAS as Mixture

🚫 Fetal Sex Differences



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Thank you! Questions?

ELSEVIER

Environment International

Volume 183, January 2024, 108433

Full length article

Associations of urinary non-persistent endocrine disrupting chemical biomarkers with early-to-mid pregnancy plasma sex-steroid and thyroid hormones

Brad A. Ryva [a b c], Diana C. Pacyga [c d], Kaitlyn Y. Anderson [b], Antonia M. Calafat [e], Jason Whalen [f], Max T. Aung [g], Joseph C. Gardiner [h], Joseph M. Braun [i], Susan L. Schantz [j k], Rita S. Strakovsky [c d]

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