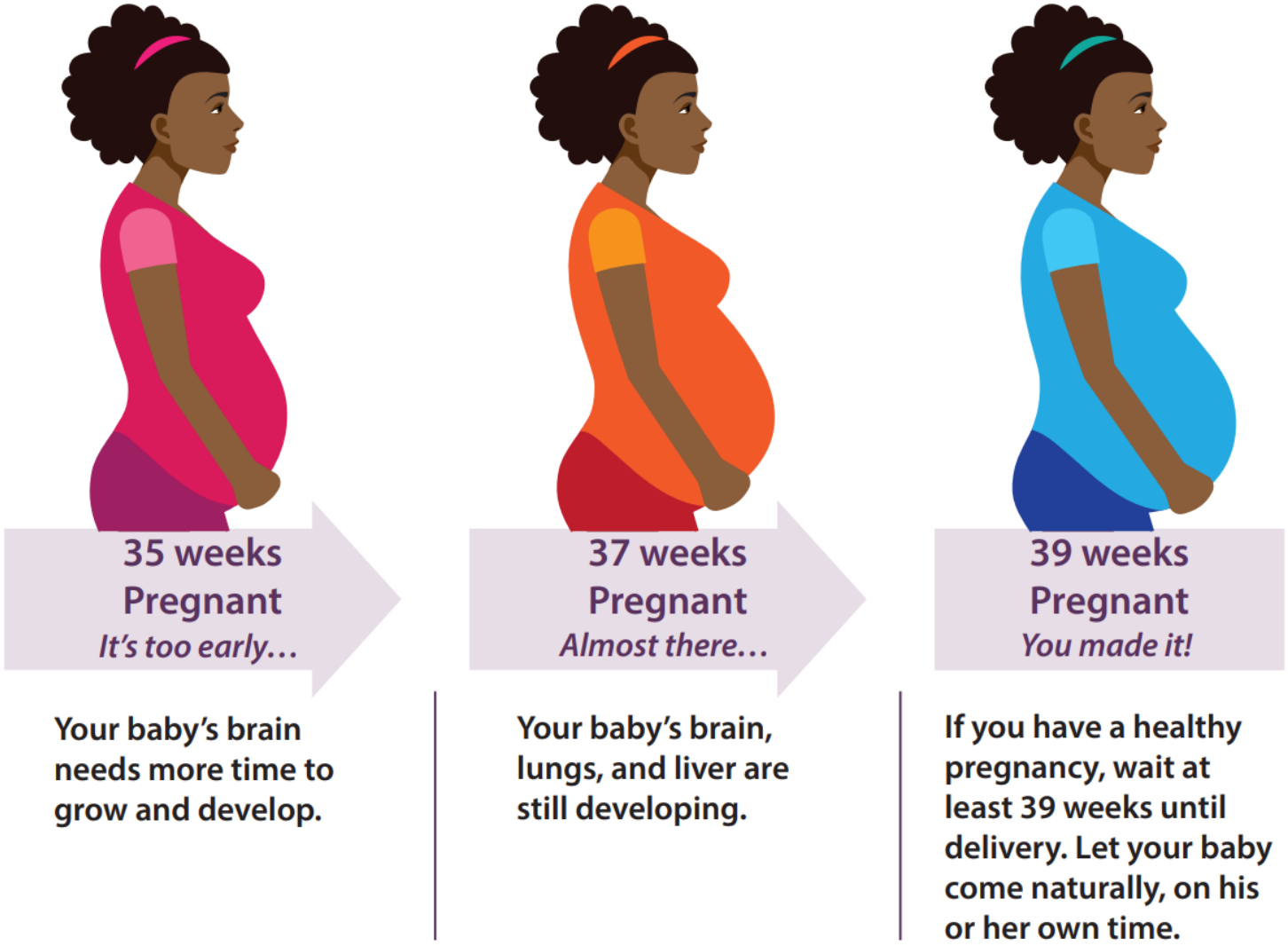
G-computation for hypothetical interventions: Applied example of phthalate mixtures in the Pooled Phthalate and Preterm Birth Study

Preconference Workshop for
ISES-ISEE 2025

PRETERM BIRTH IS AN IMPORTANT OUTCOME

Fetal development occurs throughout pregnancy, including the final weeks and months



CDC 2022 , Preterm birth graphic

PHTHALATE EXPOSURE

Environmental exposure sources

- Personal care products
- Vinyl plastics
- Food and beverage packaging

Absorption and metabolism

- Easy exposure through multiple routes
- Quick metabolism and excretion

Associated health outcomes

- Hormone disruption
- Infant reproductive tract and neurologic development

BIOLOGIC PLAUSIBILITY OF PHTHALATES AND PRETERM BIRTH

Oxidative stress and inflammation dysregulation

- Phthalates associated with oxidative stress and inflammation biomarkers in pregnant women
- Oxidative stress and inflammation pathways are well-established precursors of preterm birth

Placental dysfunction

- Phthalate exposure associated with expression of genes associated with trophoblast differentiation
- Differentiation issues are risk factors for preterm delivery

PRIOR WORK IN PHTHALATES AND PRETERM BIRTH

	LIFECODES Ferguson et al. 2014, *JAMA Pediatrics*	TIDES Ferguson et al. 2019, *Environ Int*	PROTECT Ferguson et al. 2019, *Environ Int*
MEP	1.11 (0.93, 1.32)	1.12 (0.90, 1.41)	0.98 (0.73, 1.32)
MBP	**1.27 (0.99, 1.63)**	**1.32 (0.93, 1.89)**	**1.42 (1.07, 1.88)**
MiBP	0.98 (0.72, 1.34)	**1.28 (0.86, 1.91)**	**1.32 (1.02, 1.71)**
MBzP	1.09 (0.86, 1.38)	1.06 (0.80, 1.41)	1.09 (0.84, 1.42)
ΣDEHP	**1.33 (1.04, 1.70**	**1.33 (0.87, 2.06)**	0.92 (0.69, 1.22)
MCPP	1.19 (0.95, 1.49)	1.07 (0.82, 1.39)	1.18 (0.92, 1.51)
MCOP	--	1.07 (0.83, 1.40)	1.08 (0.83, 1.41)
MCNP	--	1.17 (0.85, 1.61)	1.14 (0.88, 1.47)

DEHP and MBP metabolites

DEHP, MBP, and MiBP metabolites

MBP and MiBP metabolites

PHTHALATES AND GESTATIONAL AGE IN OTHER STUDIES

Reference	N preterm	Urine measures	Associations w/ longer gestation	Associations w/ shorter gestation
Santos 2021	35	3		
Hu 2020	115	1		
Gao 2019	134	3		MMP
Bloom 2019	28	1		
Huang 2018	--	1	MBzP, ∑DEHP	
Casas 2016	2	2		
Polanska 2016	--	1		MEP
Shoaff 2016	--	2	MBP, MCPP	
Watkins 2016	2	2		∑DBP (females only)
Weinberger 2014	7	1		∑DEHP
Suzuki 2010	2	1		
Adibi 2009	14	1	∑DEHP	
Meeker 2009	30	1		∑DEHP, MBP, MCPP
Whyatt 2009	--	1		∑DEHP
Wolff 2008	--	1	∑Low-MWP, ∑DEHP	

Small # preterm **One urine sample** **Predominantly null findings**

POOLED STUDY OF PHTHALATE AND PRETERM BIRTH (PPP)

Our primary research questions within the PPP study were:

- Study 1: Are phthalates associated with preterm birth?
  Welch et al., *JAMA Pediatrics*. 2022 *(preworkshop reading)*
- Study 2: Do racial/ethnic disparities in phthalate exposure influence preterm birth?
  Welch et al., *Environmental Health Perspectives*. 2023
- Study 3: Are there key developmental windows of susceptibility?
  Friedman et al., *Environment International. 2025*

COHORT IDENTIFICATION: 16 US STUDIES

Study	N	Preterm n (%)
PROTECT	**1101**	**100 (9.1)**
TIDES	779	69 (8.9)
LIFECODES	480	130 (27.1)
Healthy Start	444	14 (3.2)
CHAMACOS	429	27 (6.3)
CCCEH	389	14 (3.6)
HOME	389	37 (9.5)
EARTH	385	27 (7.0)
MSSM	362	28 (7.7)
SFF	353	17 (4.8)
RDS	318	28 (8.8)
HEBC	189	12 (6.3)
MARBLES	179	12 (6.7)
EPS	126	5 (4.0)
MMIP	68	2 (2.9)
Rutgers	54	17 (31.5)
Total	**6045**	**539 (9)**

- Systematic review to identify US studies with prenatal urinary phthalate metabolites
- Identified 21 unique prospective studies
- 5 studies excluded
  - 4 with sample size ≤50
  - 1 did not respond

STUDY DESIGN CHARACTERISTICS

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

Key design components

Geographic. Participants recruited from across the US and Puerto Rico

Gestational. Most (10/16) studies recruited in the first half of pregnancy

Temporal. Deliveries occurred across 3 decades

EXPOSURE ASSESSMENT

Mixture analyses evaluate 9 metabolites measures in ~98% of participants

Metabolite	Abbreviation	Cohorts with measures
Mono-ethyl phthalate	MEP	16
Mono-n-butyl phthalate	MBP	16
Mono (2-ethyl-5-hydroxyhexyl) phthalate	MEHHP	16
Mono (2-ethyl-5-oxyhexyl) phthalate	MEOHP	16
Mono-isobutyl phthalate	MiBP	15
Mono-benzyl phthalate	MBzP	15
Mono (2-ethylhexyl) phthalate	MEHP	16
Mono (3-carboxypropyl) phthalate	MCPP	14
Mono (2-ethyl-5-carboxypentyl) phthalate	MECPP	14

ANALYTIC DATASET

Multiple imputation

- Missing covariates
- Phthalate metabolite concentrations <LOD

Urine dilution standardization

- Covariate standardization (based on O'Brien et al. 2016, *EHP* and Kuiper et al. 2022, *Epidemiology*) to combine dilution measures & address possible bias

Exposures modeled as geometric mean of repeated measurements

STUDY 1

Question: Are phthalates associated with preterm birth?

Research

JAMA Pediatrics | Original Investigation

Associations Between Prenatal Urinary Biomarkers of Phthalate Exposure and Preterm Birth
A Pooled Study of 16 US Cohorts

Barrett M. Welch, PhD; Alexander P. Keil, PhD; Jessie P. Buckley, PhD; Antonia M. Calafat, PhD; Kate E. Christenbury, MBA; Stephanie M. Engel, PhD; Katie M. O'Brien, PhD; Emma M. Rosen, MSPH; Tamarra James-Todd, PhD; Ami R. Zota, ScD; Kelly K. Ferguson, PhD; and the Pooled Phthalate Exposure and Preterm Birth Study Group

G-COMPUTATION

Hypothetical question: If we could reduce the exposure of our study population to phthalates, would it reduce preterm births?

Why g-computation? Our question requires us to compare our observed scenario to an unobserved scenario. We chose g-computation because:

- Provides an intuitive way to: 1) make comparisons and 2) present results
- Highly flexible statistical programming that enabled us to create many scenarios and accommodate a mixture of predictors

Output: Probability of preterm birth following hypothetical interventions to reduce concentrations of the phthalate metabolite mixture

HOW IT WORKS

1. Fit a logistic regression model with additive terms for our phthalates and covariates

2. Create hypothetical data by copying your original data, then change the concentrations of your intervened columns
   - Example: Reduce the concentration of each exposure by 10% (observed*0.90), but ensure it doesn't go below minimum in observed data.

3. Generate predicted probability of preterm birth for each participant under two scenarios, observed and intervention data. Can be standardized to facilitate interpretation.

4. Compare mean values of predictions

5. Use nonparametric bootstrapping (sampling with replacement across 2000 iterations) to generate 95% confidence intervals (2.5^{th} and 97.5^{th} percentiles)

G-COMPUTATION ASSUMPTIONS (FOR CAUSALITY!)

G-computation can be used to improve interpretability of results **AND/OR** infer potential causal effects. However, for the latter you must assume:

- **Correct model specification**. An assumption that our primary model correctly represents the true relationship between urinary phthalates and preterm birth.
- **Exchangeability**. An assumption that there is no outstanding source of selection bias or confounding in our results.
- **Positivity**. An assumption that there is a nonzero probability that phthalate metabolite concentrations can take on all possible values under the hypothetical interventions
- **No measurement error of exposure**. An assumption that urinary phthalates were measured without systematic error.
- **Treatment variation irrelevance**. An assumption that the effect of reducing phthalates via unspecified interventions will not product unanticipated impacts that adversely influence preterm birth.

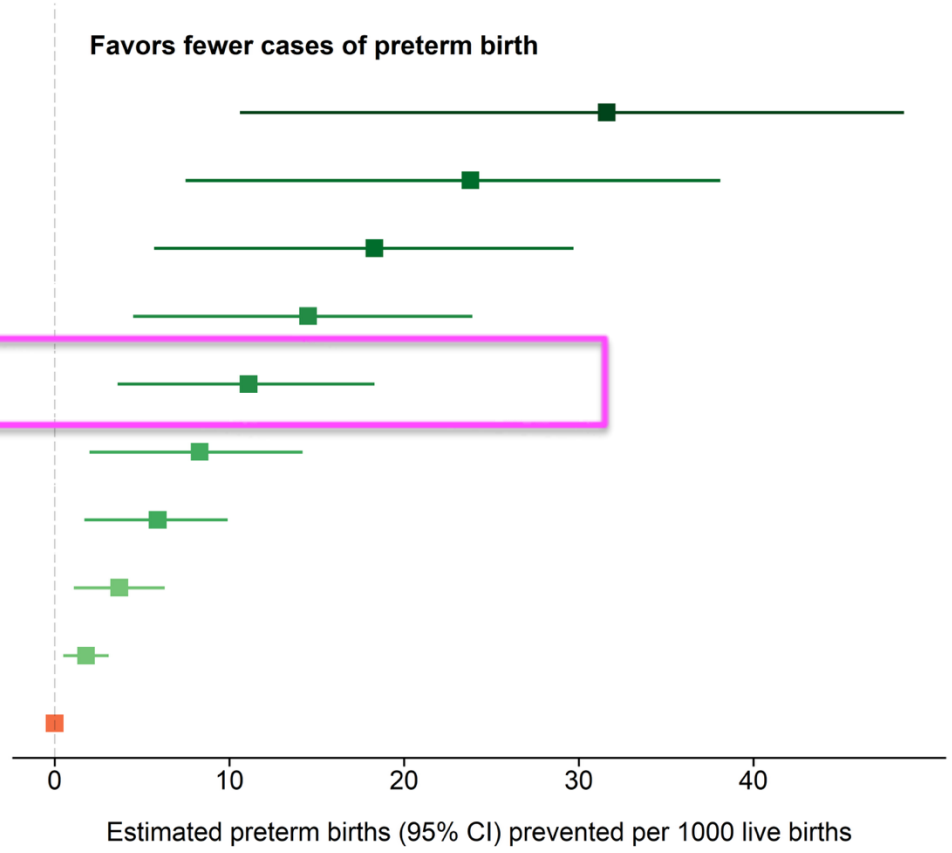
For more context on these assumptions in our study, see **eMethods E**
For more context on applying assumptions for mixtures setting, see **Keil et al. 2021, *Am J Epidemiol***

JOINT EFFECT OF INTERVENING ON PHTHALATE MIXTURE

We created hypothetical interventions for metabolite mixture that ranged from 10-90% reductions

We highlighted results towards the middle of that intervention group (50%)

Exposure intervention	Estimated preterm births (95% CI) prevented per 1000 live births
90% reduction	31.6 (10.6, 48.6)
80% reduction	23.8 (7.5, 38.1)
70% reduction	18.3 (5.7, 29.7)
60% reduction	14.5 (4.5, 23.9)
50% reduction	11.1 (3.6, 18.3)
40% reduction	8.3 (2, 14.2)
30% reduction	5.9 (1.7, 9.9)
20% reduction	3.7 (1.1, 6.3)
10% reduction	1.8 (0.5, 3.1)
0% reduction	Reference



For a hypothetical intervention reducing exposure to the phthalate mixture by 50%,
we would expect to prevent roughly 11 preterm births per 1000 live births (~10% of preterms)

Welch et al. 2022, *JAMA Ped*

STUDY 2

Focus: Do racial and ethnic disparities in phthalate exposure influence preterm birth?

PMID: 38117586

Research

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP12831.

Racial and Ethnic Disparities in Phthalate Exposure and Preterm Birth: A Pooled Study of Sixteen U.S. Cohorts

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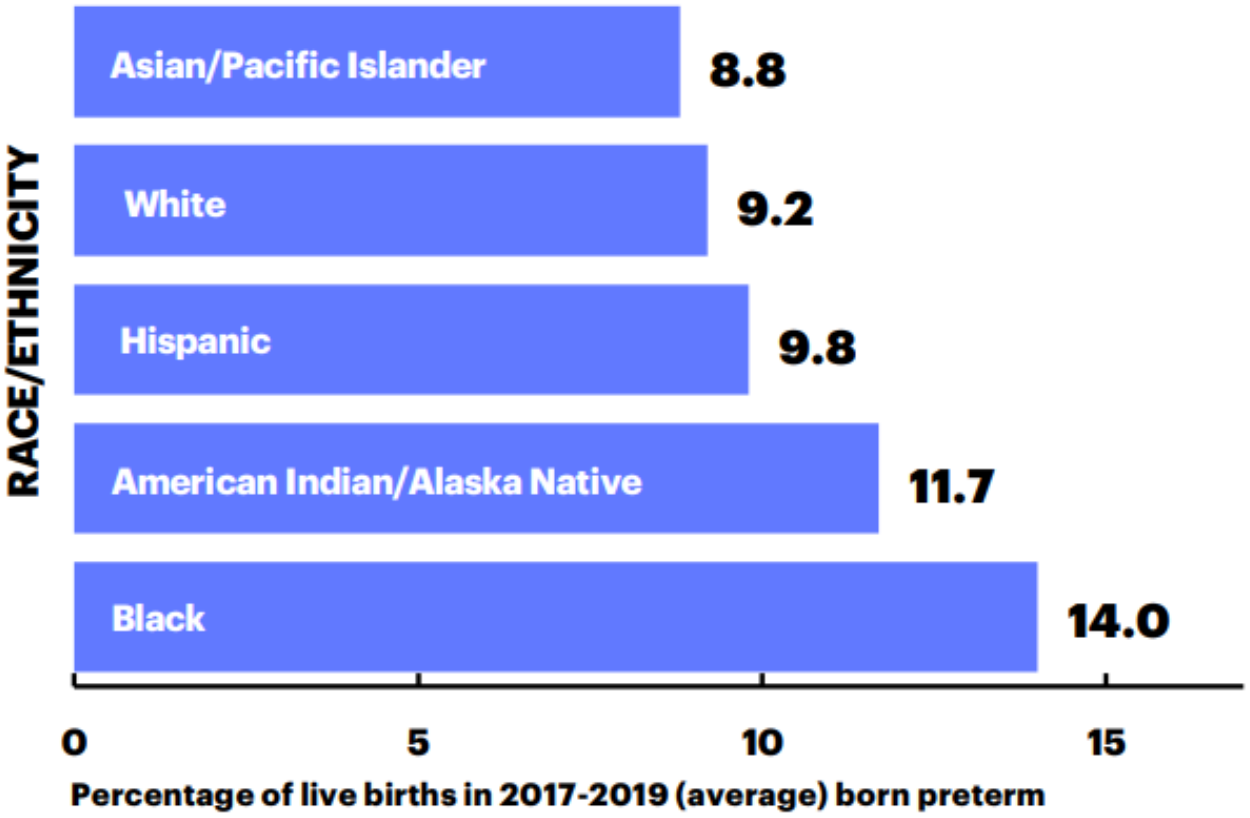
RACIAL AND ETHNIC DISPARITIES IN PRETERM BIRTH



The US disparity ratio of preterm birth is **1.27** and has worsened over time.

Preterm birth rate among Black women is **51% higher** than the among all others

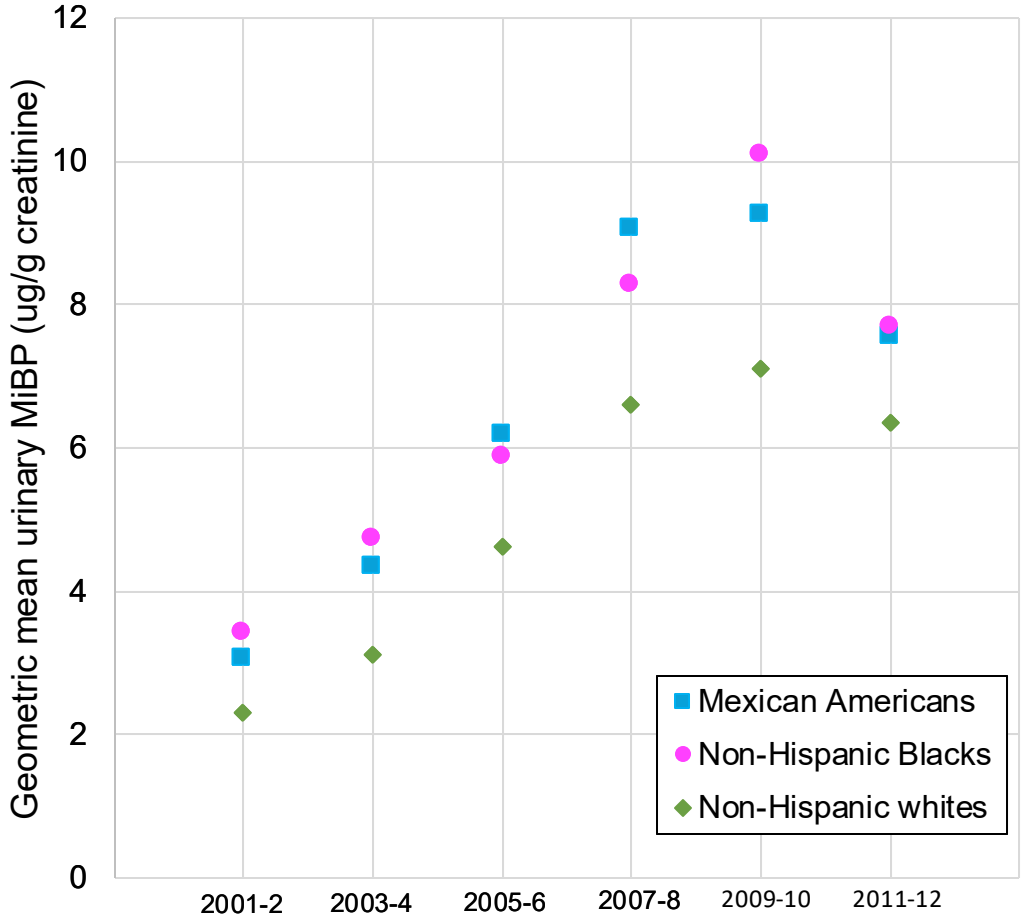
Differences are <u>not</u> due to genetics

Therefore, social and environmental exposures must play an important role

March of Dimes 2021, Preterm Birth Report Card

RACIAL AND ETHNIC DISPARITIES IN PHTHALATE EXPOSURE

Urinary MiBP concentrations by race and ethnicity in NHANES 2001-2012



CDC Fourth National Exposure Report, 2015

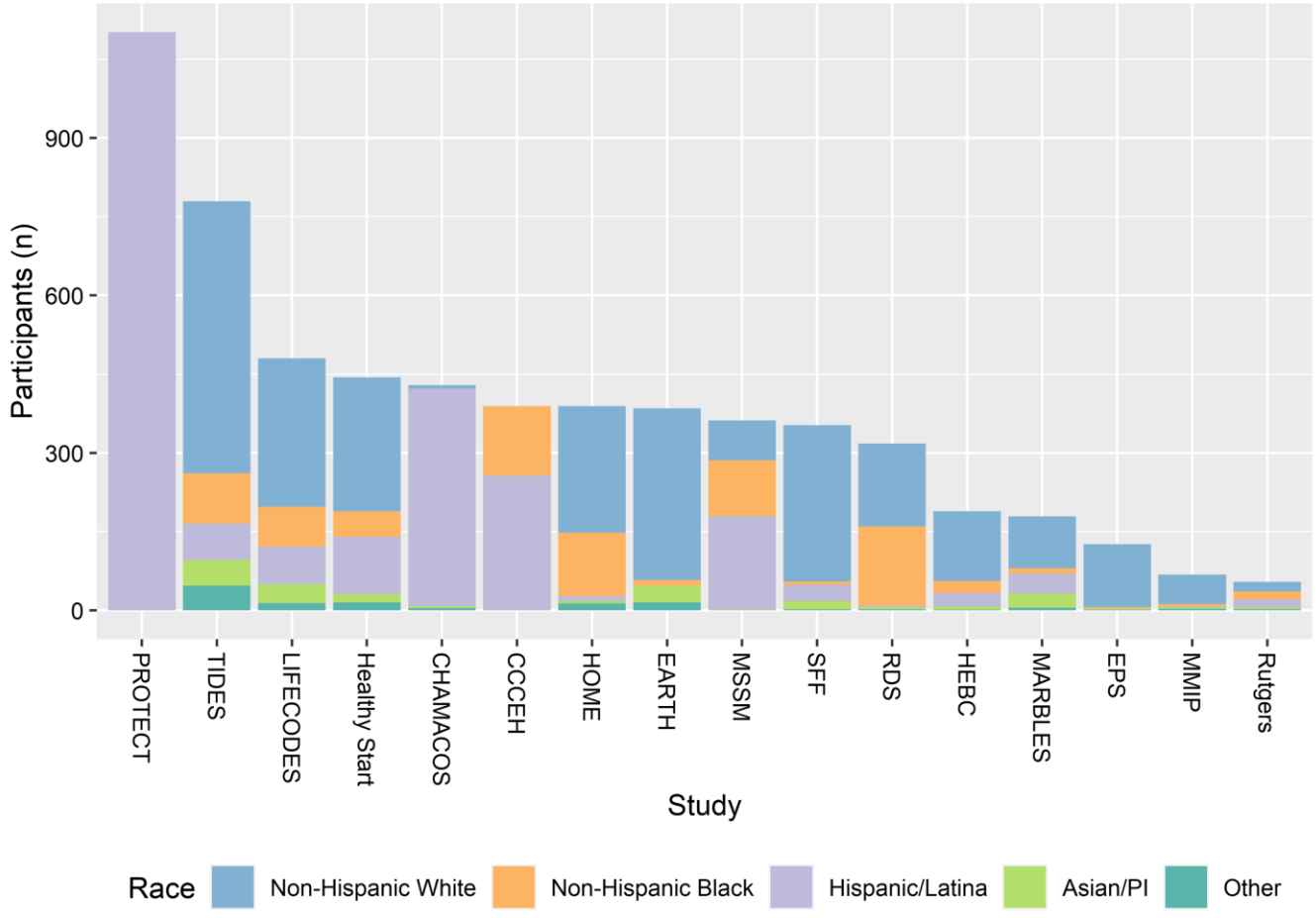
Exposure to phthalates (among other chemicals) disproportionately affects people of color. The same issue exists for pregnant women.

Disparities can be attributed to factors driven by systemic and institutionalized racism, e.g.:

- Personal care product use (Zota and Shamasunder 2017, *AJOG, "The environmental injustice of beauty"*)
- Food landscapes in racially segregated areas (Kwate et al. 2009, *Health Place*)

RACE AND ETHNICITY IN THE POOLED STUDY

The Pooled Study of Phthalate Exposure and Preterm Birth is uniquely suited to examine race differences in exposure during pregnancy because of its sample size and diversity

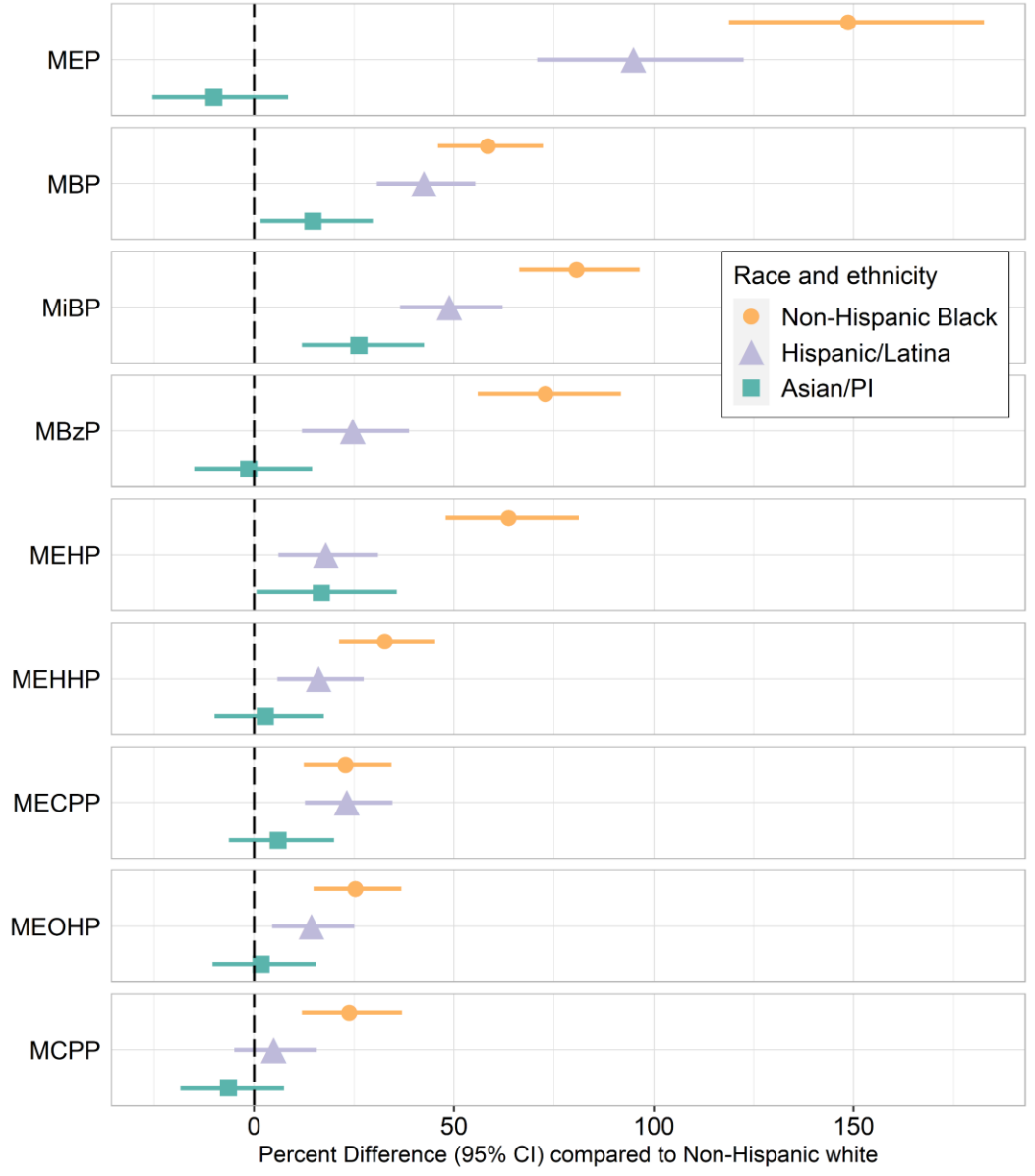


Welch et al. 2023, *EHP*

RACIAL AND ETHNIC DISPARITIES IN PHTHALATES

Examined proportional differences in covariate-adjusted* geometric means (GMs)

- Non-Hispanic Black participants had 25-150% higher phthalate metabolite levels compared to non-Hispanic white participants
- Hispanic/Latina participants had up to 50% higher phthalate levels compared to non-Hispanic white participants
- Greatest differences in exposure were for phthalates typically found in personal care products



*Adjusted for maternal age, education, pre-pregnancy BMI, and study

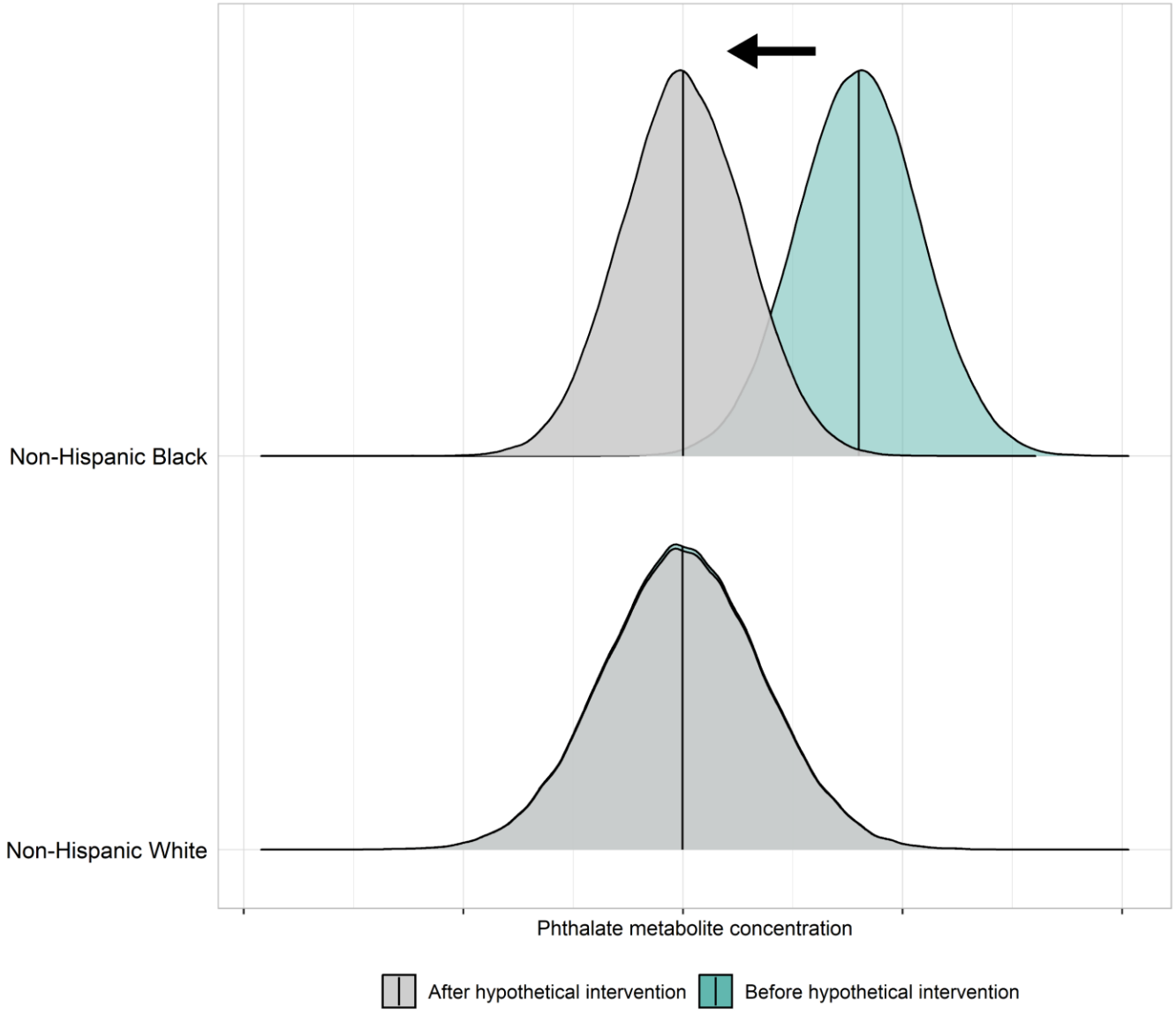
Welch et al. 2023, *EHP*

G-COMPUTATION APPROACH TO REDUCE EXPOSURE DISPARTIES

Central question: Could equitably reducing or eliminating disparities in phthalate exposure reduce rates of preterm birth?

Approach: Among each group with higher exposure (NH-Black, Hispanic/Latina), implement a reduction to each metabolite in the phthalate mixture that would make their distribution approximately equal to group with lower exposure (NH-White)

EQUITABLE REDUCTION IN PHTHALATE METABOLITE

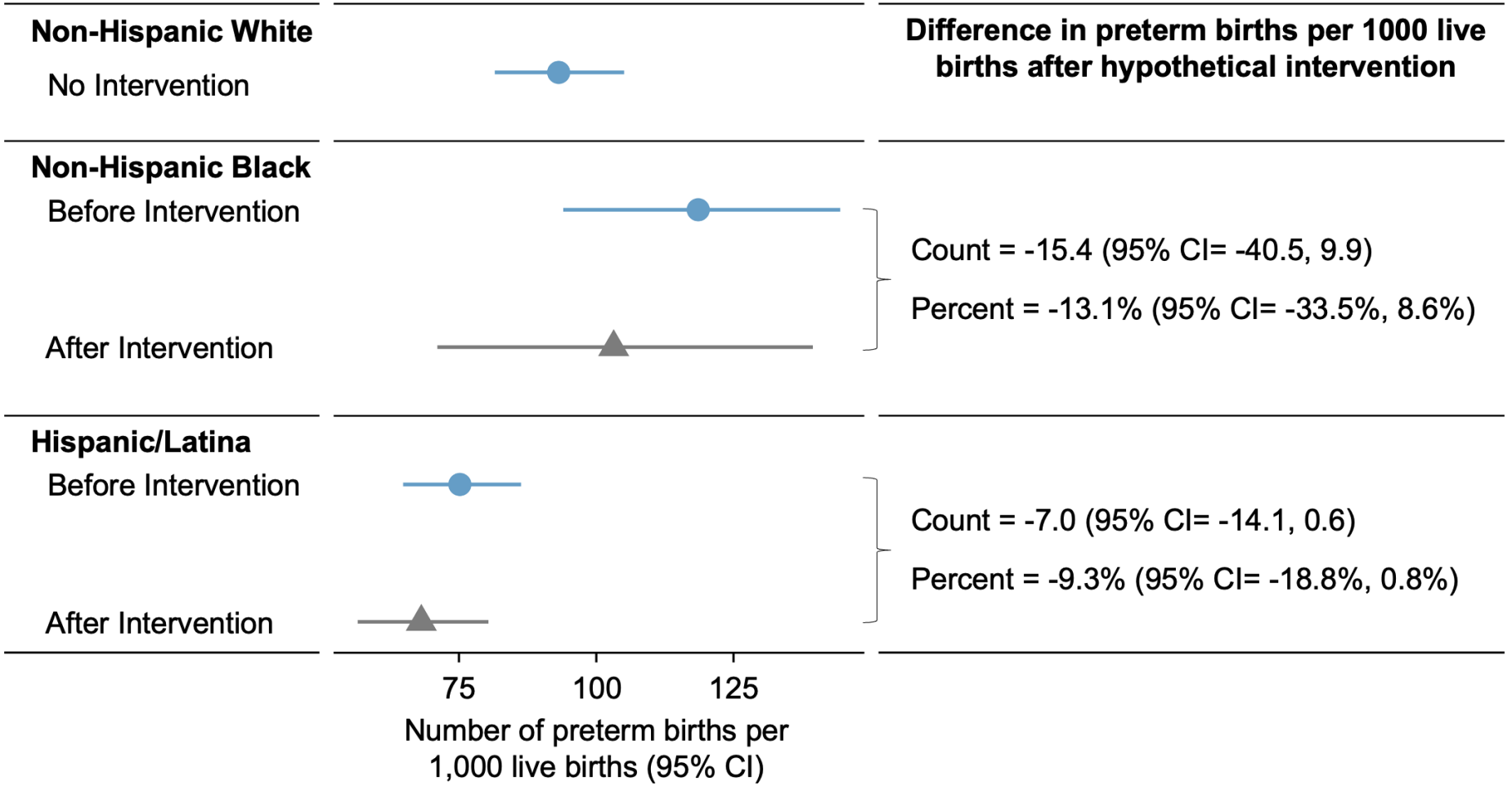


Apply percent reduction to exposure that shifts the overall distribution

Apply same process to all metabolites in the mixture, then repeat for Hispanic/Latina

Welch et al. 2023, *EHP*

RESULTS OF HYPOTHETICAL INTERVENTION



Potentially large reductions in preterm birth were observed between each group

We provide careful interpretations of the results in context of confidence intervals

INTERPRETATION OF RESULTS

Are the hypothesized reductions worth pursuing?
Yes. Reducing the disparities in phthalate exposures were associated with fewer preterm births among systematically marginalized groups

Are the hypothesized reductions possible?
Yes. The hypothetical exposure distributions we modeled already exist among non-Hispanic White participants

How can hypothesized reductions happen?

- Interventions must account for intersectionality of racism, sexism, and social inequity
- Will require combined approach to personal care products (hair products targeted to Black women) and diet (low pre-processed food)
- Prioritization of actions at the population-level (legislative policies, voluntary market removal) rather than the individual-level (organic food, fragrance-free items)

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