Robert L. Brent Lecture

Developmental Origins of Health and Disease in the ECHO Program

Matthew W. Gillman, MD, SM
Program Director
Environmental influences on Child Health Outcomes (ECHO)
Office of the Director, US National Institutes of Health
28 June 2022

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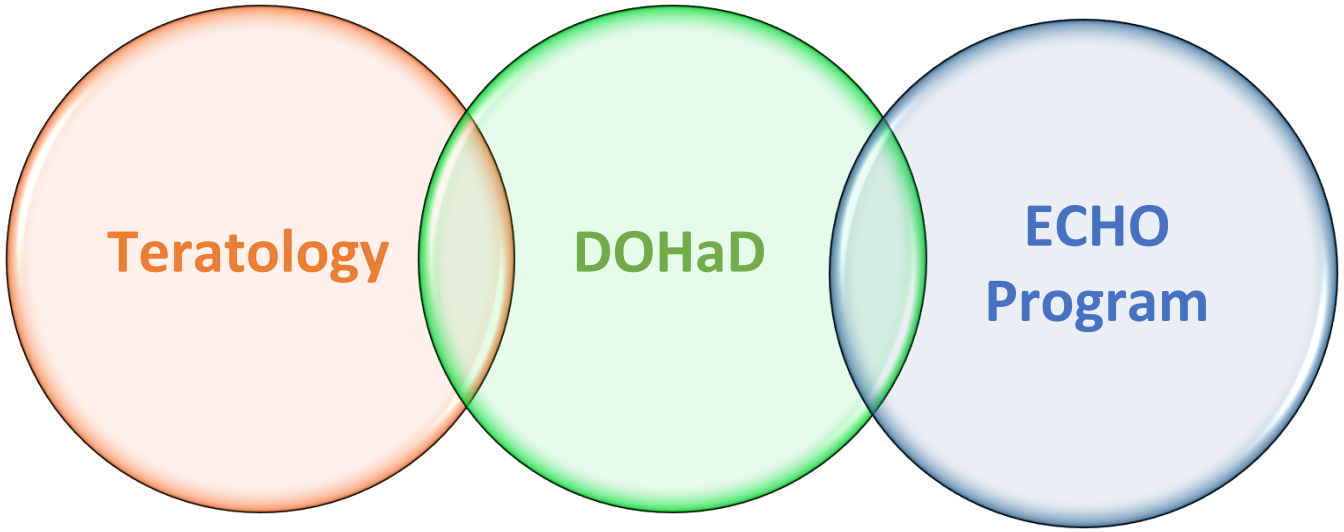
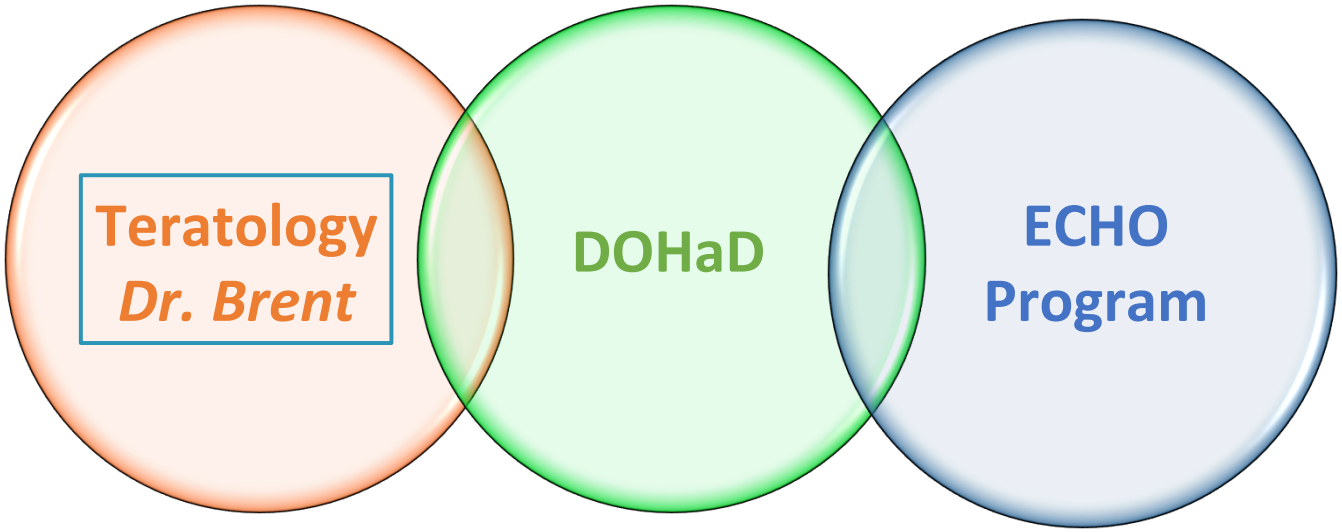
National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Today



To set the stage…



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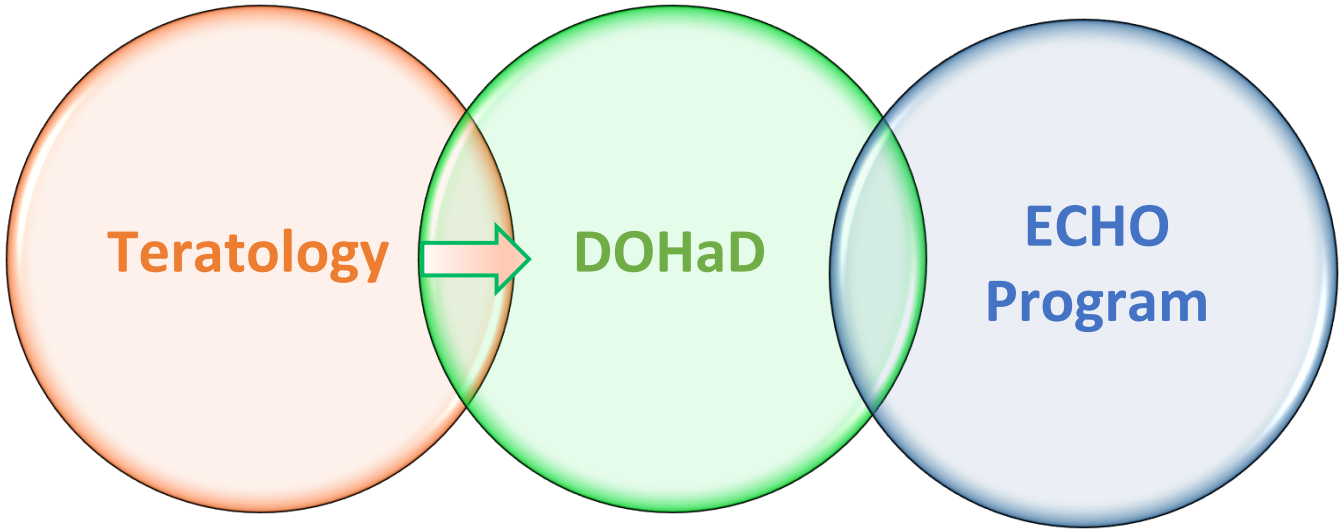

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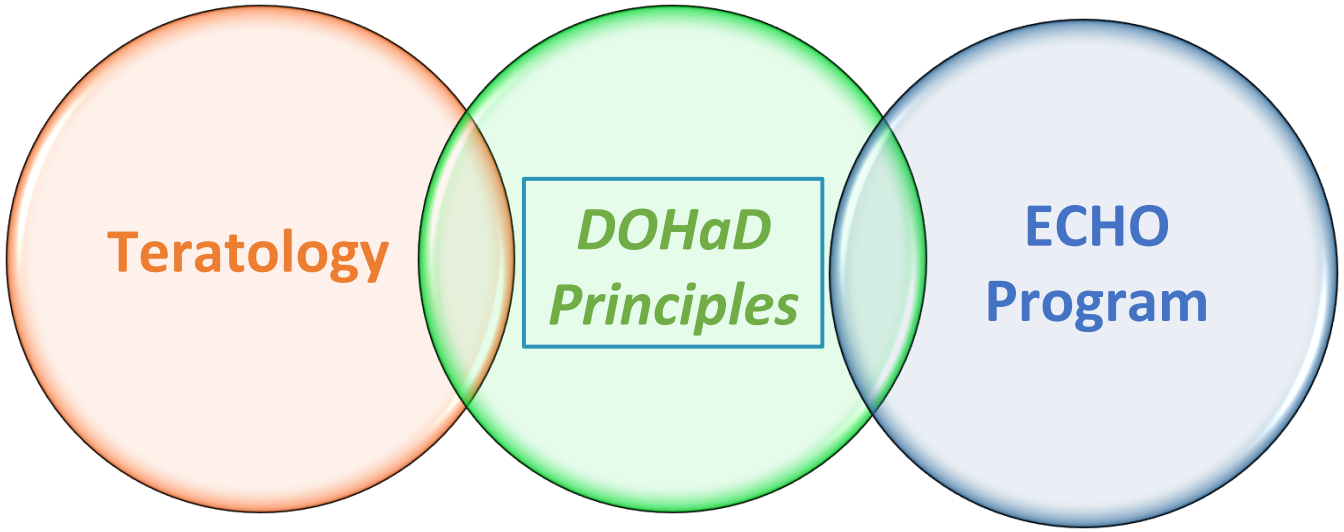

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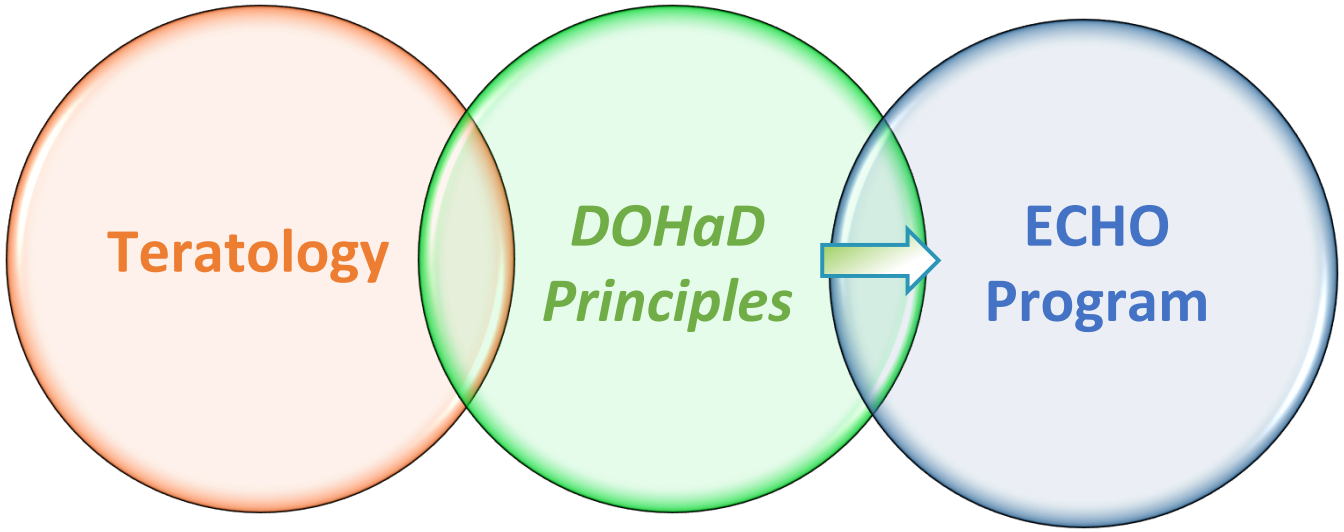
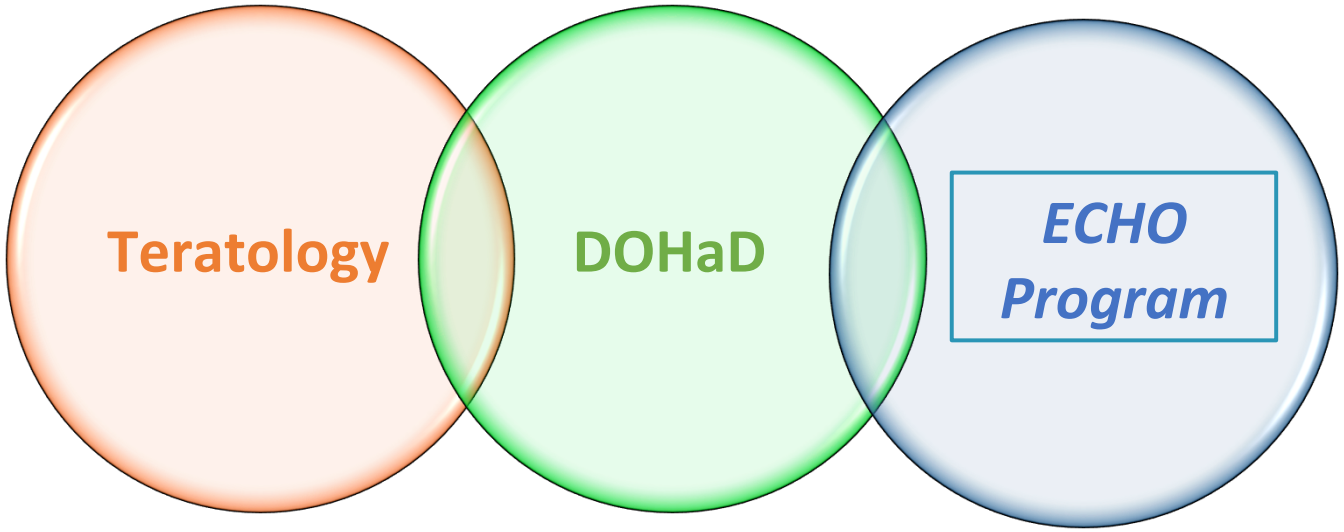


The Stage



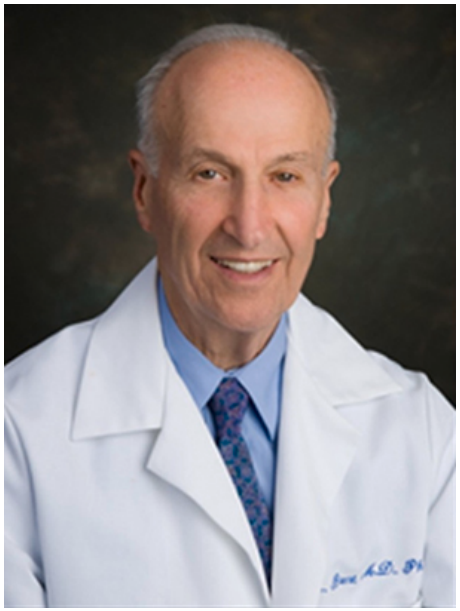
- What is ECHO?
- What are we finding?
- What can ECHO do for you?

Messages

- Newer endocrine-disrupting chemicals may be “regrettable substitutions”

- Air pollution in critical windows may underlie disparities in child airways outcomes

Robert L. Brent, MD, PhD (1927–2021)



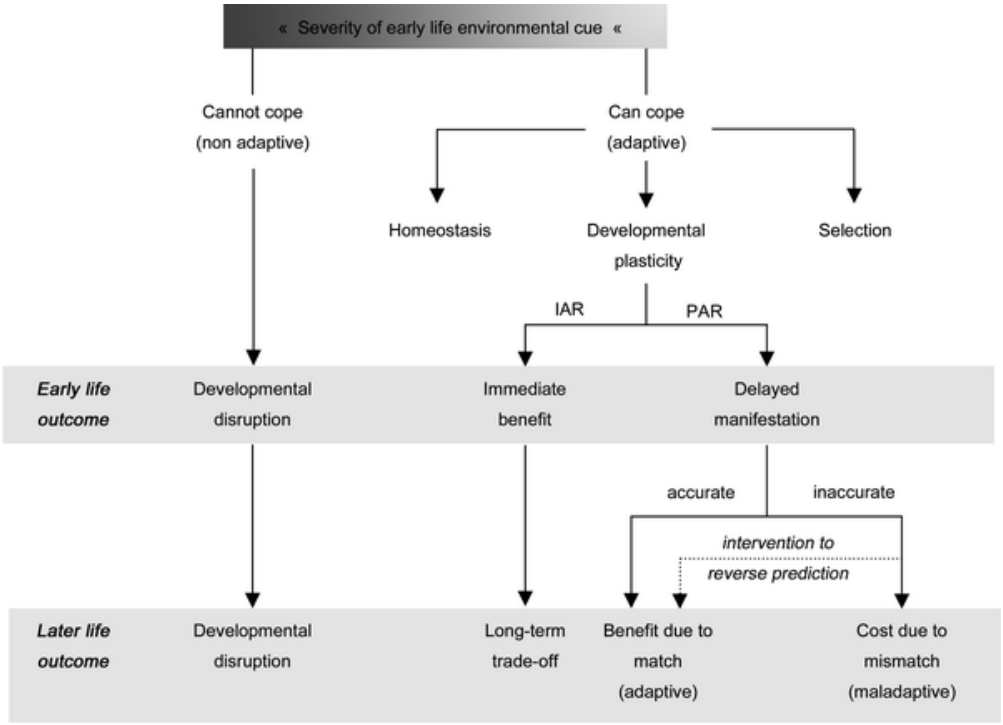
- Thomas Jefferson Medical College > 60 years
  - Chair, Department of Pediatrics 30 years
  - Research continuously funded by the National Institutes of Health
  - Distinguished Professor Award of Thomas Jefferson University
    - 3 in 175 years of Jefferson Medical College
- "…one of the greatest perinatologists of all time."

Robert L. Brent, MD, PhD (1927–2021)

- Research contributions
  - Systematic methodology for evaluating the risk of reproductive toxicants
  - Birth defects, growth retardation, mental retardation, miscarriage threshold effects of radiation exposure
  - Vast majority of diagnostic radiological tests no additional risk to fetus.
  - Young embryos vulnerable to radiation
    - But survivors no increased risk for congenital malformations (“all or none”)
    - ***What about consequences of less severe perturbations to embryo or fetus?***
      - ***“Teratology meets DOHaD”***

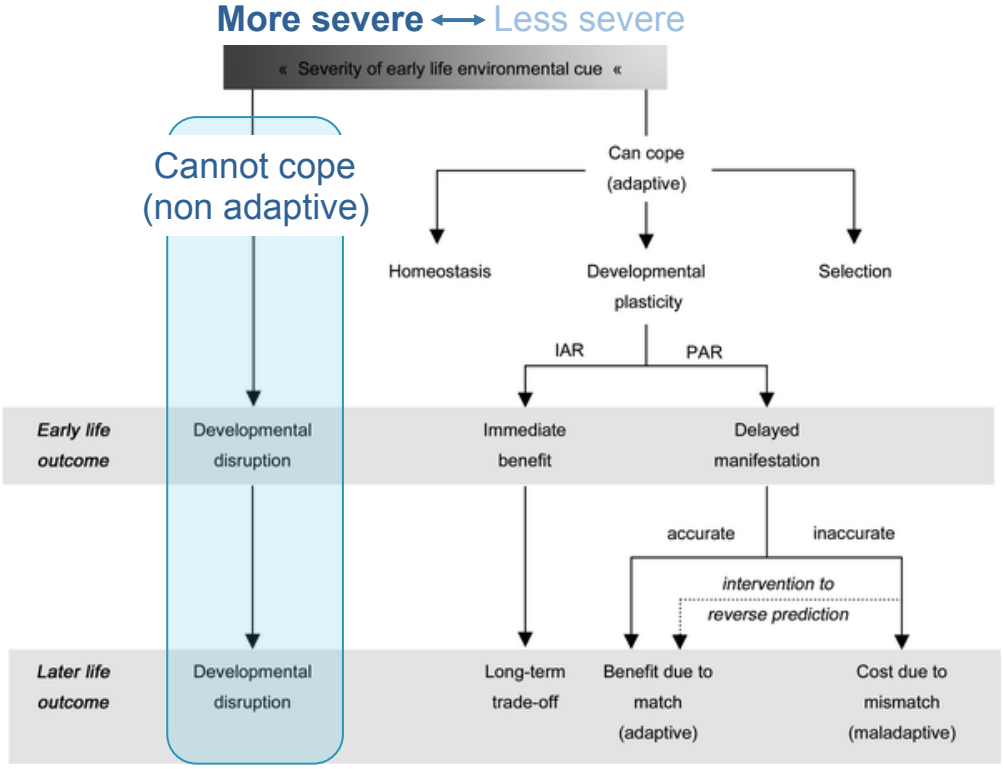
Early Environmental Cues

More severe ⟷ Less severe



Low et al. Evol Biol (2012) 39: 650
Kuzawa, Fried (2017)

Early Environmental Cues—More Severe



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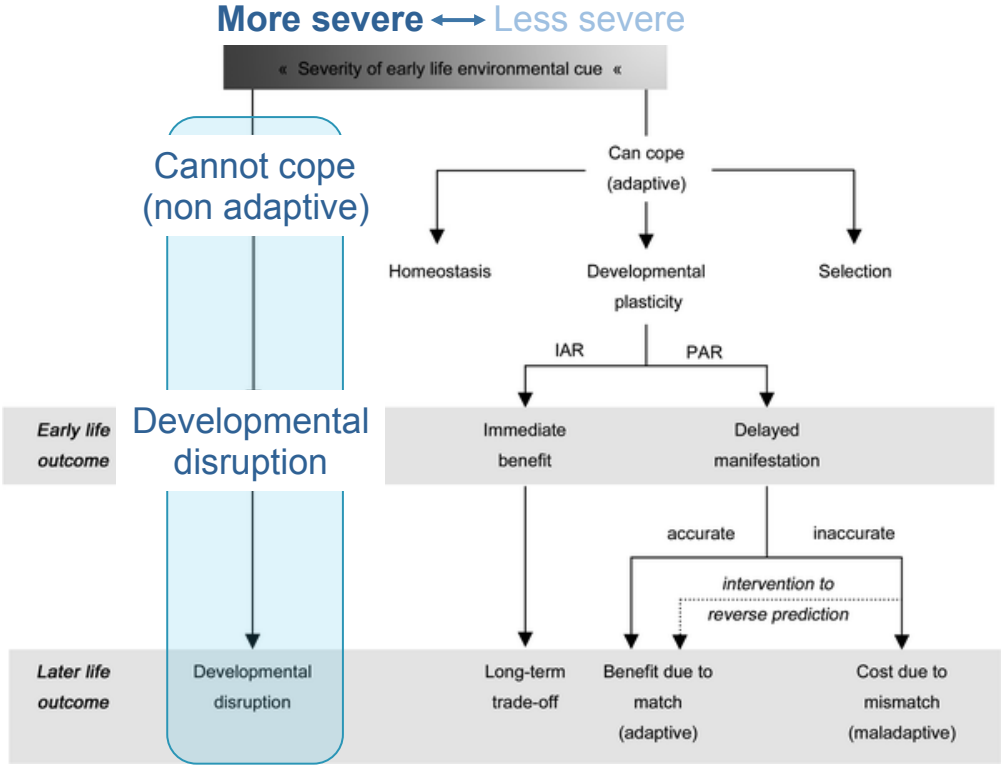
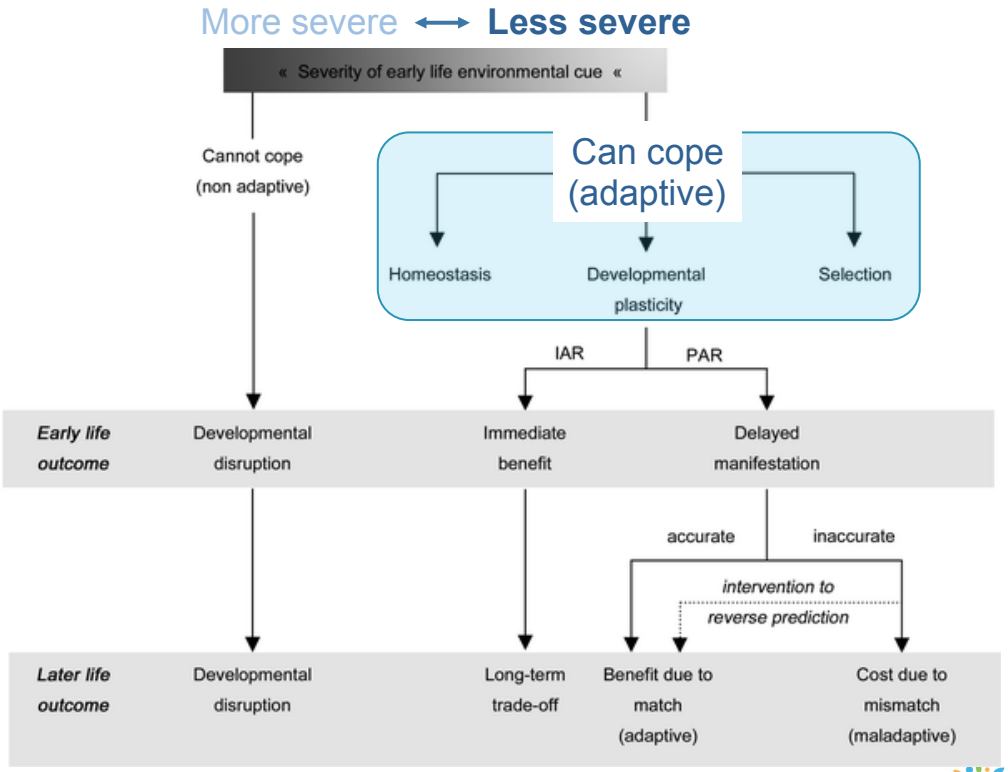
Early Environmental Cues—More Severe



Low et al. Evol Biol (2012) 39: 650
Kuzawa, Fried (2017)

Early Environmental Cues—Less Severe

Ecological cycle duration		Adaptation	
Years		Mode	Process
0.00000001	seconds		
0.0001	hours	Physiologic	Homeostasis & Allostasis
0.001	days		
0.1	months		
1	years	Developmental	Plasticity
10	decades	Intergenerational	Inertia
100	centuries		
1000	millenia	Genetic	Natural selection
1000000	millions		



Low et al. Evol Biol (2012) 39:150
Kuzawa, Fried (2017)

Developmental Origins of Health and Disease (DOHaD)

Ecological cycle duration		Adaptation	
Years		Mode	Process
0.00000001	seconds		
0.0001	hours	Physiologic	Homeostasis & Allostasis
0.001	days		
0.1	months		
1	years	Developmental	Plasticity
10	decades	Intergenerational	Inertia
100	centuries		
1000	millenia	Genetic	Natural selection
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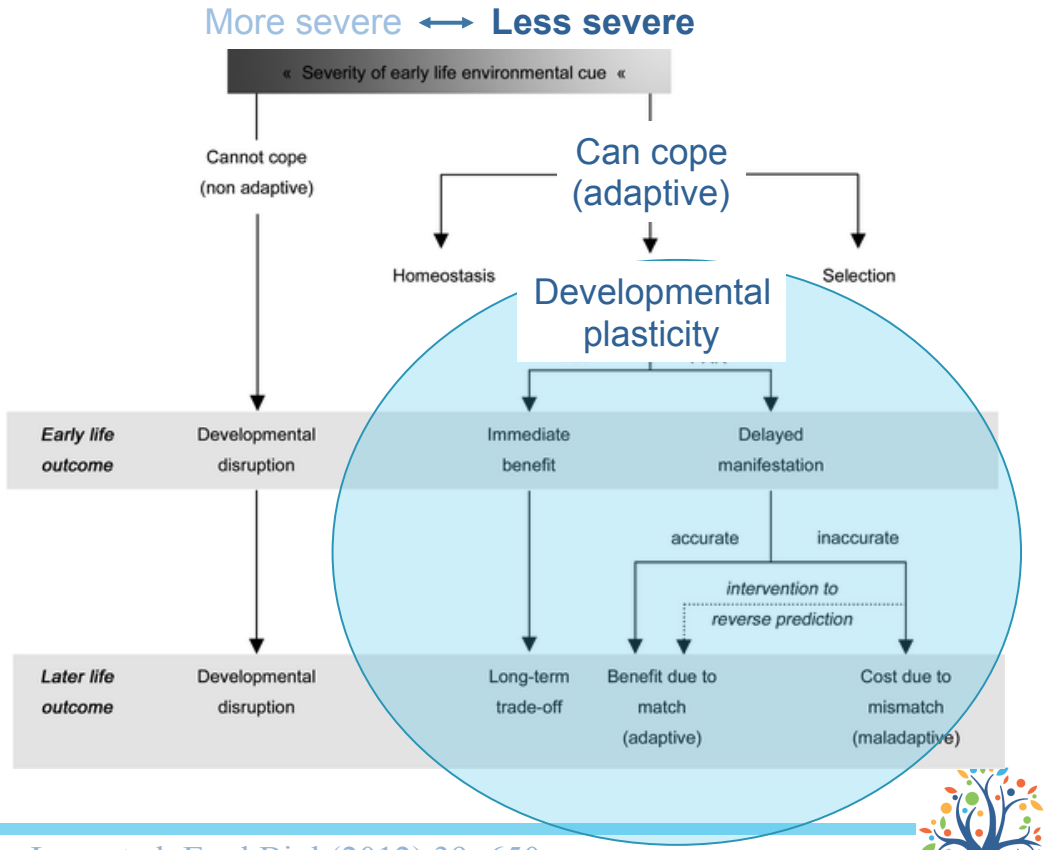


Low et al. Evol Biol (2012) 39: 650
Kuzawa, Fried (2017)

Developmental Origins of Health and Disease

- DOHaD emphasizes prenatal period and early childhood as important periods for development of chronic disease throughout life.

Ann Nutr Metab 2013;63:291–292

Appreciating David Barker (1938–2013)

Matthew W. Gillman[a, b] Vincent W.V. Jaddoe[c]

DOHaD

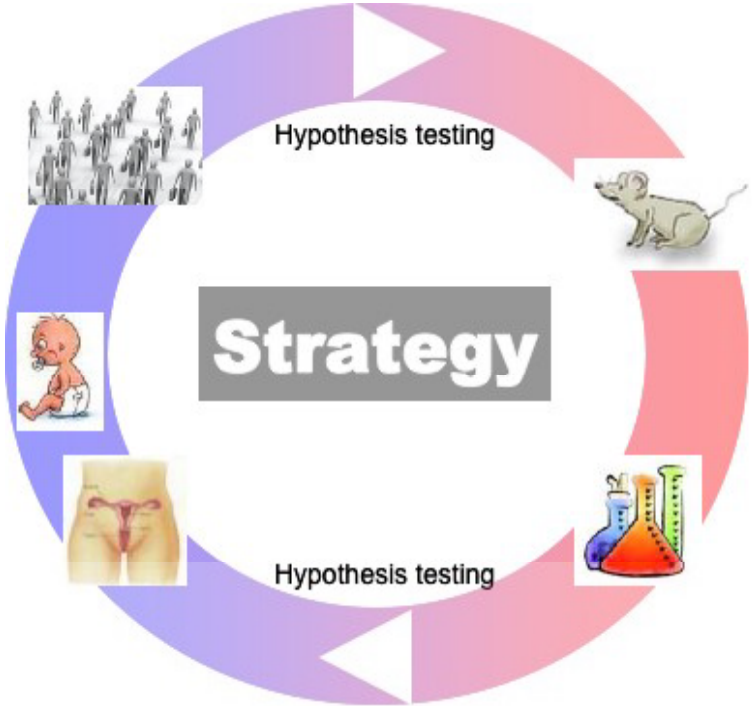
Early Exposures Have Lasting Effects

- Development is highly integrated process and sensitive time for exposure
  - Rapid Growth
  - Active and extensive cell differentiation
  - Developing immune system
  - Increased metabolic rate
  - Programming, e.g., via epigenetics

DOHaD benefits from interactions among multiple disciplines

Population-based Studies

- Cohort studies
- Randomized trials
- Biomarkers



Animal Models

- Physiology
- Metabolism
- Genetic Susceptibility
- Epigenetic mechanisms

Clinical Studies

- Tissue biopsies
- Molecular markers
- Small trials

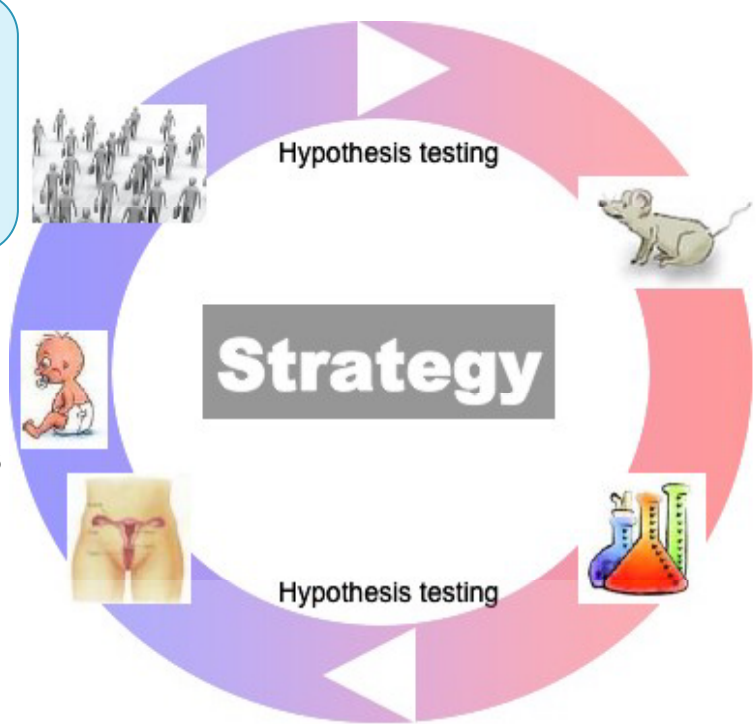
In Vitro Studies

- Isolated tissue studies
- Molecular markers
- Epigenetic mechanisms

DOHaD benefits from interactions among multiple disciplines

Population-based Studies

- Cohort studies
- Randomized trials
- Biomarkers



Animal Models

- Physiology
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Clinical Studies

- Tissue biopsies
- Molecular markers
- Small trials

In Vitro Studies

- Isolated tissue studies
- Molecular markers
- Epigenetic mechanisms

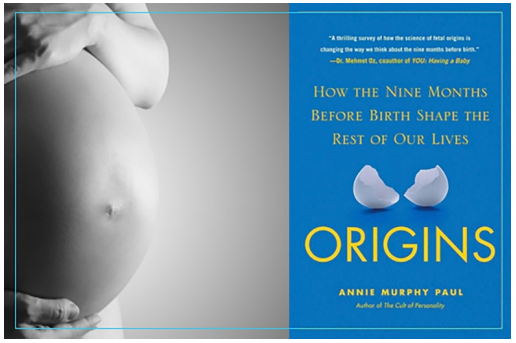
What is ECHO?

Environmental influences on Child Health Outcomes

ECHO Mission

Enhance the health of children for generations to come

A good start to life…

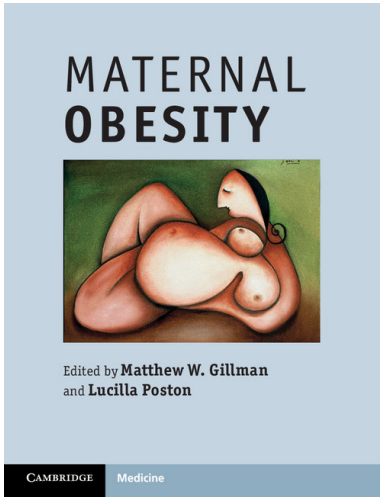


…can last a lifetime

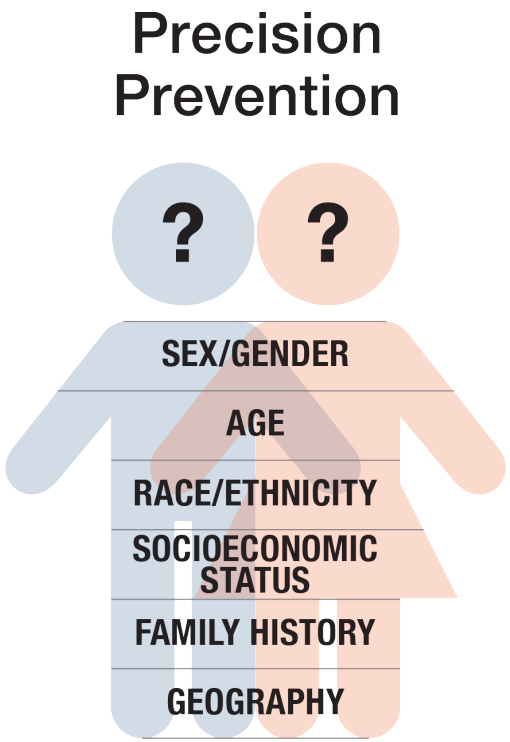
…can last a lifetime

…and over generations

To ensure a good start, need to understand potential risks & resiliencies…



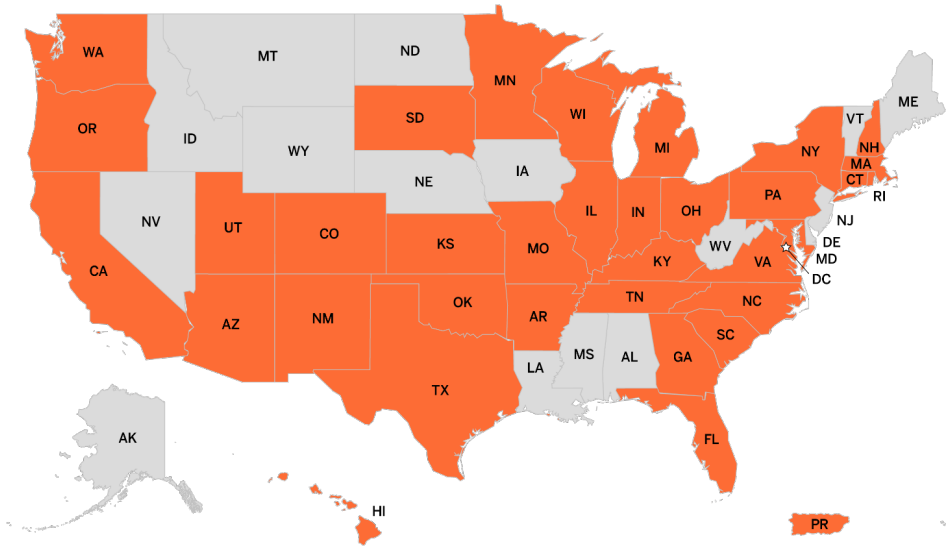
…and when & to whom they apply…



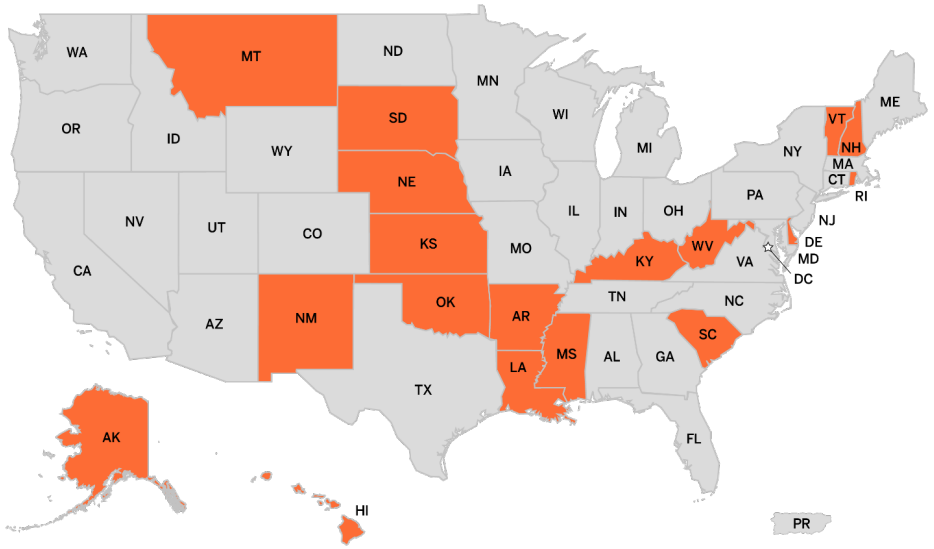
… then take action

Observational & Intervention Research

ECHO Cohorts

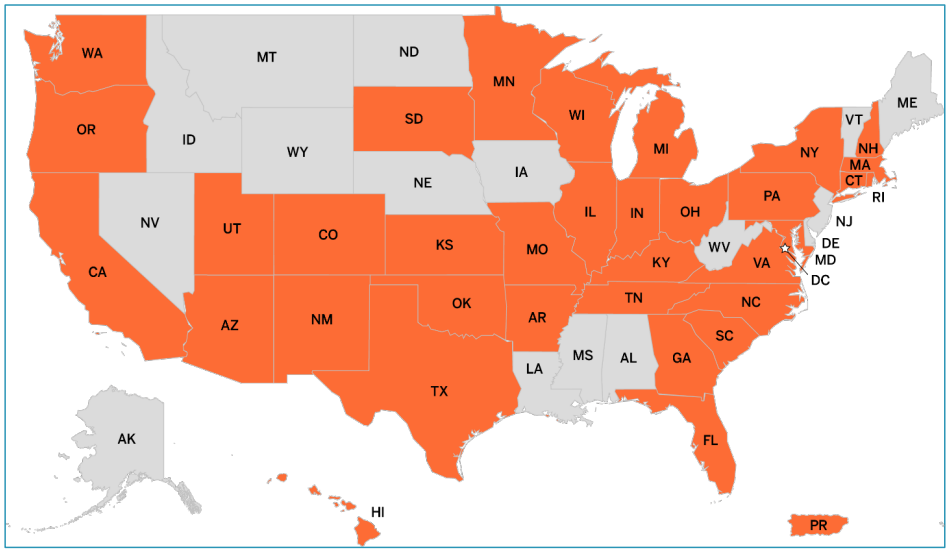


ECHO IDeA States
Pediatric Clinical Trials Network



Observational & Intervention Research

ECHO Cohorts



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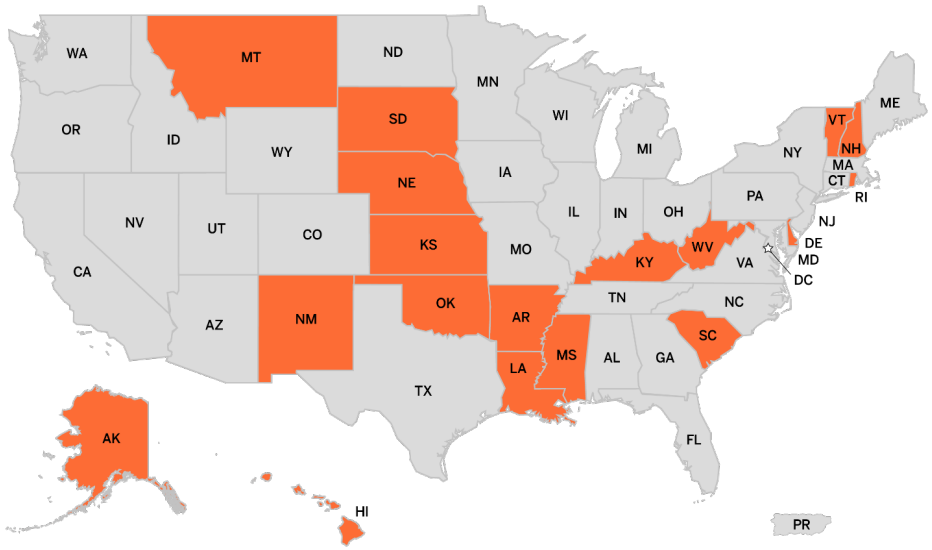


ECHO Cohorts Overall Scientific Goal

Answer **solution-oriented questions** about effects

of

broad range of **early environmental exposures**

on

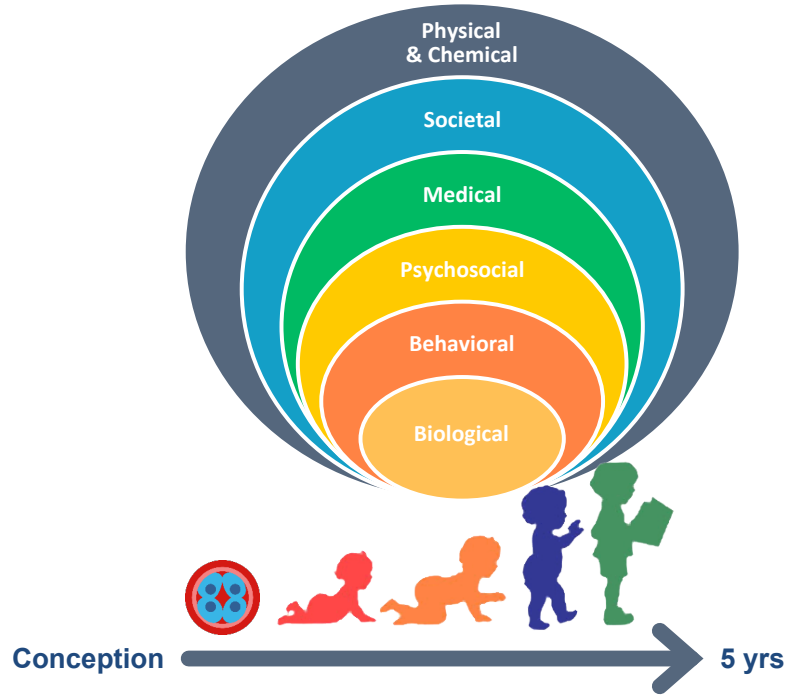
child health and development

Solution-oriented

Inform programs, policies, and practices
to
enhance the health of children

Broad range of early environmental exposures

From society to biology



Child Health and Development

5 key pediatric outcomes with high public health impact

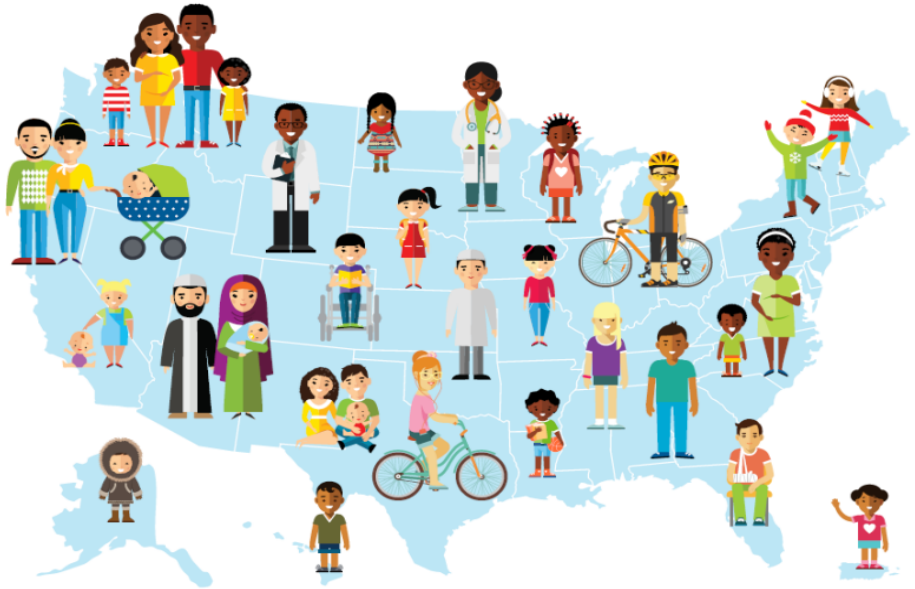
Throughout childhood and adolescence


ECHO-wide Cohort
Weaving together data from 69 ongoing maternal-child cohort studies

ECHO-wide Cohort Data Platform

- Data from 101,000+ participants from 69 cohort studies
  - ~59,000 children
    - ~33,000 active follow up (growing)
  - >40,000 biospecimens
- Becoming nationwide research resource
  - Harmonized existing measures & standardized new measures
    - Common data collection protocol
      - echochildren.org/about/echo-program-protocol/

Diverse Geography, Sex, Age, SES, Race/ Ethnicity

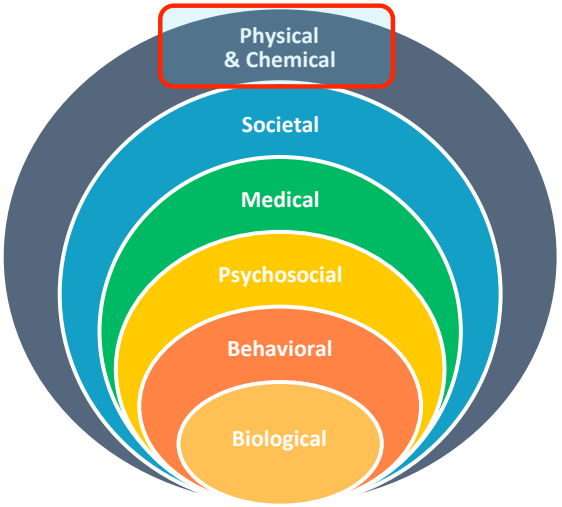


26% Hispanic
43% White
12% Black
4% Asian
3% AI/AN
4% More than one race
7% Unknown/not reported/other

What are we* finding?

*ECHO investigators

Today's focus: prenatal chemical exposures and air pollution



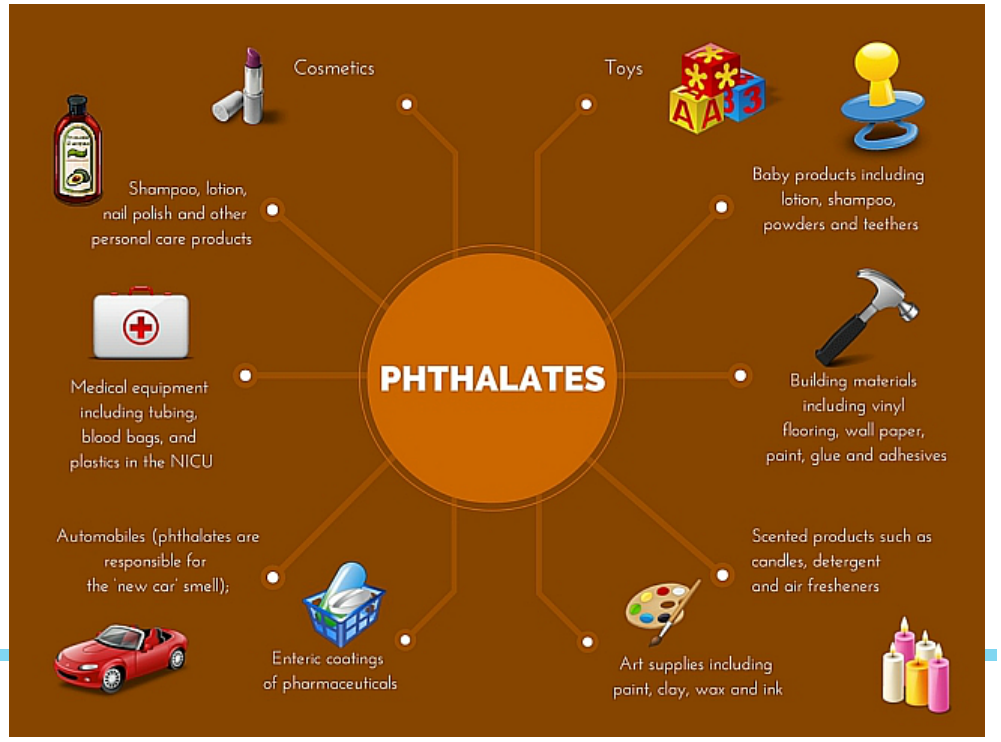
Chemical Exposures

- Phthalates & Per- and Polyfluoroalkyl Substances (PFAS)
- Ubiquitous
- Need to know their effects on offspring
  - Traditional compounds

    and
  - Contaminants of emerging concern
    - "Regrettable substitutions"

Phthalates

- Make plastics soft and flexible
- Ubiquitous
- Older (phasing out, e.g., DBP & DEHP) and newer (replacement) chemicals
- Metabolized
- Measurable in urine
- Endocrine disruptors



Recent Calls for More Regulation Based on Neurotoxicity

AJPH
A PUBLICATION OF THE AMERICAN PUBLIC HEALTH ASSOCIATION

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Home » American Journal of Public Health (AJPH) » **April 2021**

Neurotoxicity of Ortho-Phthalates: Recommendations for Critical Policy Reforms to Protect Brain Development in Children

Stephanie M. Engel PhD, **Heather B. Patisaul** PhD, **Charlotte Brody** RN, **Russ Hauser** MD, ScD, MPH, **Ami R. Zota** ScD, MS, **Deborah H. Bennet** PhD, **Maureen Swanson** ... (show all authors)

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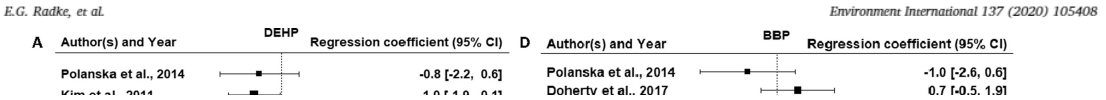
Home » American Journal of Public Health (AJPH) » **April 2021**

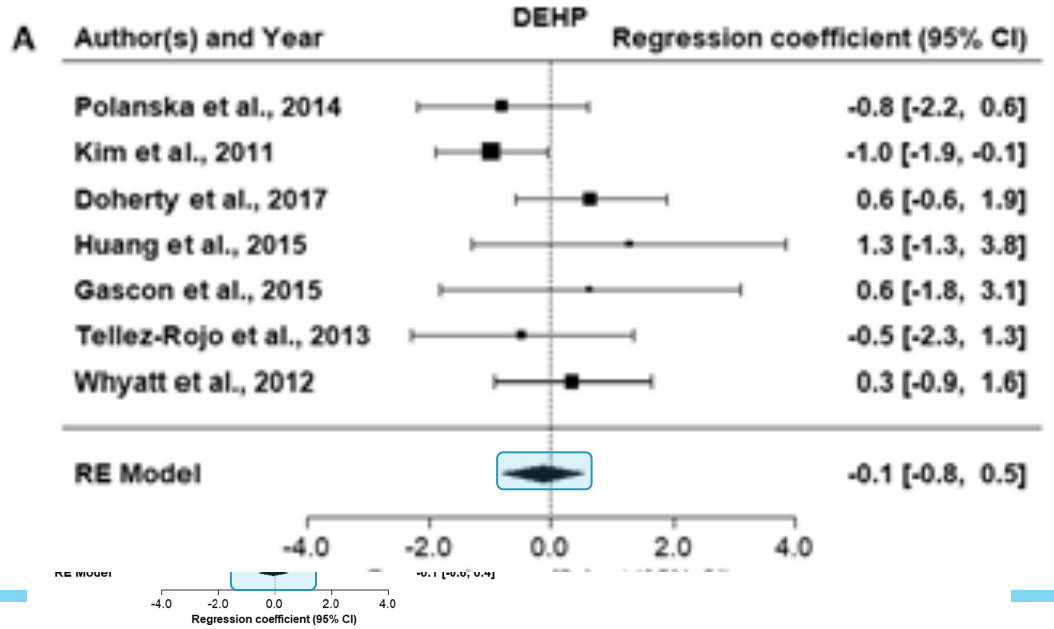
Phthalates Should Be Regulated as a Class to Protect the Brains of Our Children

Linda S. Birnbaum PhD, and **Carl-Gustaf Bornehag** PhD

Meta-analysis does not show associations of each of 5 prenatal phthalates with child cognition up to age 4 y



E.G. Radke, et al.



But level of confidence in findings not high

For cognition and other neurodevelopmental outcomes

E.G. Radke, et al.

Outcome	DEHP	DINP	DBP	DIBP	BBP	DEP
Cognition	S	I	S	S	S	S
Motor	S	S	S	S	M*	I
Behavior	S	I	S	I	S	I
Infant behavior	I	I	S	I	I	I
Social behavior	S	I	S	I	I	S

Robust (R) Moderate (M) Slight (S) Indeterminate (I)

Level of confidence in association

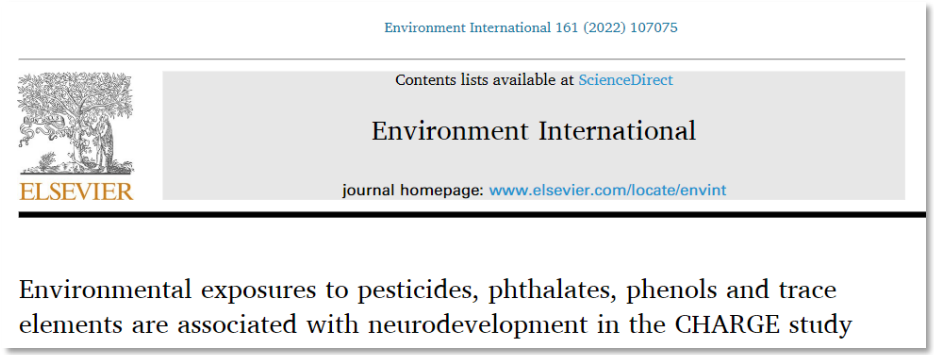
Fig. 5. Summary of epidemiologic evidence of neurodevelopmental effects associated with phthalates. *In girls.

Limitations of Studies on Phthalates and Offspring Neurodevelopment

- Exposure misclassification
  - Non-persistent chemical measured once
- Periods of heightened susceptibility
  - Typically measured in late pregnancy
- Lack of information on sex-specific effects
- Single chemicals rather than phthalate mixture effects
- Shorter-term, intermediate endpoints
  - Need longer follow-up, repeated exposure assessment and larger N for clinical diagnoses

- *How are ECHO cohorts addressing these challenges?*

Phthalates and Health Outcomes
ECHO Single Cohort Analyses


Environment International 161 (2022) 107075

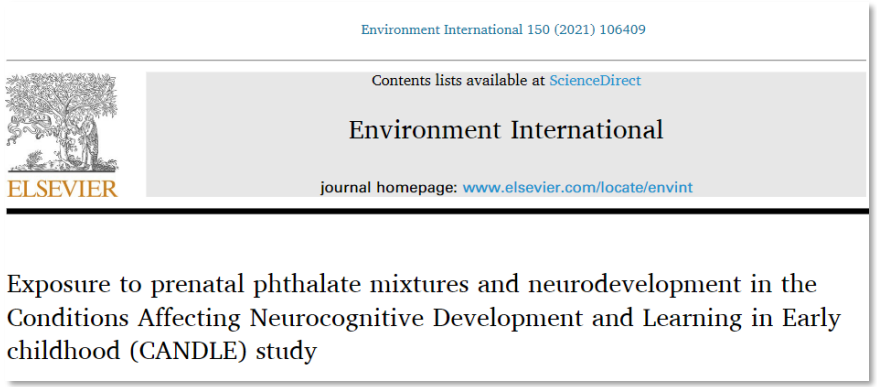
Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

ELSEVIER

Environmental exposures to pesticides, phthalates, phenols and trace elements are associated with neurodevelopment in the CHARGE study


Environment International 150 (2021) 106409

Contents lists available at ScienceDirect

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Exposure to prenatal phthalate mixtures and neurodevelopment in the Conditions Affecting Neurocognitive Development and Learning in Early childhood (CANDLE) study


ehp Environmental Health Perspectives

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Vol. 130, No. 3 | Research

Biomarkers of Exposure to Phthalate Mixtures and Adverse Birth Outcomes in a Puerto Rico Birth Cohort


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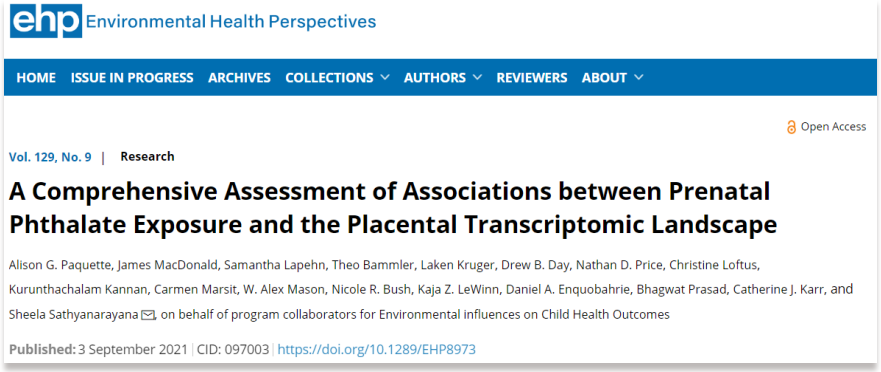
Vol. 130, No. 4 | Research

Prenatal Phthalate Exposure and Child Weight and Adiposity from *in Utero* to 6 Years of Age

Phthalates and Mediators
Placenta and cord blood



ehp Environmental Health Perspectives

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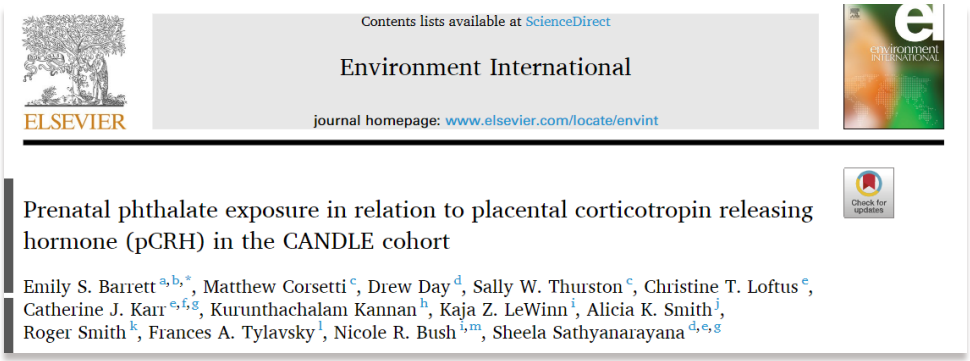
Vol. 129, No. 9 | Research

A Comprehensive Assessment of Associations between Prenatal Phthalate Exposure and the Placental Transcriptomic Landscape

Alison G. Paquette, James MacDonald, Samantha Lapehn, Theo Bammler, Laken Kruger, Drew B. Day, Nathan D. Price, Christine Loftus, Kurunthachalam Kannan, Carmen Marsit, W. Alex Mason, Nicole R. Bush, Kaja Z. LeWinn, Daniel A. Enquobahrie, Bhagwat Prasad, Catherine J. Karr, and Sheela Sathyanarayana ✉ on behalf of program collaborators for Environmental influences on Child Health Outcomes

Published: 3 September 2021 | CID: 097003 | https://doi.org/10.1289/EHP8973



ELSEVIER

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Prenatal phthalate exposure in relation to placental corticotropin releasing hormone (pCRH) in the CANDLE cohort

Emily S. Barrett [a,b,*], Matthew Corsetti [c], Drew Day [d], Sally W. Thurston [c], Christine T. Loftus [e], Catherine J. Karr [e,f,g], Kurunthachalam Kannan [h], Kaja Z. LeWinn [i], Alicia K. Smith [j], Roger Smith [k], Frances A. Tylavsky [l], Nicole R. Bush [i,m], Sheela Sathyanarayana [d,e,g]

frontiers in Genetics

ORIGINAL RESEARCH
published: 31 March 2022
doi: 10.3389/fgene.2022.793278

Prenatal Exposures to Common Phthalates and Prevalent Phthalate Alternatives and Infant DNA Methylation at Birth

Rebekah L. Petroff[1], Vasantha Padmanabhan[1,2,3], Dana C. Dolinoy[1,3], Deborah J. Watkins[1], Joseph Ciarelli[2], Diana Haggerty[4], Douglas M. Ruden[5] and Jaclyn M. Goodrich[1]

ECHO-wide Cohort Advantages

- Sample size, diversity
- Harmonized exposure data
  - Timing
  - Newer and older chemicals
- Harmonized outcome data
- Analytic framework
  - Single chemicals
  - Mixtures

ECHO-wide Cohort Analyses in Progress
Phthalates

Effects of bisphenols and phthalates on fetal and postnatal growth

In utero exposure to metals and phthalates in relation to communication from birth to 3 years of age

Association between phthalate biomarkers at birth and infant electrocortical parameters

Impact of early childhood exposures to phthalates on attention deficit hyperactivity disorder (ADHD)

Prenatal phthalate exposures and Autism Spectrum Disorder symptoms in low-risk children

Solution Orientation

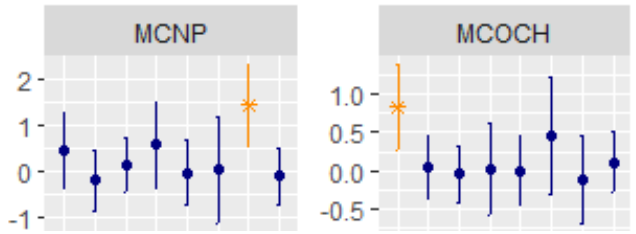
- **Nancy R. Cardona Cordero, PhD**
  - **Postdoctoral Training in Global Health Disparities**
  - **ECHO Puerto Rico Cohort (PROTECT)**
  - **PI: Akram N. Alshawabkeh**

Overarching Goal: To inform women of reproductive age about ways to reduce or eliminate exposure to phthalate-containing consumer products.

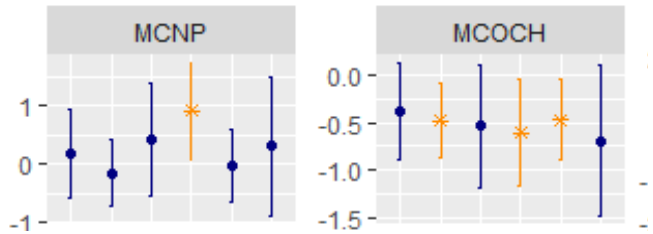
- **Aim 1 - Phthalate-containing consumer product use in relation to phthalate metabolite levels among pregnant women.**
- **Aim 2** – Social determinants of health and disparities among likely users vs. non-users of these products.
- **Aim 3** -- Qualitative interviews to identify differences in knowledge, attitudes, beliefs, and perceived risks about these products

Different phthalate patterns according to product brand

Deodorant
8 brands

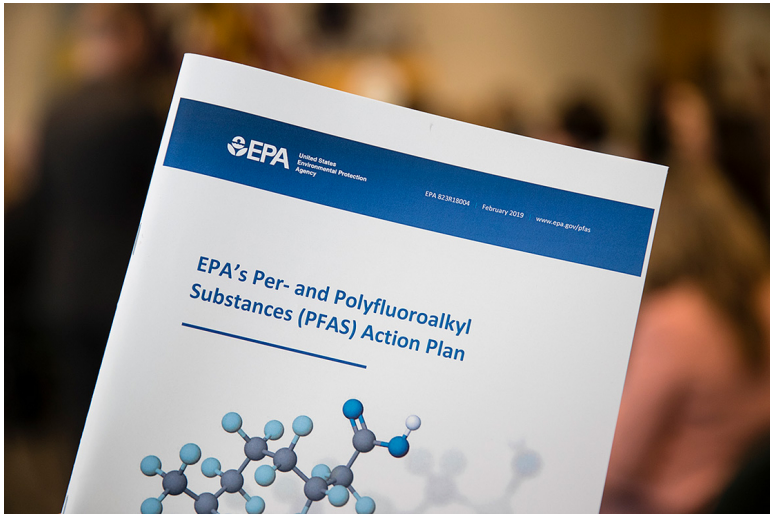


Bar Soap
6 brands



2 of 23 phthalates

Per- and Polyfluoroalkyl Substances (PFAS)



The Washington Post
Democracy Dies in Darkness

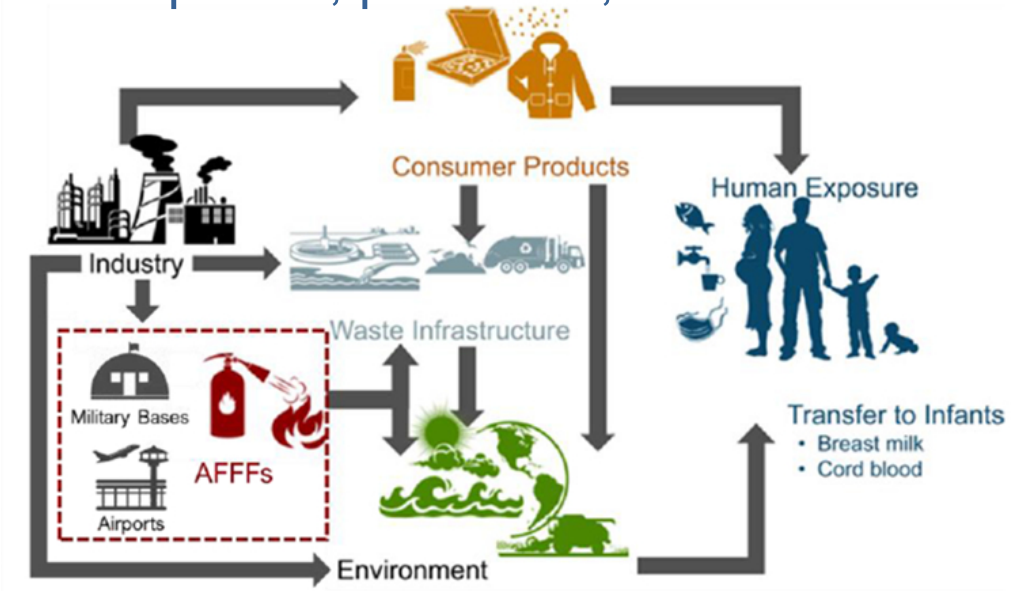
Health | Health Care | Medical Mysteries | Science | Wellness

The dangers of PFAS, often called 'forever chemicals'

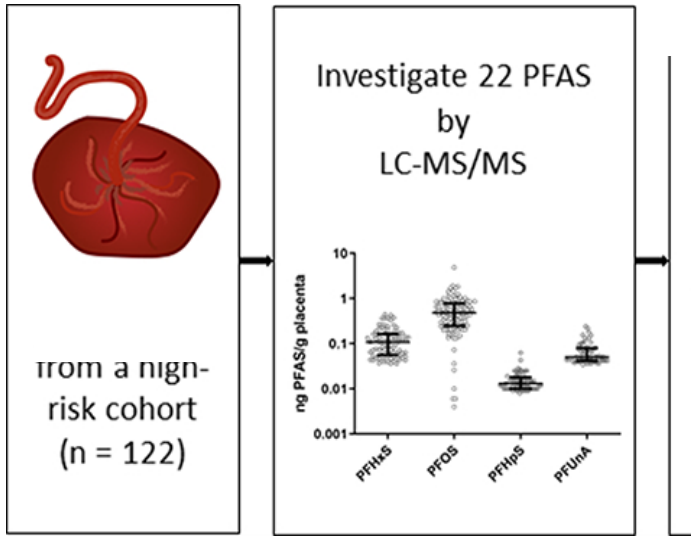
By Kevin Loria
May 23, 2022 at 2:00 p.m. EDT

Per- and Polyfluoroalkyl Substances (PFAS)

Repel dirt, grease, water, stains
But ubiquitous, persistent, bioaccumulative



Also, present in placenta



Bangma et al., Environ Sci Technol. 2020 Jul; 54(13): 8158–8166.

Blake, Fenton. Toxicology. 2020 Oct;443:152565.

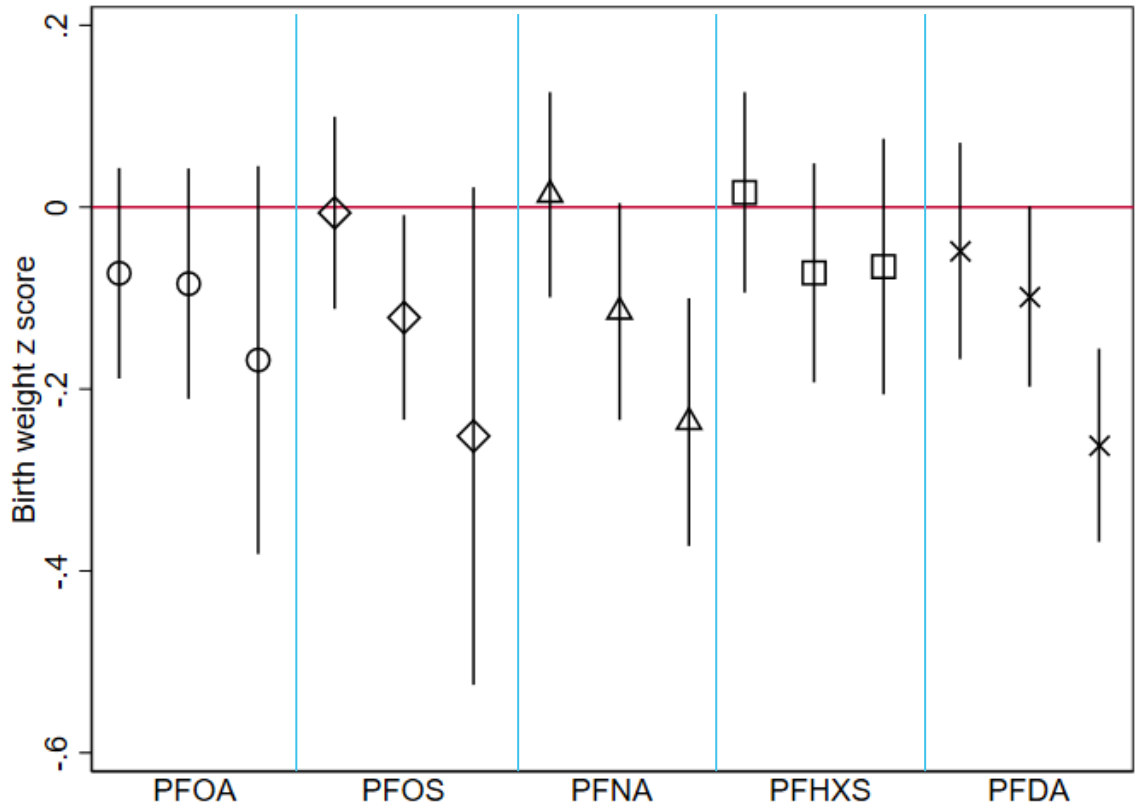
ECHO-wide Cohort Analyses in Progress
PFAS

PFAS and psychosocial stress during pregnancy and effects on perinatal outcomes
Maternal exposure to PFAS in relation to infections during pregnancy
Prenatal exposure to mixtures of PFAS and autism-related outcomes
Perfluoroalkyl compounds and child growth, adiposity, and metabolic health
Prenatal exposures to PFAS: Associations with behavior in childhood

Methods

- **3339** participants from **11** prenatal cohorts, 1999-2019
- 5 prenatal PFAS (>60% of values >limit of detection)
  - **PFOA, PFOS, PFNA, PFHxS, PFDA**
- Singly and mixture analysis of multiple PFAS
- Adjusted for maternal age, education, race/ethnicity, parity
- Trimester-specific sensitivity analysis

Higher amounts of each PFAS associated with lower fetal growth



Padula et al., in press

Individually and in mixtures, higher PFAS associated with…

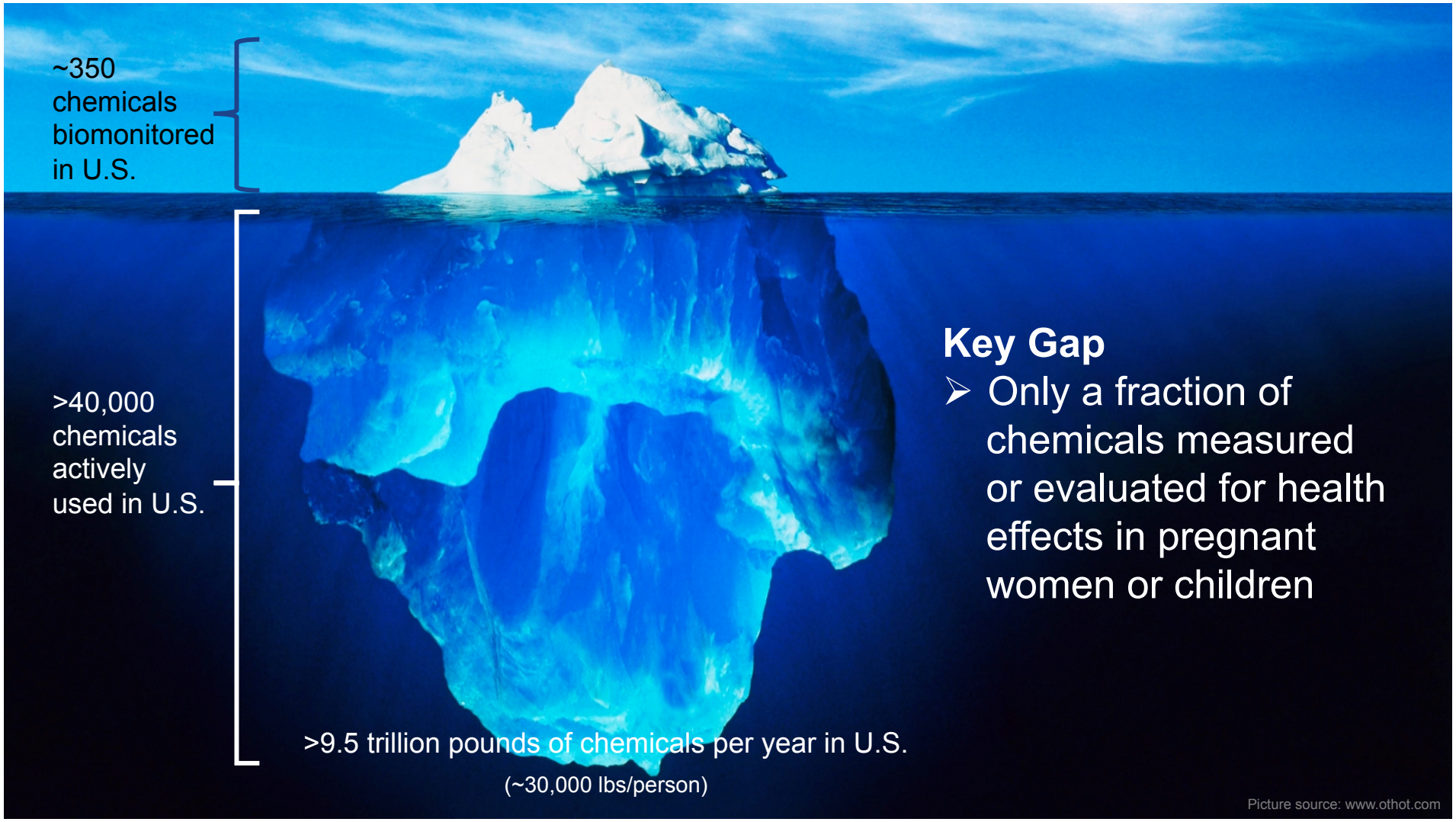
- **Lower** birth weight for gestational age
- **Decreased** risk of large-for-gestational age
- **Increased** risk of small-for-gestational age

→ Smaller babies

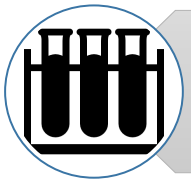
- **Increased** risk of preterm birth

→ Born too soon

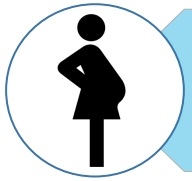
- Associations appeared **stronger**
  - among participants with **male infants**
  - With **1st** vs. 2nd or 3rd **trimester** exposure


~350 chemicals biomonitored in U.S.
>40,000 chemicals actively used in U.S.
>9.5 trillion pounds of chemicals per year in U.S.
(~30,000 lbs/person)
Key Gap
➢ Only a fraction of chemicals measured or evaluated for health effects in pregnant women or children
Picture source: www.othot.com

Assessing novel chemical exposures in ECHO



Recommend priority chemicals for biomonitoring in pregnant women/children



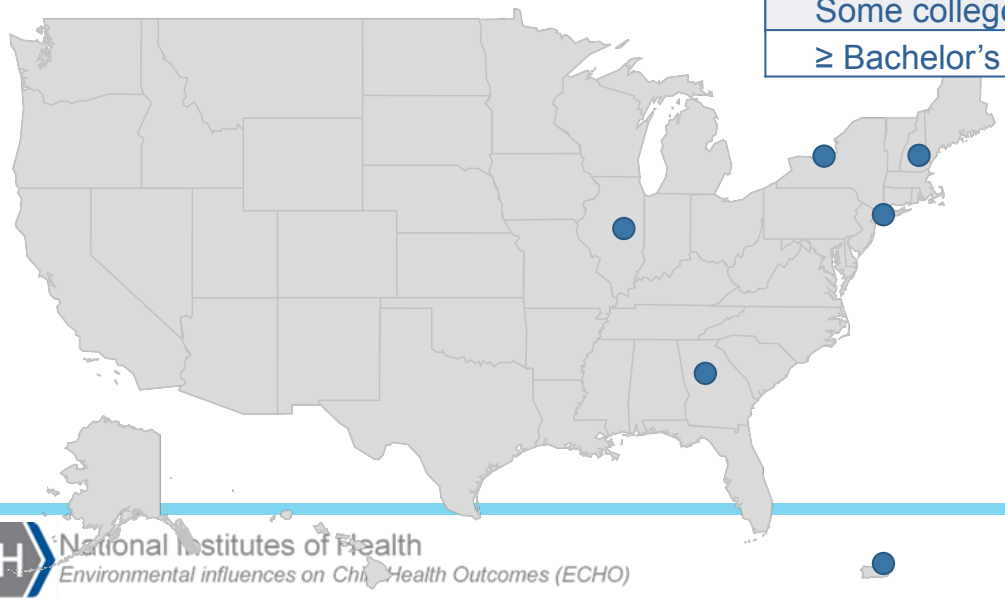
Conduct a pilot study to measure novel chemicals in urine collected from pregnant women

Launch a full-scale study to assess associations of prenatal novel chemical exposures with birth outcomes

Perform future studies evaluating associations of novel chemicals with additional child health outcomes

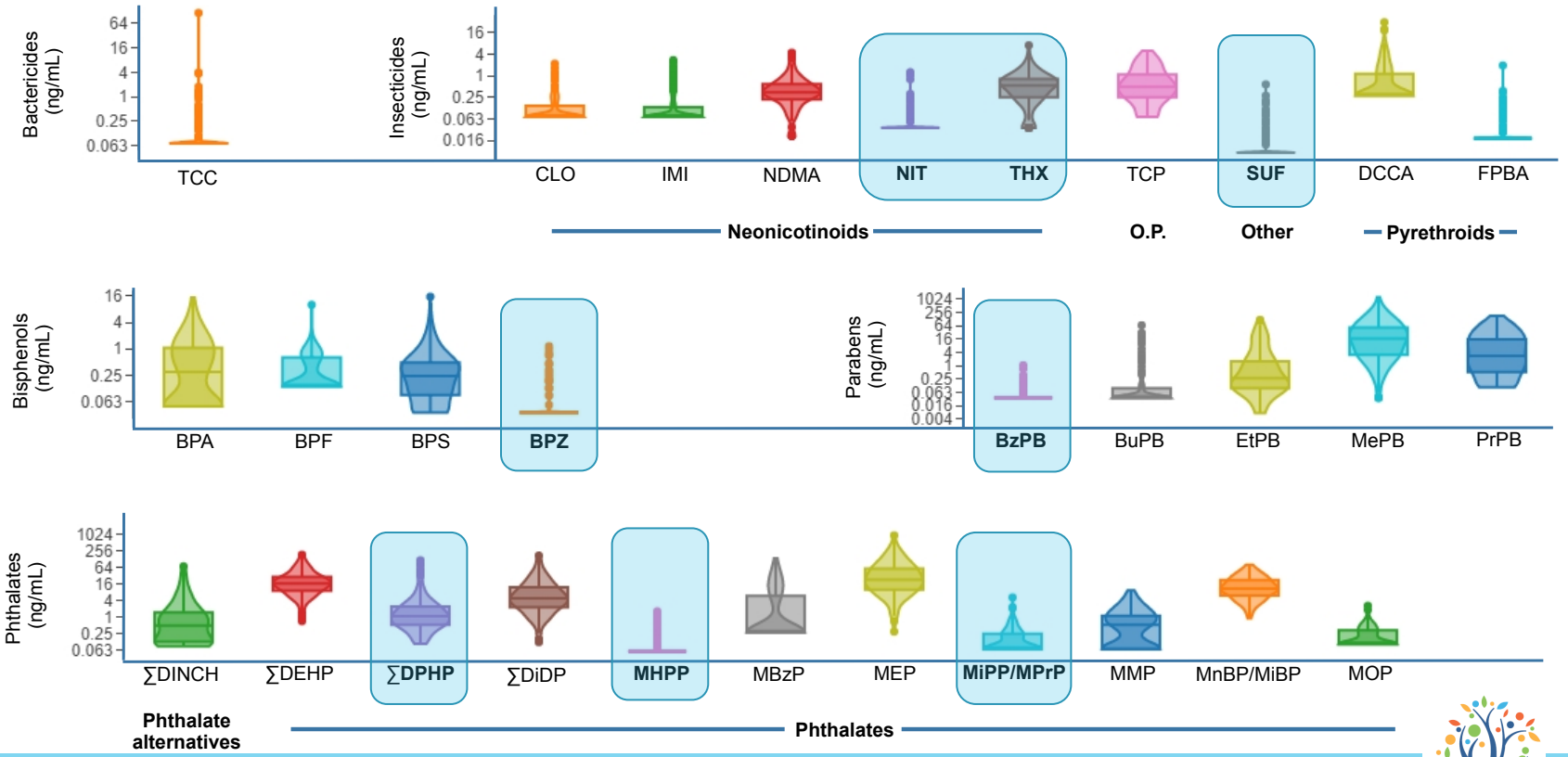
Pilot study measuring novel chemicals among 171 pregnant women from 9 ECHO cohorts

Sample characteristic	N (%)
Year of sample collection	
2008–2015	19 (11)
2016	20 (12)
2017	40 (23)
2018	46 (27)
2019–2020	46 (27)
Highest educational attainment (missing: n = 7)	
≤ HS or equivalent	44 (27)
Some college, AA degree, or Trade school	45 (27)
≥ Bachelor's degree	75 (46)



Chemicals in 3+ cohorts and 10% of study sample

BOLD = not included in NHANES monitoring



Pilot Study Conclusions

- Universal exposure to multiple chemicals during pregnancy
- Many chemicals measured for the first time
  - Raises possibility of “regrettable replacements”
- Resource for ECHO/child health research
- Underpins potential solutions

EXPOSURE REDUCTION STRATEGIES

Individual actions

Household maintenance and purchasing

Consumer, healthcare, and public health actions

Prevention/intervention via local and national policies

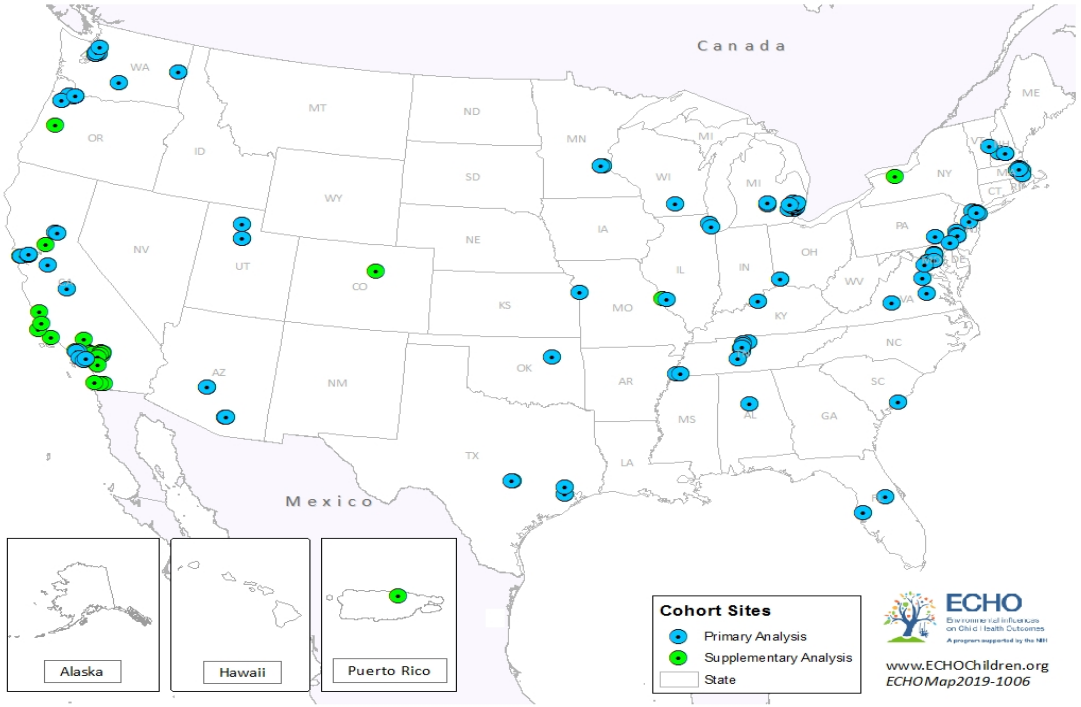
Air Pollution

Disparities in Asthma Incidence

- Most research on frequency of asthma focuses on prevalence, not incidence
  - Incidence data can reveal more about etiology

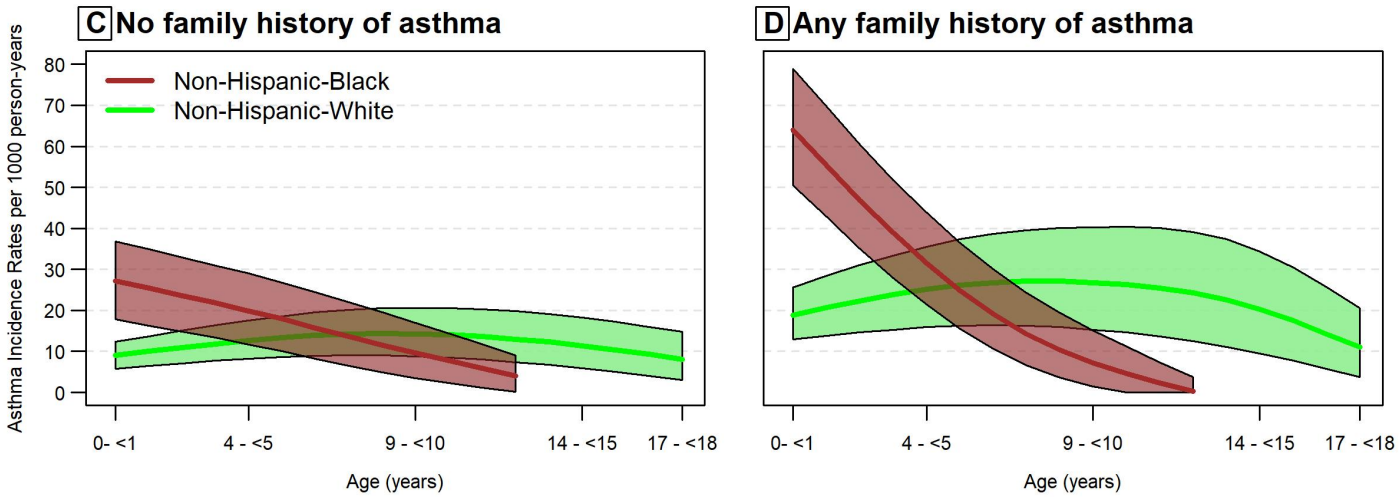
Disparities in Asthma Incidence

- 32 ECHO cohorts
- N = 12,471
- Distributed meta-analysis



Johnson et al., JAMA Pediatr (2021): e210667-e210667

Black children with higher asthma incidence rates that white children
But only in early childhood



Johnson et al., JAMA Pediatr (2021): e210667-e210667

Asthma Incidence

- Higher risk of asthma among Black children in early childhood
- Suggests prenatal determinants of disparities in asthma risk
- Air pollution is one such potential determinant
  - Socially patterned

‘Place-based’ Exposures: Geomarker Data

Addresses → **Geocode** → **Link / Derive Geomarker Data**

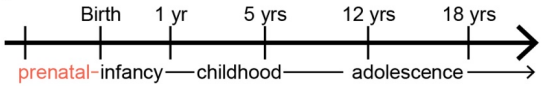
Home, school, work, etc addresses

Convert address to coordinates to facilitate GIS

Link spatial locations to environmental, census, EHR data, etc.

1) Collect Addresses and Dates

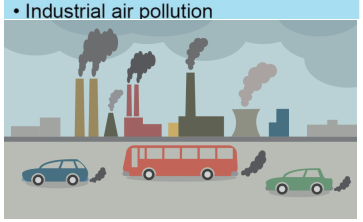
2) Construct Individual Residential Timelines



3) Geocode Addresses (lat/lon coordinates)

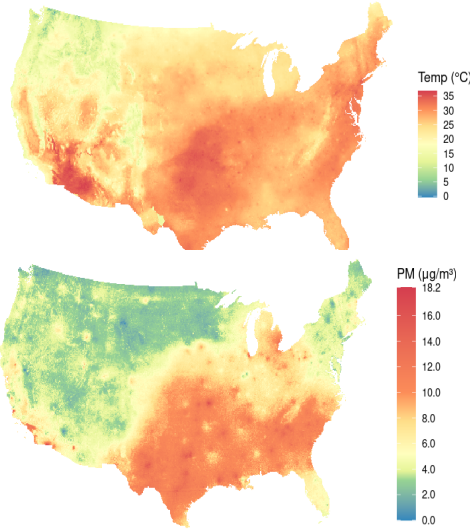
4) Assign Exposures

- Crime/violence
- Green space
- Traffic related air pollution
- Industrial air pollution



Air Pollution: Daily high-resolution $PM_{2.5}$ and temperature

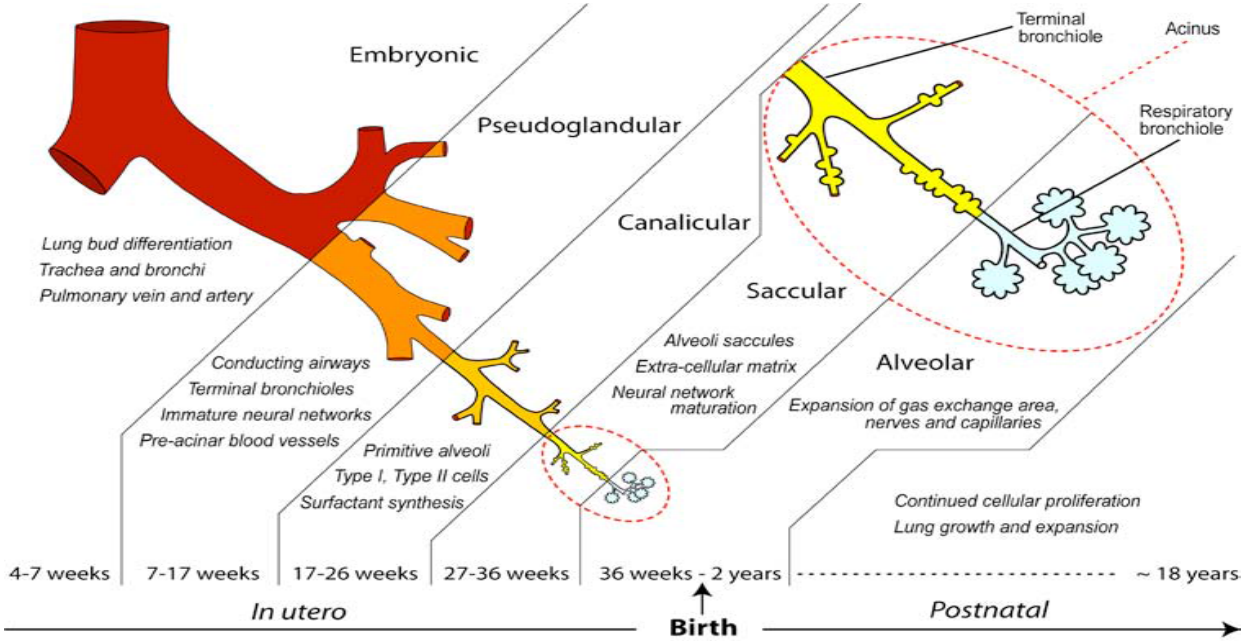
- ***Daily*** **exposures for 2003-2020**
- **24-hour $PM_{2.5}$ and min/mean/max temperature**
- **Across continental USA**
- **Uses privacy-protected exact latitude/ longitude**



Example: 24-hour $PM_{2.5}$ and minimum temperature July 22nd, 2011

Allan Just, PhD
Icahn School of Medicine at Mount Sinai,
OIF recipient

Critical Windows for Air Pollution and Airways Outcomes
Late pregnancy?



ENVIRONMENTAL EPIDEMIOLOGY
Official Journal of the International Society for Environmental Epidemiology

Articles and Issues | For Authors | Journal Info | ISEE

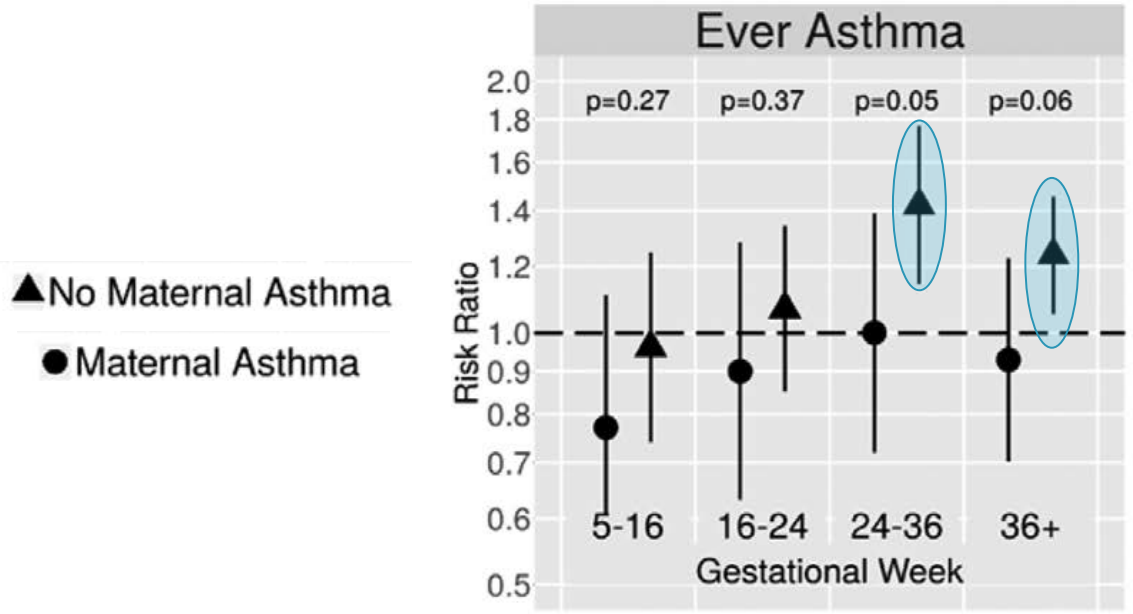
ORIGINAL RESEARCH ARTICLE

Maternal exposure to $PM_{2.5}$ during pregnancy and asthma risk in early childhood

Consideration of phases of fetal lung development

Hazlehurst, Marnie F.[a]; Carroll, Kecia N.[b]; Loftus, Christine T.[c]; Szpiro, Adam A.[d]; Moore, Paul E.[e]; Kaufman, Joel D.[a,c,f]; Kirwa, Kipruto[c]; LeWinn, Kaja Z.[g]; Bush, Nicole R.[g,h]; Sathyanarayana, Sheela[c,i,j]; Tylavsky, Frances A.[k]; Barrett, Emily S.[l]; Nguyen, Ruby H. N.[m]; Karr, Catherine J.[a,c,j]

Mid- (to late-) pregnancy exposure to $PM_{2.5}$ associated with wheeze and asthma among 4 yo children whose mothers had no asthma



Similar findings for current wheeze and current asthma

Risk ratio per 2 mcg/m³ (>2 SD) increment in $PM_{2.5}$

ECHO PATHWAYS (CA, MN, NY, TN, WA), N = 1469, 46% Black
Hazlehurst et al., Environ Epidemiol. 2021 Apr;5(2):e130

Research to date on outdoor air pollution and early life respiratory outcomes largely "criteria pollutants"

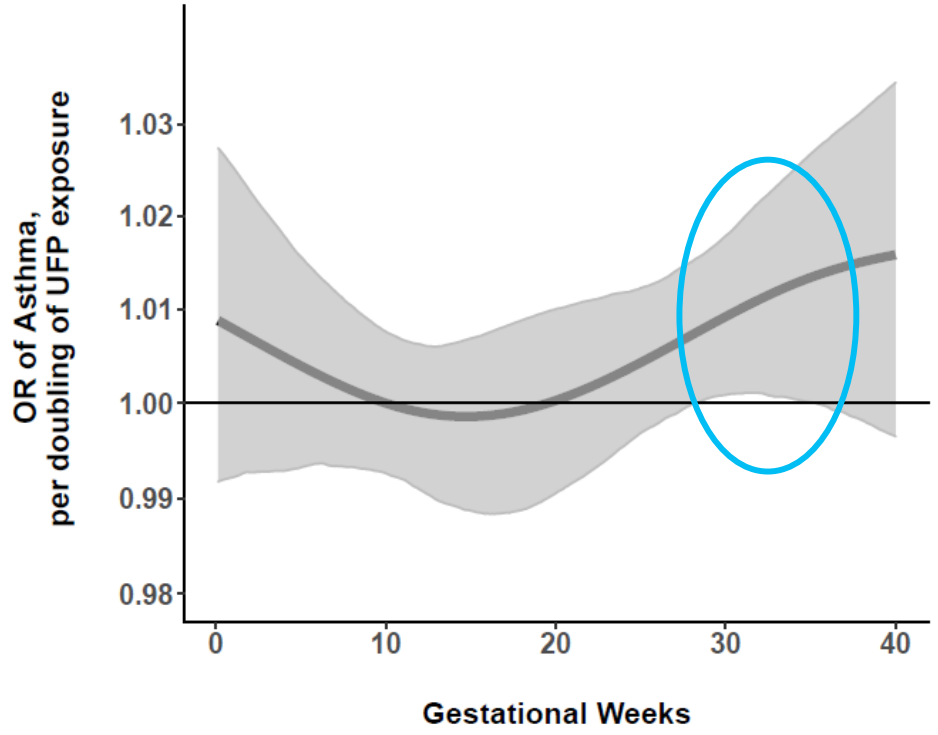
- Criteria pollutants
  - pollutants routinely monitored to assess air quality
    - fine particulate matter ≤2.5 micrometers (μm) ($PM_{2.5}$)
    - PM with a diameter of 10 to 2.5 μm (PM_{10})
    - ambient nitrogen dioxide (NO_2) or nitrates (NO_3)

Ultra-fine particles (UFPs) may have enhanced toxicity

- Air quality regulations currently do not address UFPs ≤0.1 µm, sub-micron sized particles

- May exert greater toxic effects than larger molecules
  (Ohlwein S et al., IJPH 2019; Li N, et al., JACI 2016)
  - larger surface area/mass ratio
  - enhanced oxidative capacity
  - deeper lung penetration
  - ability to translocate to the systemic circulation

Risk of asthma higher highest among children exposed to ultra-fine particles late in pregnancy



Wright et al, Am J Respir Crit Care Med 2021; 204:788-796

Prenatal Air Pollution and Childhood Asthma

- Childhood asthma related to prenatal air pollution exposure
  - Later pregnancy—critical period
  - Small particles—may lead to new regulations
  - May help explain early childhood racial differences in asthma incidence

What ECHO Can Do For You

ECHO as nationwide research resource

ECHO-wide Cohort
Controlled-Access Public Use Database

- De-identified data on NICHD Data and Specimen Hub
  - Deposited at regular intervals by ECHO Data Analysis Center
- First public release Summer 2022
  - Biospecimens later
- Access requests undergo NICHD DASH administrative review

Overall Summary/Conclusions

- ECHO is major investment in understanding early environmental influences on child health
  - Longitudinal data and biospecimen assays
- Emphasis on chemicals, air pollution, other exposures
  - 5 key pediatric outcomes
- ECHO-wide Cohort findings starting to fill evidence gaps on long-term influences of prenatal factors
  - Sample size, diversity, generalizability
  - Chemical exposures, older and newer
  - Air pollution and disparities
- US nationwide research resource


ngiyabonga
danke
謝謝
teşekkür ederim
спасибо
dank je
thank you
gracias
tapadh leat
mochchakkeram
hvala
mauruuru
bedankt
dziękuje
go raibh maith agat
obrigado
sukriya
kop khun krap
arigato
grazie
takk
dakujem
terima kasih
мерси
merci

Extra slides

Methods

- Largest exposure study to measure 100+ contemporary/emerging chemicals simultaneously in diverse population of pregnant people in the U.S.
  - Pilot study; 171 pregnant women from 9 ECHO cohorts in 5 states (CA, GA, IL, NH, NY)
  - New method for measuring multiple chemicals in a small amount of urine
  - Measure 89 analytes; biomarkers of 103 chemicals
    - Includes analytes not currently included in National Health and Nutrition Examination Survey (NHANES) biomonitoring
  - Assessed how demographic characteristics and the year of sample collection related to measured levels of the chemicals.

Demographics

- 34% White
- 40% Latina
- 20% Black
- 6% from other or multiple groups

Results

- More than 80% of the chemicals were present in at least one of the women in the study
- More than a third of the chemicals were found in a majority of the participants.
- 19 analytes were detectable in 90–100% of pregnant women, including two benzophenones, three insecticides, one octylphenol ethoxylate (OPE), two parabens, 10 phthalate metabolites, and one Polycyclic aromatic hydrocarbons (PAH)
- Rising levels of replacement chemicals: chemicals meant to replace chemicals that have previously been banned or phased out (e.g., BPA, phthalate)
- Many women exposed to neonicotinoids, a widely used type of pesticide
- Higher exposures in Latinas
  - Pilot study; wider study planned

Methods

- Pregnant women in Memphis, Tennessee
  - Between 16-40 years old, mostly Black, relatively healthy pregnancies
- Measured the amount of 16 phthalates in urine collected from the participants during the 2nd and 3rd trimester of pregnancy.
- Measured expression of each gene in the placenta.

Results

- Several phthalates were associated with changes in the expression of 38 genes within the placenta.
- Some changes in gene expression were only significant in male or female infants.
  - Phthalates may change how the placenta works in different ways for the two sexes.
- Found 27 specific pathways that may have been affected by phthalate exposure.

APS European Society for Paediatric Research SPR Society for Pediatric Research

www.nature.com/pr

CLINICAL RESEARCH ARTICLE

Differential placental CpG methylation is associated with chronic lung disease of prematurity

Wesley M. Jackson[1✉], Hudson P. SantosJr[2,3], Hadley J. Hartwell[2], William Adam Gower[1], Divya Chhabra[4], James S. Hagood[1], Matthew M. Laughon[1], Alexis Payton[2,5], Lisa Smeester[2,5], Kyle Roell[2,5], T. Michael O'Shea[1] and Rebecca C. Fry[2,5]

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-022-28365-x OPEN

Placental genomics mediates genetic associations with complex health traits and disease

Arjun Bhattacharya[1,2✉], Anastasia N. Freedman[3], Vennela Avula[3], Rebeca Harris[4], Weifang Liu[5], Calvin Pan[6], Aldons J. Lusis[6,7,8], Robert M. Joseph[9], Lisa Smeester[3,10,11], Hadley J. Hartwell[3], Karl C. K. Kuban[12], Carmen J. Marsit[13], Yun Li[5,14,15], T. Michael O'Shea[16], Rebecca C. Fry[3,10,11,17✉] & Hudson P. Santos Jr[4,10,17✉]

OXFORD SOT Society of Toxicology academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 183(2), 2021, 269–284

doi: 10.1093/toxsci/kfab089
Advance Access Publication Date: 13 July 2021
Research Article

Comparing the Predictivity of Human Placental Gene, microRNA, and CpG Methylation Signatures in Relation to Perinatal Outcomes

Jeliyah Clark,[*,†] Vennela Avula,[*,†] Caroline Ring,[‡] Lauren A. Eaves,[*,†] Thomas Howard,[†] Hudson P. Santos Jr,[†,§] Lisa Smeester,[*,†] Jacqueline T. Bangma,[*] Thomas Michael O'Shea,[¶] Rebecca C. Fry,[*,†,‖] and Julia E. Rager[*,†,‖,1]

Shorey-Kendrick et al. Clin Epigenet (2021) 13:177
https://doi.org/10.1186/s13148-021-01161-y

Clinical Epigenetics

RESEARCH Open Access

Impact of vitamin C supplementation on placental DNA methylation changes related to maternal smoking: association with gene expression and respiratory outcomes

Lyndsey E. Shorey-Kendrick[1*], Cindy T. McEvoy[2], Shannon M. O'Sullivan[1], Kristin Milner[2], Brittany Vuylsteke[2], Robert S. Tepper[3], David M. Haas[4], Byung Park[5,6,7], Lina Gao[5,6], Annette Vu[8], Cynthia D. Morris[8,9] and Eliot R. Spindel[1]

Approaches to mirror solution-oriented questions

- Why do we care about mechanisms?

  ~Pathways, explanations, mediators, modes of transmission

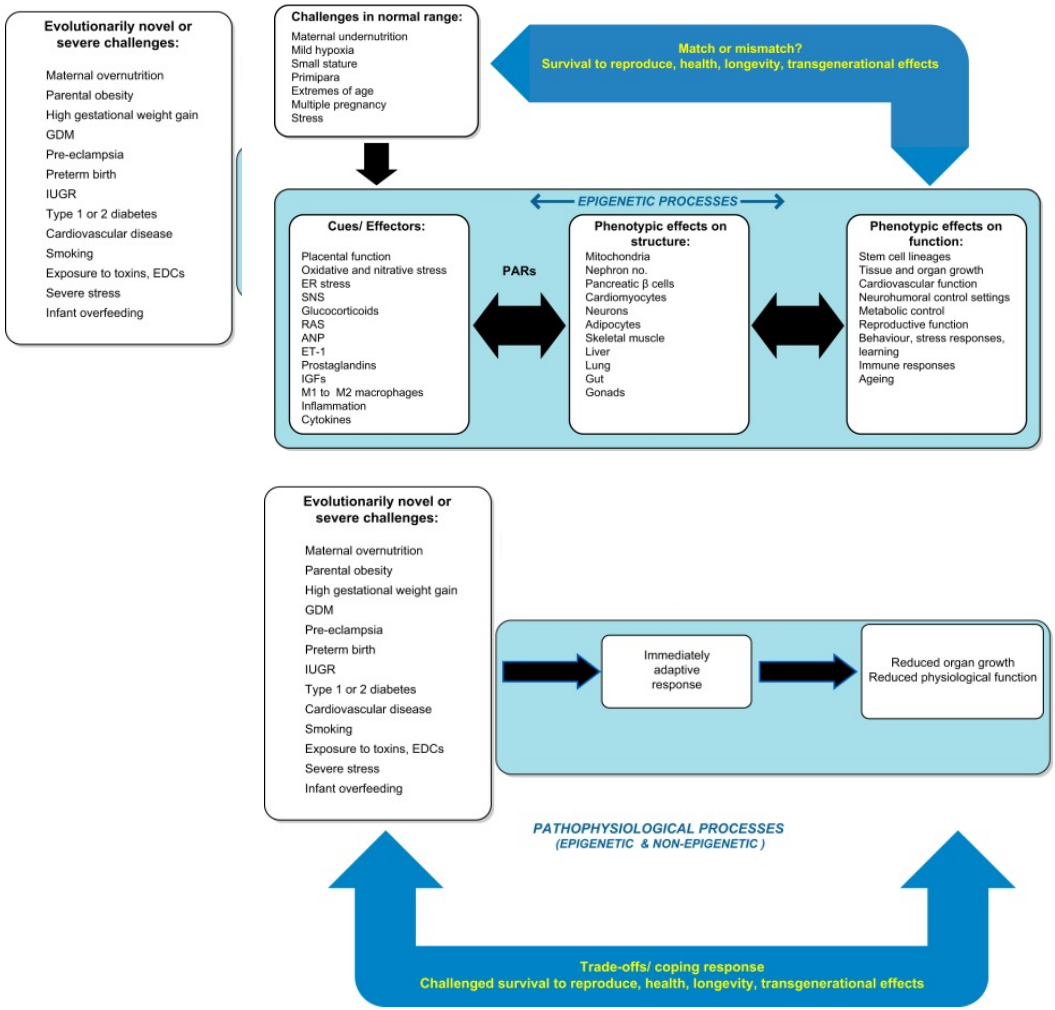
Approaches to mirror solution-oriented questions

- Why do we care about mechanisms?

Mechanism (def):

> "One level of reductionism lower than you work in."

--T. Insall



Hanson, Gluckman.
Physiol Rev. 2014
Oct;94(4):1027-76

Then

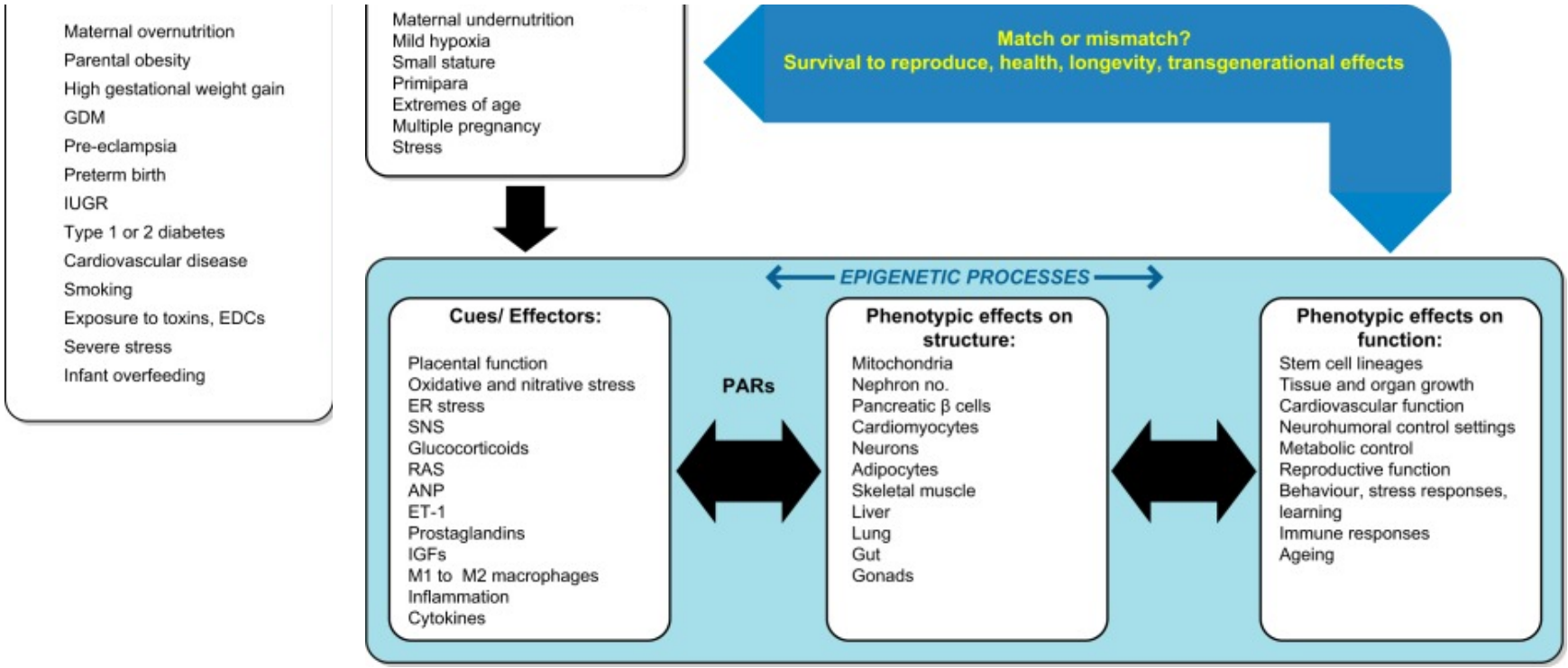
Now

The National Academies of | SCIENCES ENGINEERING MEDICINE

Proceedings of a Workshop
IN BRIEF

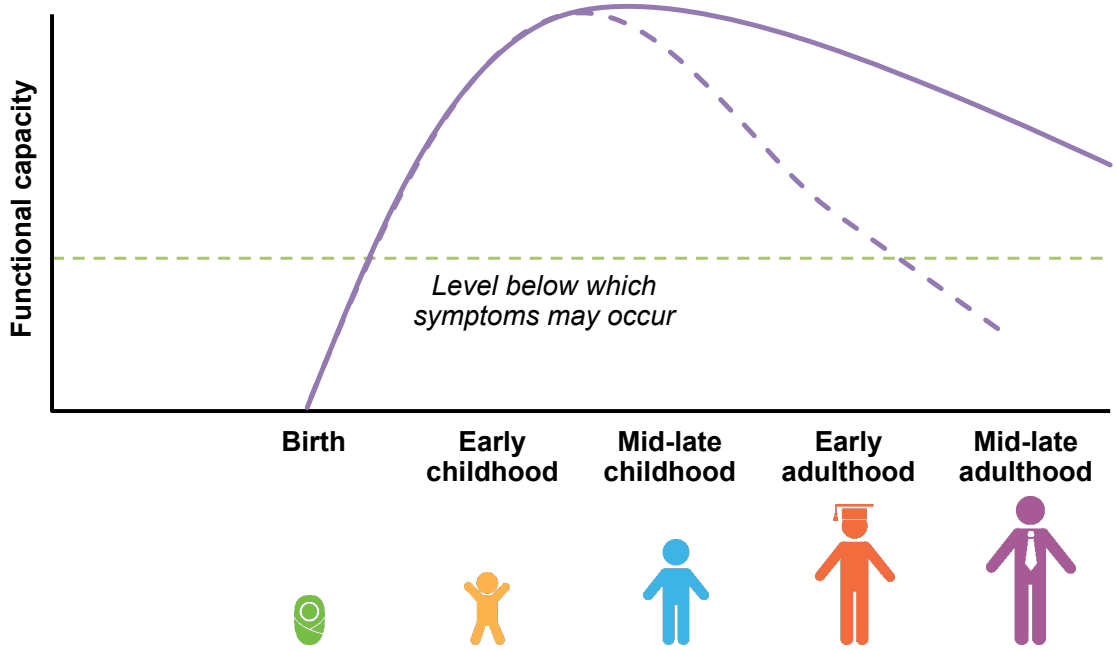
August 2020

Understanding, Controlling, and Preventing Exposure to PFAS
Proceedings of a Workshop—in Brief

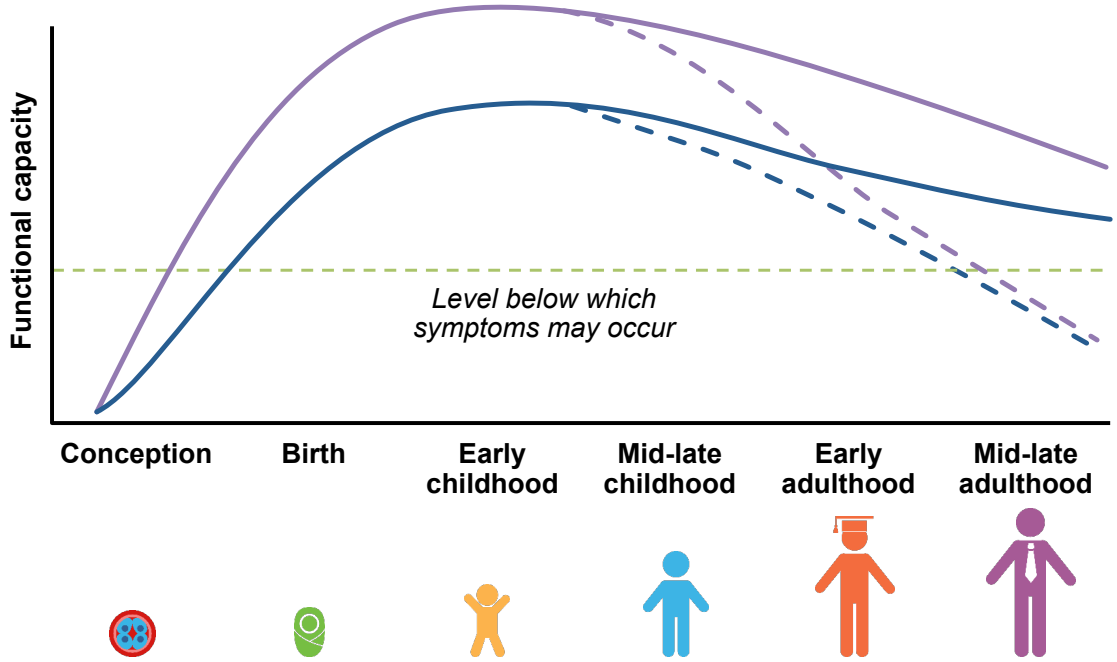


Hanson, Gluckman.
Physiol Rev. 2014
Oct;94(4):1027-76

Pre-existing life course framework

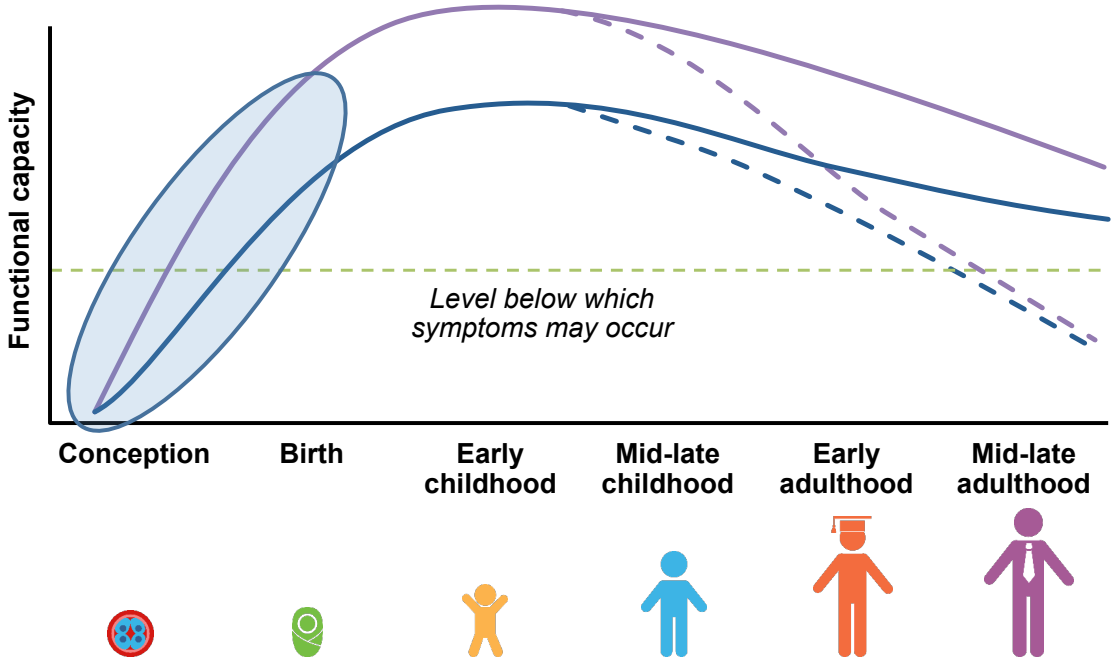


Post-DOHaD Life Course Framework



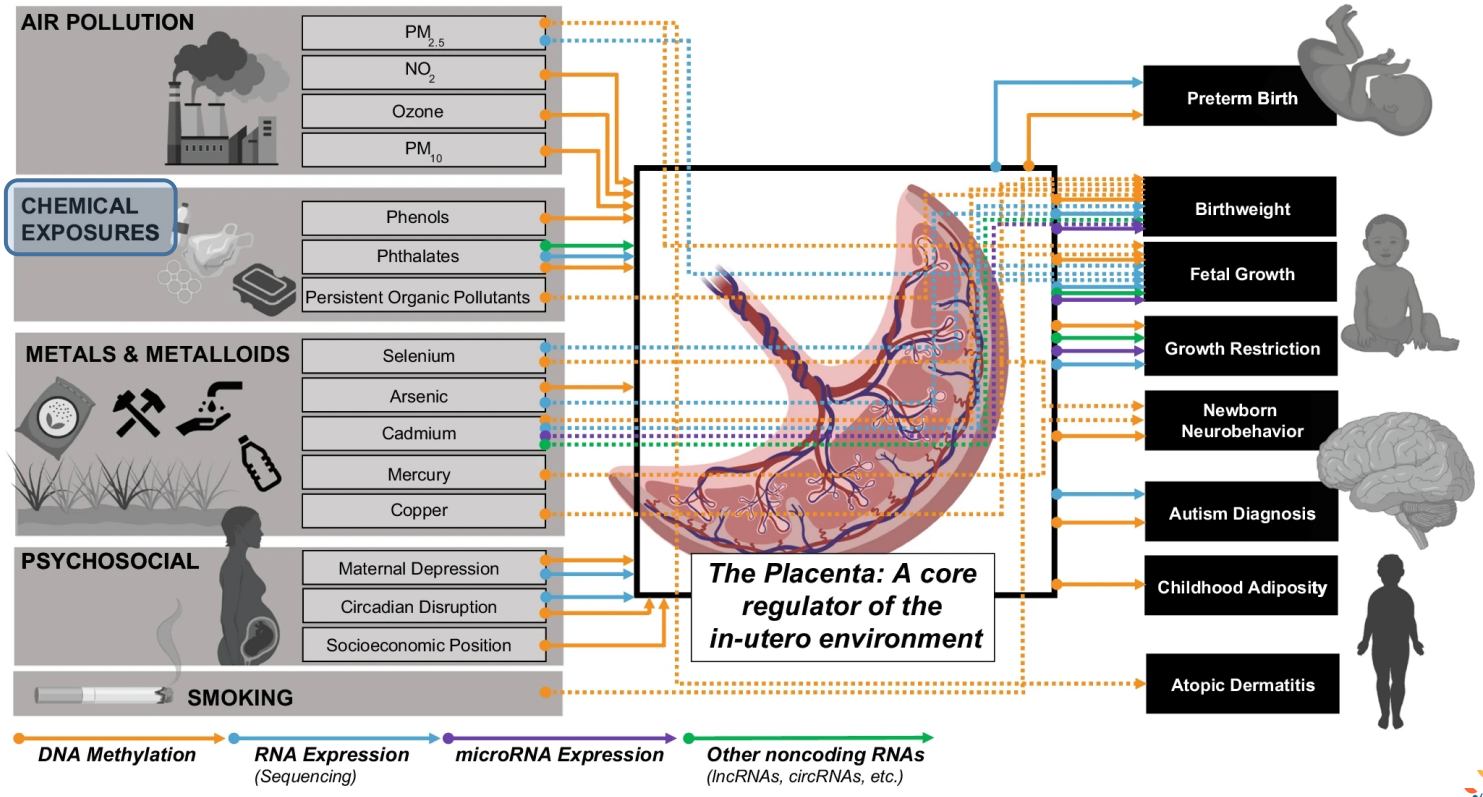
National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Post-DOHaD Life Course Framework



NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

ECHO investigators have begun to examine how prenatal environment affects offspring outcomes via placental 'omics



Lapehn, Paquette. *Curr Envir Health Rpt* 2022

Prenatal PFAS and SGA/ LGA

- 11 ECHO cohorts
- N = 3386
- Births 1999-2019
- Maternal PFAS in serum or plasma
  - Preexisting

  or
  - Measured in HHEAR lab

Characteristic	
Maternal age, mean (SD)	31 (5.7)
Maternal race/ethnicity, %	
Non-Hispanic White	51
Non-Hispanic Black	15
Non-Hispanic Other	15
Hispanic	20
Maternal education, %	
Less than high school	9
High school degree, GED or equivalent	16
Some college, no degree	21
Bachelor's degree and above	52
Unknown	2
Preterm birth, %	7.6
Small for gestational age, %	5.4
Large for gestational age, %	16.6

Padula et al., in press