Developmental Origins of Health and Disease in the ECHO Program

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Program Director
Environmental influences on Child Health Outcomes (ECHO)
Office of the Director, US National Institutes of Health
28 June 2022

Email: NIHKidsandEnvironment@nih.gov
Today

Teratology  DOHaD  ECHO Program
To set the stage...

Teratology
*Dr. Brent*

DOHaD

ECHO Program
To set the stage…

- Teratology
- DOHaD
- ECHO Program
To set the stage…

Teratology

**DOHaD Principles**

ECHO Program
To set the stage…

Teratology

DOHaD Principles

ECHO Program
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

- Severity of early life environmental cue
- Cannot cope (non-adaptive)
  - Early life outcome: Developmental disruption
  - Late life outcome: Developmental disruption
- Can cope (adaptive)
  - Homeostasis
  - Developmental plasticity
  - Selection
  - Immediate benefit
    - IAR
    - PAR
  - Delayed manifestation
    - Intervention to reverse prediction
    - Accurate
    - Inaccurate
    - Benefit due to mismatch (misadaptive)
    - Cost due to mismatch (misadaptive)
Early Environmental Cues—More Severe

More severe $\leftrightarrow$ Less severe

- Severity of early life environmental cue
- Homeostasis
- Developmental plasticity
- Selection
  - IAR
  - PAR

Immediate benefit
- Accurate
- Inaccurate

Delayed manifestation
- Intervention to reverse prediction

Long-term trade-off
- Benefit due to mismatch (adaptive)
- Cost due to mismatch (maladaptive)

Early life outcome
- Developmental disruption
- Cannot cope (non adaptive)

Later life outcome
- Developmental disruption
- Can cope (adaptive)
Early Environmental Cues—More Severe

More severe ↔ Less severe

Cannot cope (non adaptive)

Developmental disruption

Early life outcome

Developmental disruption

Later life outcome

Can cope (adaptive)

Homeostasis

Developmental plasticity

Selection

Immediate benefit

Delayed manifestation

IAR

PAR

accurate

inaccurate

intervention to reverse prediction

Long-term trade-off

Benefit due to mismatch (adaptive)

Cost due to mismatch (misadaptive)
Early Environmental Cues—Less Severe

<table>
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<th>Adaptation</th>
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<td>Mode</td>
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<tr>
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<tr>
<td>0.001 hours</td>
<td>Homeostasis &amp; Allostasis</td>
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<tr>
<td>1 days</td>
<td>Developmental</td>
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<td>0.1 months</td>
<td>Plasticity</td>
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<td>1 years</td>
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<td>10 decades</td>
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<td>1000 millennia</td>
<td>Natural selection</td>
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<td>1000000 millions</td>
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</table>

More severe ↔ Less severe

Can cope (adaptive)

Cannot cope (non adaptive)

- Homeostasis
- Developmental plasticity
- Selection

Early life outcome → Developmental disruption

Immediate benefit → Delayed manifestation

Later life outcome → Developmental disruption

Long-term trade-off → Benefit due to mismatch (adaptive)

Cost due to mismatch (maladaptive)

Intervention to reverse prediction

Accurate → Inaccurate
Developmental Origins of Health and Disease (DOHaD)

More severe ↔ Less severe

Cannot cope (non adaptive)

Can cope (adaptive)

Early life outcome → Developmental disruption

Immediate benefit → Delayed manifestation

Accurate intervention to reverse prediction

Later life outcome → Developmental disruption

Long-term trade-off → Benefit due to mismatch (adaptive) → Cost due to mismatch (maladaptive)

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<td>10000000 millions</td>
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Developmental Origins of Health and Disease

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

**Clinical Studies**
- Tissue biopsies
- Molecular markers
- Small trials

**Animal Models**
- Physiology
- Metabolism
- Genetic Susceptibility
- Epigenetic mechanisms

**In Vitro Studies**
- Isolated tissue studies
- Molecular markers
- Epigenetic mechanisms

Thanks to Sue Ozanne
DOHaD benefits from interactions among multiple disciplines

Population-based Studies
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In Vitro Studies
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- Molecular markers
- Epigenetic mechanisms

Hypothesis testing

Thanks to Sue Ozanne
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...

Precision Prevention

SEX/GENDER
AGE
RACE/ETHNICITY
SOCIOECONOMIC STATUS
FAMILY HISTORY
GEOGRAPHY
... then take action
Observational & Intervention Research

ECHO Cohorts

ECHO IDeA States Pediatric Clinical Trials Network

44 states, DC, PR
ECHO Cohorts Overall Scientific Goal

Answer **solution-oriented questions** about effects of a 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

**Neurotoxicity of Ortho-Phthalates: Recommendations for Critical Policy Reforms to Protect Brain Development in Children**
Stephanie M. Engel PhD, Heather B. Patissaul PhD, Charlotte Brody RN, Russ Hauser MD, ScD, MPH, Ami R. Zota ScD, MS, Deborah H. Bennet PhD, Maureen Swanson... (show all authors)

**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
But level of confidence in findings not high
For cognition and other neurodevelopmental outcomes

*E.G. Radke, et al.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DEHP</th>
<th>DINP</th>
<th>DBP</th>
<th>DIBP</th>
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<td>Motor</td>
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<td>Social behavior</td>
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<td>I</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>S</td>
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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

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

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

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

Prenatal Phthalate Exposure and Child Weight and Adiposity from in Utero to 6 Years of Age.
Phthalates and Mediators
Placenta and cord blood

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


Published: 3 September 2021 | DOI: 0.97003 | https://doi.org/10.1289/EHP973

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

Emily S. Barrett, Matthew Corsetti, Drew Day, Sally W. Thurston, Christine T. Lofthus, Catherine J. Karr, Krunulchalam Kannan, Kaja Z. LeWinn, Alicia K. Smith, Roger Smith, Frances A. Tylavsky, Nicole R. Bush, Sheela Sathyarayana

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

Rebekah L. Petroff, Vasantina Partimonaharesi, Diana C. Deloney, Deborah J. Watkins, Joseph Caster, Diana Hapgood, Douglas M. Rudin, and Jaclyn M. Goodrich
ECHO-wide Cohort Advantages

• Sample size, diversity
• Harmonized exposure data
  – Timing
  – Newer and older chemicals
• Harmonized outcome data
• Analytic framework
  – Single chemicals
  – Mixtures
<table>
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<tr>
<td>Effects of bisphenols and phthalates on fetal and postnatal growth</td>
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<tr>
<td>In utero exposure to metals and phthalates in relation to communication from birth to 3 years of age</td>
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<tr>
<td>Association between phthalate biomarkers at birth and infant electrocortical parameters</td>
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<tr>
<td>Impact of early childhood exposures to phthalates on attention deficit hyperactivity disorder (ADHD)</td>
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<tr>
<td>Prenatal phthalate exposures and Autism Spectrum Disorder symptoms in low-risk children</td>
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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

Confidential: Do not share or cite

Cardona Cordero, in preparation
Per- and Polyfluoroalkyl Substances (PFAS)
Per- and Polyfluoroalkyl Substances (PFAS)

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

Also, present in placenta


**ECHO-wide Cohort Analyses in Progress**

| 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

Confidential: Do not cite or share

Padula et al., in press
Higher amounts of each PFAS associated with lower fetal growth

Confidential: Do not cite or share

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

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

Smaller babies

Born too soon

Confidential: Do not cite or share

Padula et al., in press
Key Gap

➤ Only a fraction of chemicals measured or evaluated for health effects in pregnant women or children

~350 chemicals biomonitoried 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)

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

<table>
<thead>
<tr>
<th>Sample characteristic</th>
<th>N (%)</th>
<th>Unit</th>
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<td>Year of sample collection</td>
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<td>2008–2015</td>
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<td>2016</td>
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<td>2017</td>
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<td>2018</td>
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<td>2019–2020</td>
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<tr>
<td>Highest educational attainment (missing: n = 7)</td>
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<tr>
<td>≤ HS or equivalent</td>
<td>44 (27)</td>
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<tr>
<td>Some college, AA degree, or Trade school</td>
<td>45 (27)</td>
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<tr>
<td>≥ Bachelor’s degree</td>
<td>75 (46)</td>
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## Chemicals in 3+ cohorts and 10% of study sample

**BOLD** = not included in NHANES monitoring

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<th>O.P.</th>
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<td>MnBP/MiBP</td>
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<td>MOP</td>
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### Phthalate alternatives

|                  |         |

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**National Institutes of Health**

*Environmental influences on Child Health Outcomes (ECHO)*

60
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
Black children with higher asthma incidence rates than white children, but only in early childhood.
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

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

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.

Thanks to Roz Wright
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

allan.just@mssm.edu
Critical Windows for Air Pollution and Airways Outcomes

Late pregnancy?

Thanks to Roz Wright
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.$^{a, receiving}$; Kirwa, Kipruto$^{c}$; LeWinn, Kaja Z.$^{f}$; Bush, Nicole R.$^{g,h}$; Sathyanarayana, Sheela$^{c, i}$; Tylavsky, Frances A.$^{l}$; Barrett, Emily S.$^{i}$; Nguyen, Ruby H. N.$^{m}$; Karr, Catherine J.$^{a, c, i}$
Mid- (to late-) pregnancy exposure to PM$_{2.5}$ associated with wheeze and asthma among 4 yo children whose mothers had no asthma

Risk ratio per 2 mcg/m$^3$ (>2 SD) increment in PM$_{2.5}$

Similar findings for current wheeze and current asthma.
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 $\leq 0.1 \mu m$, 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
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
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.
CLINICAL RESEARCH ARTICLE
Differential placental CpG methylation is associated with chronic lung disease of prematurity
Wesley M. Jackson1,2, Hudson F. Santour3,4, Hadley J. Hartwell1, William Adam Gower1, Divya Chhabra1, James S. Haggard1, Matthew M. Laughon1, Alexis Payton1,6, Lisa Smeester1,6, Kyle Ross1,6, T. Michael O'Shea1 and Rebecca C. Fry1,6

Comparing the Predictivity of Human Placental Gene, microRNA, and CpG Methylation Signatures in Relation to Perinatal Outcomes
Jelihah Clark1, Vennela Avula1, Caroline Ring1, Lauren A. Eaves1, Thomas Howard1, Hudson F. Santos Jr.1, Lisa Smeester1, Jacqueline T. Bangma1, Thomas Michael O'Shea3, Rebecca C. Fry1,6,8 and Julia E. Rager1,6,9

ARTICLE
Placental genomics mediates genetic associations with complex health traits and disease
Arjun Bhattacharya1,2,3, Anastasia N. Freedman2,3, Vennela Avula1,2, Rebeca Harris1,6, Wei Wang1,6, Calvin Pan1,6, Alison J. Lusis1,6,7,8, Robert M. Joseph9, Lisa Smeester1,6,9, Hadley J. Hartwell1, Kari C. Kukan1,2, Carmen J. Marzetti1,3, Yun Li1,6,10,11, T. Michael O'Shea3, Rebecca C. Fry1,6,9,10,11,12 and Hudson F. Santos Jr.1,6,10,11

RESEARCH
Impact of vitamin C supplementation on placental DNA methylation changes related to maternal smoking: association with gene expression and respiratory outcomes
Lyndsay E. Shoey-Kendrick1,2, Cindy T. McEvoy2, Shannon M. O'Sullivan1, Kristen Miner1, Brittany Wayko1,2, Robert S. Tepper1,2, David M. Haas1,2, Byung Park1,2, Lina Gao1,2, Annette Vu1, Cynthia D. Morris1,2 and Eliot R. Spindel1
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

Seemed like a good idea at the time...

PFOA and PFOS are really good at repelling dirt, grease, water & stains

Now

PFOA & PFOS
U.S. manufacturers voluntarily phased out PFOA and PFOS, two specific PFAS chemicals.

GenX Chemicals
GenX chemicals are a replacement for PFOA.

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

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)
Cues/Effectors:
- Placental function
- Oxidative and nitritative stress
- ER stress
- SNS
- Glucocorticoids
- RAS
- ANP
- ET-1
- Prostaglandins
- IGFs
- M1 to M2 macrophages
- Inflammation
- Cytokines

PARs

Phenotypic effects on structure:
- Mitochondria
- Nephron no.
- Pancreatic β cells
- Cardiomyocytes
- Neurons
- Adipocytes
- Skeletal muscle
- Liver
- Lung
- Gut
- Gonads

Phenotypic effects on function:
- Stem cell lineages
- Tissue and organ growth
- Cardiovascular function
- Neurohumoral control settings
- Metabolic control
- Reproductive function
- Behaviour, stress responses, learning
- Immune responses
- Ageing

Match or mismatch?
Survival to reproduce, health, longevity, transgenerational effects
Pre-existing life course framework

- Pre-existing life course framework

- Level below which symptoms may occur

- Birth
- Early childhood
- Mid-late childhood
- Early adulthood
- Mid-late adulthood

- Functional capacity

National Institutes of Health
Environmental Influences on Child Health Outcomes (ECHO)
Post-DOHaD Life Course Framework

Level below which symptoms may occur

Functional capacity

Conception  Birth  Early childhood  Mid-late childhood  Early adulthood  Mid-late adulthood

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)
Post-DOHaD Life Course Framework

- Functional capacity
- Level below which symptoms may occur

Event timeline:
- Conception
- Birth
- Early childhood
- Mid-late childhood
- Early adulthood
- Mid-late adulthood

Logos:
- 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’
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

<table>
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<tr>
<th>Characteristic</th>
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<td>Maternal age, mean (SD)</td>
<td>31 (5.7)</td>
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<tr>
<td>Maternal race/ethnicity, %</td>
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<tr>
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<tr>
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<tr>
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<td>Maternal education, %</td>
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<tr>
<td>Large for gestational age, %</td>
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</tbody>
</table>

Padula et al., in press