ECHO Cohort Consortium Spring 2025 Meeting

April 3-4, 2025

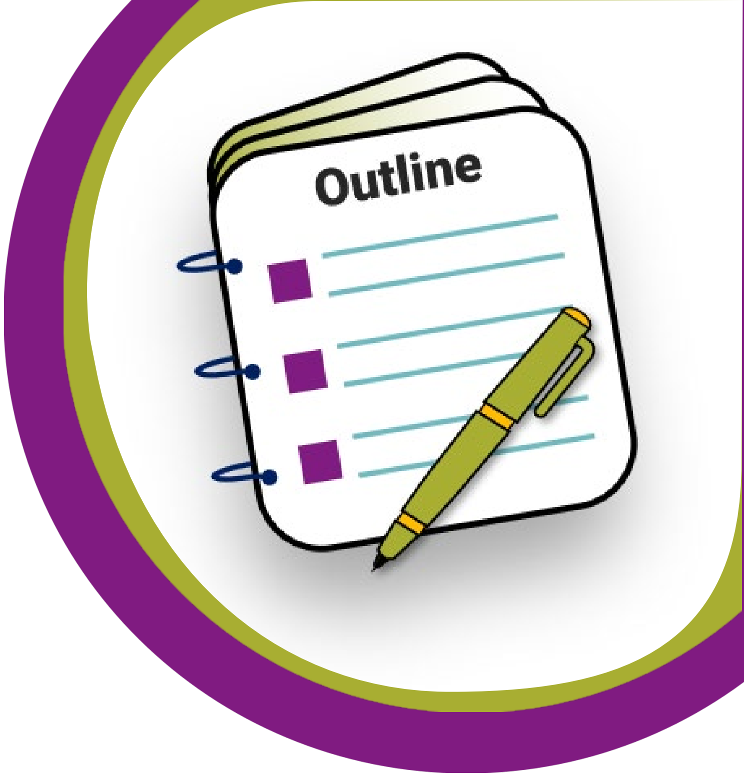
ECHO Environmental influences on Child Health Outcomes

ECHO Cohort Consortium
Successes & Challenges, Spring 2025

Matthew W. Gillman, MD, SM
Director, ECHO Program Office
April 3, 2025

Today

- Welcome and thank you
- Highlighting successes
- Navigating challenges
- Looking to the future



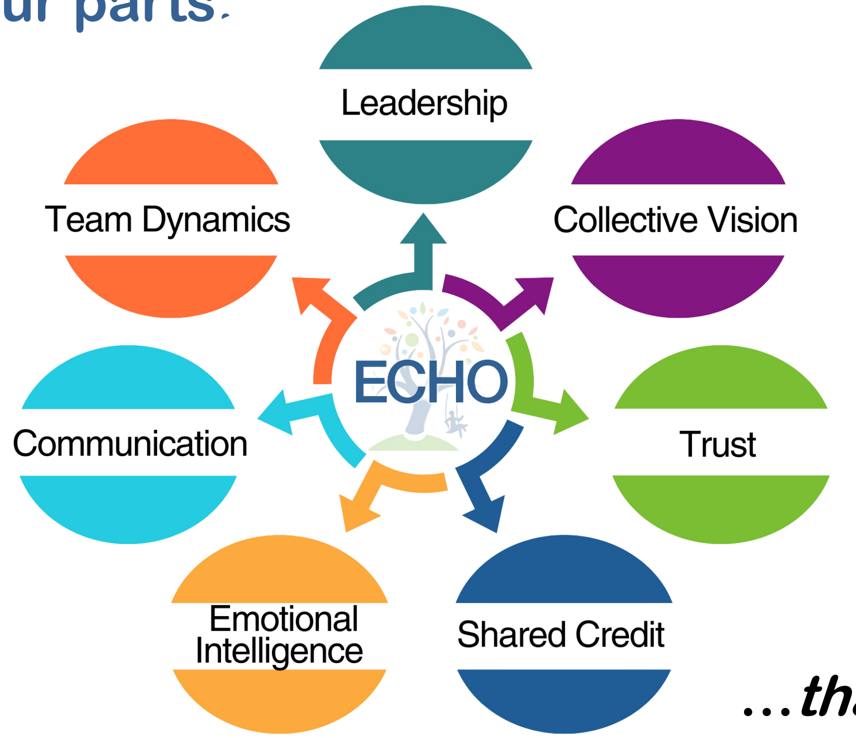
Welcome and Thank you

Thank you!

Planning Committee	
Michelle Jansen	Wei Perng*
Kaja LeWinn	Michelle Schreiner
Kristen Lyall	Lila Schweins
Debra MacKenzie*	Sam Simons
Christina Park	

*Co-chairs

ECHO's whole is greater than the sum of our parts.



Science of team science

...*thank you* for working together during challenging times!

Highlighting Successes

Great Achievements in Cycle 2

Congratulations!

- You all are doing a great job!
  - Amazing progress in <2 years in Cycle 2
- Overall
  - Exceeded minimum expectations for almost all UG3 metrics through 2.28.25
  - Came close to or exceeded many Goals-Objectives-Indicators-**Targets** (GOIT) aspirational targets—for 5.31.25

Excellent Overall Enrollment

All Participants	Other than Non-Hispanic White Participants
29,564 Cumulative MAP Up to Feb. 28, 2025	**13,673** Cumulative MAP Up to Feb. 28, 2025
28,768 Cumulative N Enrolled	**15,589** Cumulative N Enrolled
97 % % of MAP Enrolled	**114 %** % of MAP Enrolled

UG3 Minimum: 75% of MAP projected participants
GOIT: 90%

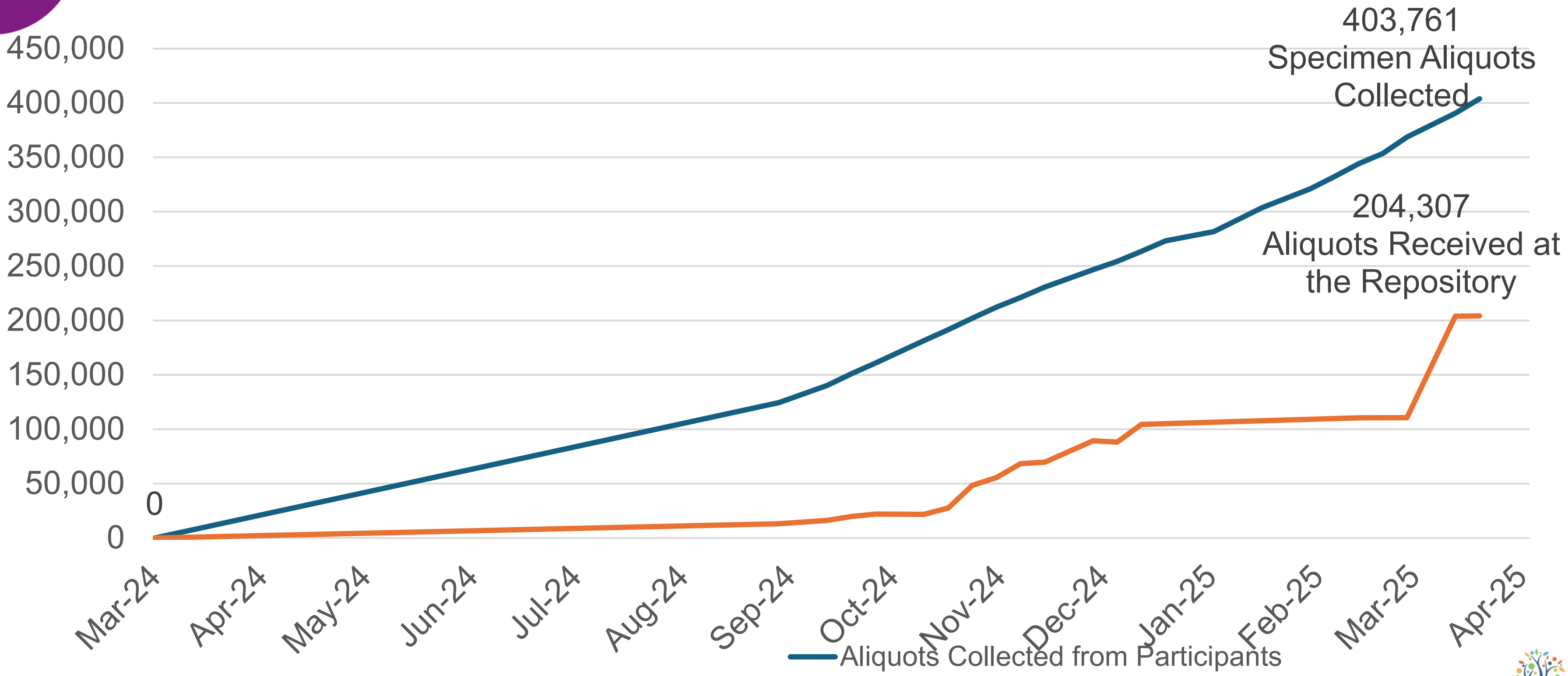
Excellent Enrollment in Pregnancy & Childhood

Participant type	% of Milestone Accrual Plan
Overall	97%
All Pregnancies	108%
Pregnancies Other than NH-White	119%
All Children	94%
Children Other than NH-White	112%

Data Collection	Biospecimens Collection
691,142 Cumulative N core Data Elements Expected	23,912 N Biospecimens Expected
624,178 Cumulative N Core Data Elements Collected	17,649 Cumulative N Biospecimens Collected
90% % Collected of Expected	74% % Collected of Expected

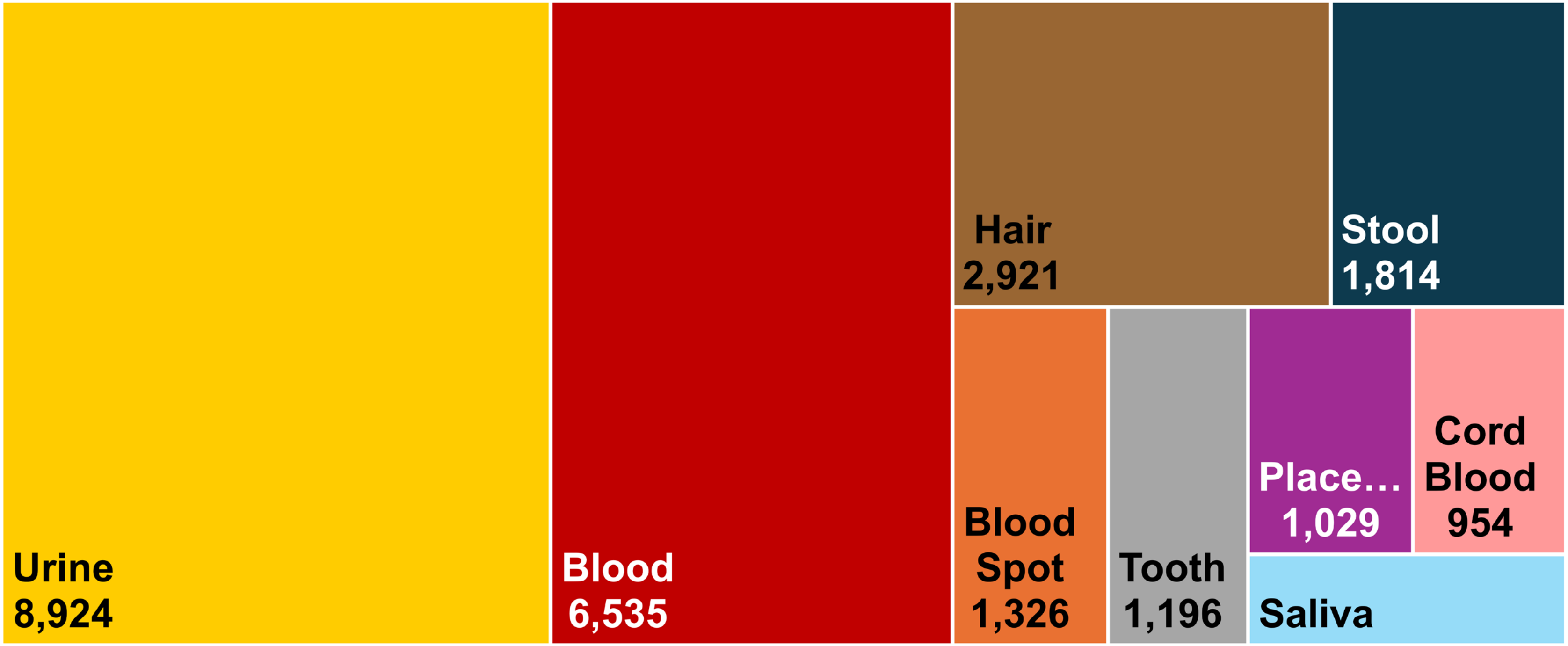
UG3 Minimum: 85% of expected **core data elements**, GOIT: 95%
UG3 Minimum: 50% of expected **core biospecimens**, GOIT: 70%

>400K Aliquots in 1 Year!



See DAC Table C1 for assumptions and definitions

Wide Variety of Biospecimens Collected



See DAC Table C3 for details

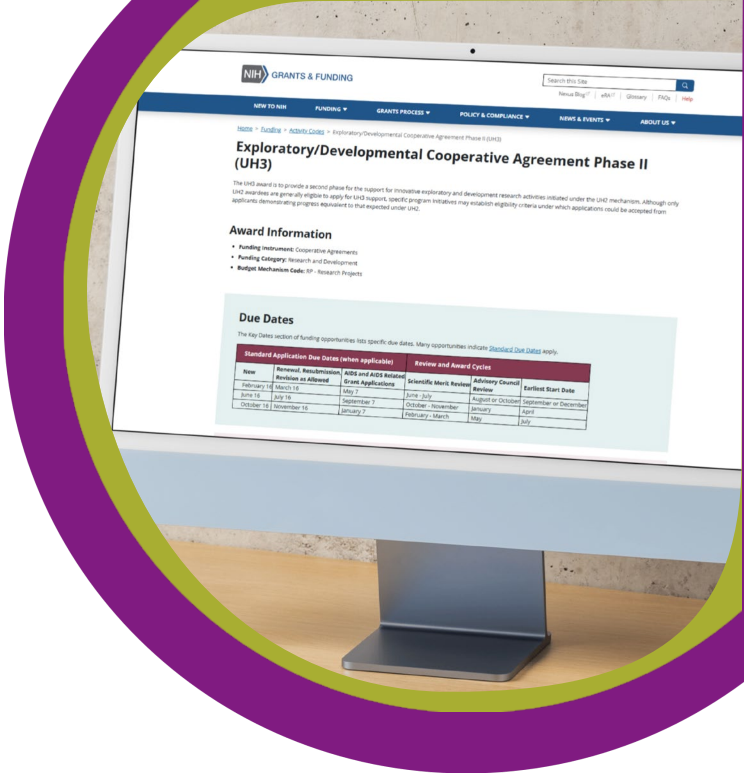
Looking to (Recent) Past and to Future

- UG3 metrics (recent past)
  - Individual site eligibility for UH3 transition
  - Minimum standards
- Goals-Objectives-Indicators-Targets (GOIT: past, present, & future)
  - Focus on measurable traits of healthy cohort study
    - Recruitment
    - Retention
    - Data & specimen collection
    - Analyses and publication
  - Aspirational targets
  - Success depends on working together—Sites, Centers, Cores
  - Address challenges at system level
    - Problem solving can be at site, core, or center level—usually combination
  - Culture of continuous quality improvement

What’s not in GOIT but still vital?

ECHO Funding
Moving into UH3 Phase

- Continuing Resolution in place through September 2025
  - ECHO's Congressional funding levels same as FY 2024



ECHO Turns 10 in 2026!

External Evaluation

- By Abacus, at UNC-Chapel Hill

How Internal and External Evaluation Complement Each Other

Input	Process	Output	Outcome	Impact
•People •Funding •End users <u>Cycle 2 Efficiencies</u> •Governance •Streamlined protocol •Single IRB •Central data capture	•Protocol enhancement •**Recruitment** •Follow up (**retention**) •Protocol **implementation** •**Analysis** proposals •Biospecimen handling •Biospecimen assays •Data analysis •**Manuscript** development	•High enrollment •High retention •Protocol -Updates -Fidelity •Data Analysis -Data platform -DASH dataset -Biorepository •Publications	•Body of literature •Citations in program, policy, practice	•Enhancements in children's health (for generations to come)

Cross-cutting themes

•Team science •Engagement

GOIT

External Evaluation

External Evaluation Well Along

Design 2024-25

- Engage Coordinating Center and NIH
- Define scope
- Draft questions & methods
- **Feedback from governance committees**

Measure 2025-26

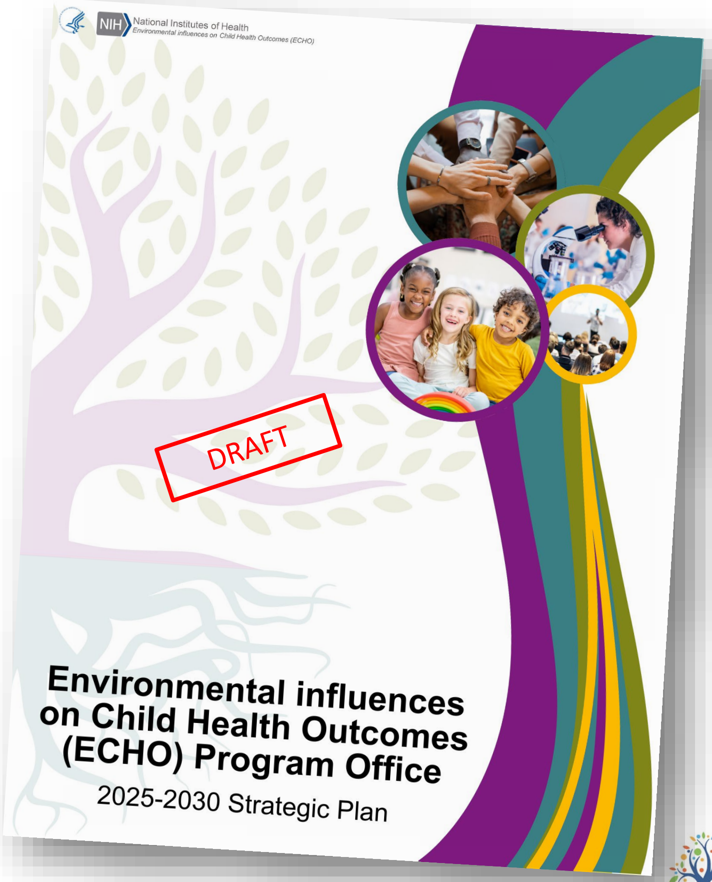
- Measure bibliometrics and collaboration
- **Survey, interview investigators & staff at Study Sites, Cores, Centers**
- Investigate career development

Finalize 2026

- Report back to governance committees
- 10-Year Evaluation Report
- Quality improvement deliverables

ECHO Office 2025-2030 Strategic Plan

- Purpose: Align Program Office activities with current and future needs, guiding principles, and mission
  - Refines strategic goals, restructures objectives from 2020-2024 Plan
  - Highlights scientific priorities and accomplishments
  - Includes success measures
- Target Completion Date: May 2025



High-level peek…

- **3 Strategic Goals**
  - Span internal to external

Goal 3:
Expand ECHO's Reach

Goal 2:
Enable High Impact Research

Goal 1:
Enhance Organizational Effectiveness

Cohort Scientific Priorities

- Identify **modifiable early developmental exposures** that, if addressed by programs, policies, and practices, would enhance child health outcomes across the life course and decrease health disparities.
- Identify **pathways** to ECHO health outcomes that incorporate state-of-the-art analytic biochemical and statistical methods.
- Identify **resilience or susceptibility factors** that buffer or amplify the effects of adverse early life exposures on child health outcomes.
- Identify **periods of development most sensitive** to specific beneficial or detrimental exposures to inform new strategies to promote child health.
- Measure the effects of **natural experiments** or new health innovations or paradigms on child health outcomes.

Expand ECHO’s Reach

ECHO Data & Specimen Access

ECHO Researchers | **Broader Scientific Community**

ECHO Program
ECHO Funding

- **Who:** ECHO investigators
- **What:** Contribute and access identifiable data and biospecimens
- **Where:** ECHO Data Platforms + ECHO Cohort Biorepository

UG3/UH3

Now

Incentivize DASH Use
ECHO Funding

- **Who:** Non-ECHO pre- & post doctoral trainees
- **What**: Can access de-identified ECHO data
- **Where**: NICHD Data and Specimen Hub (DASH)

R36/F32

Past & Future

Ancillary Studies
Non-ECHO Funding

- **Who:** ECHO and non-ECHO investigators
- **What:** Can access identifiable data and biospecimens
- **Where:** ECHO Data Platforms + ECHO Cohort Biorepository

X01

Future

Ancillary Studies Timeline

- Launch Ancillary Studies Website in April or early May 2025

	First Round	Second Round	Third Round
Letter of Support Request	June 2025	October 2025	February 2026
Letter of Support Review	July 2025	November 2025	March 2026
ECHO X01 Due Date	November 2025	March 2026	July 2026

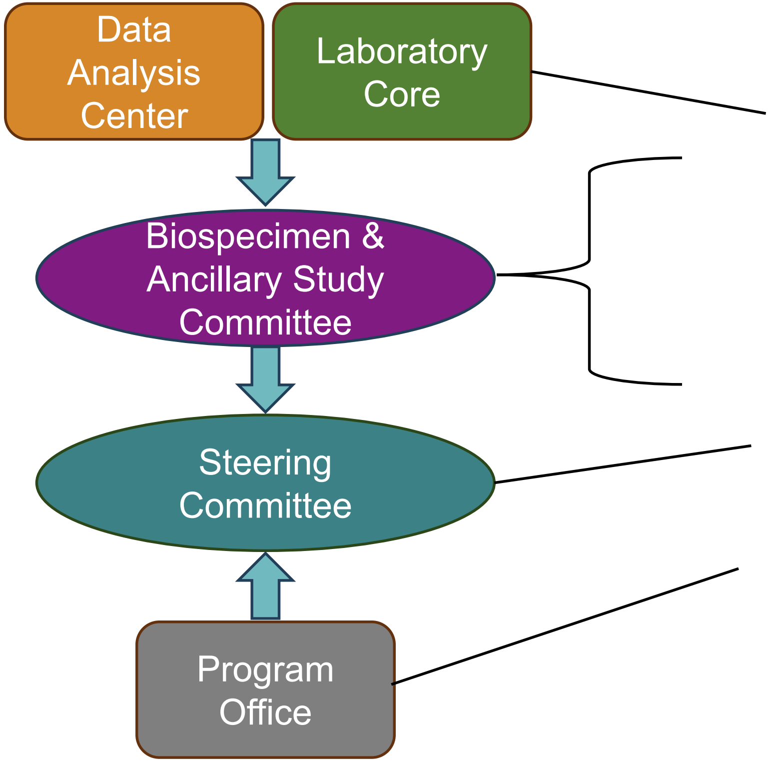
Huge thanks to Ancillary Studies Task Force!

"Navigating complexities with superb spirit of collaboration"

Next Steps for Ancillary Studies Task Force

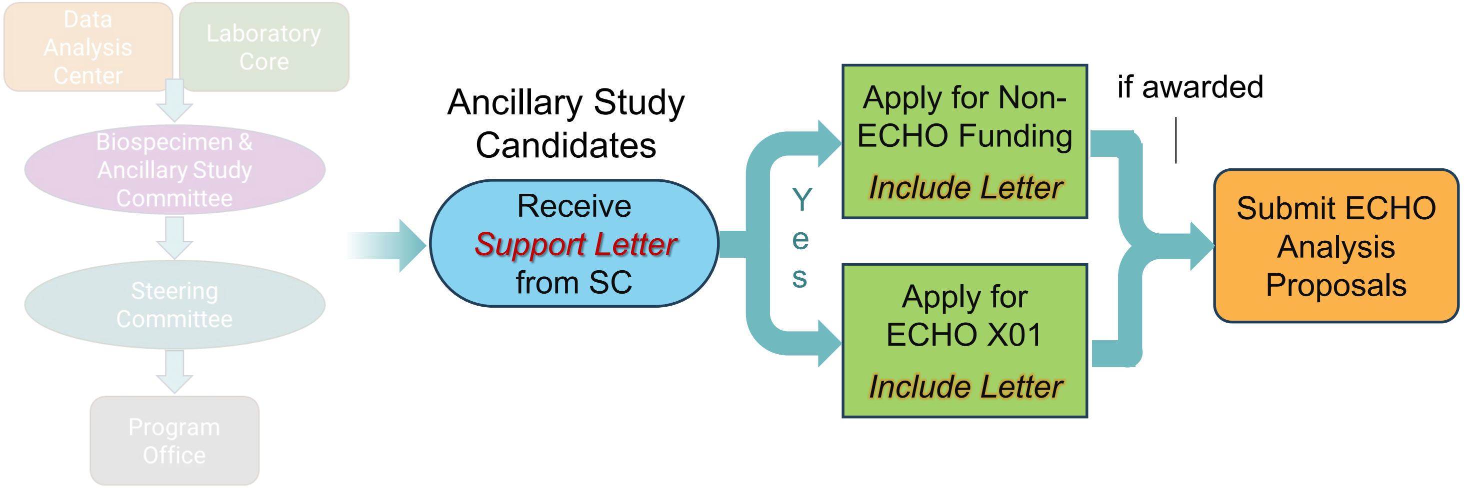
- Launch Ancillary Studies web page
  - —Information for applicants
    - —Including estimating costs for cores & centers
  - —Form to request Letter of Support from Steering Committee
- Finalize review process
  - Including centralized review of requests for biospecimens

Getting a Steering Committee Letter of Support for Funding Application



- High-level feasibility check
- Potential impact, ethics, biospecimen use
- Recommendation to Steering Committee
- *Letter of support*
- Scope review

What the Applicant Does with the Letter

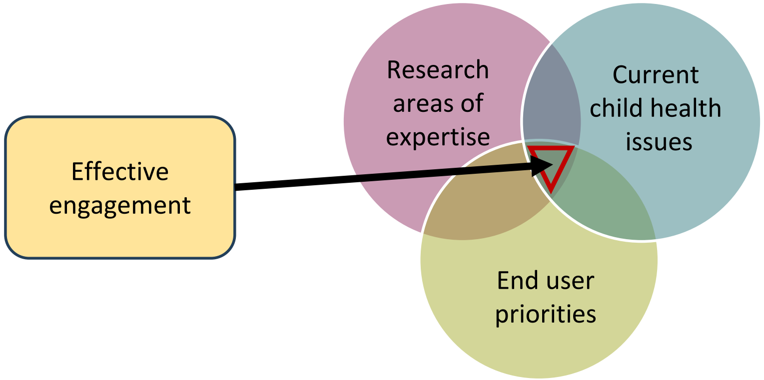


Expanding ECHO's Reach

ECHO Storyteller Local Champion Program

- **Goal:** Facilitate communication between ECHO investigators and their local/state representatives
  - Disseminate ECHO research findings
  - Showcase how ECHO's child health research benefits communities and constituents in each ECHO storyteller's locale.
- **Pilot Participants:** 8 ECHO PIs
  - 5 Cohort
  - 4 ISPCTN

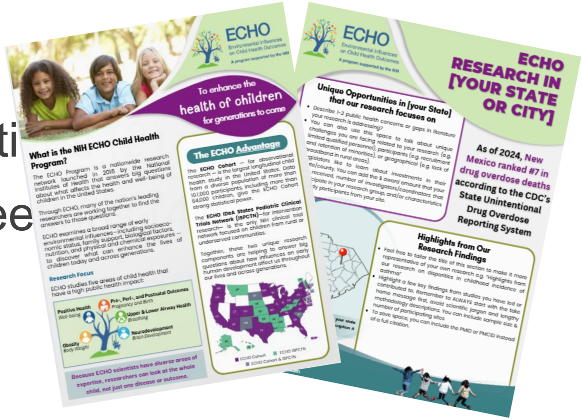
ECHO Storyteller Local Champion Pilot



- Pilot goal:
  - Empower ECHO grantees with tools and resources to engage with local representatives

Storyteller Local Champions
Pilot Outcomes & Next Phase

- Investigators' Engagement Activities in Pilot
  - Mailing/emailing one-page research updates (2)
  - Calls with representati
  - Briefing mee



- Next Phase
  - Expand participation among ECHO researchers
  - Launch communication hub for participating investigators
    - Research update templates
    - Communication training materials
    - Digital spaces for peer-to-peer knowledge sharing
  - Investigator guide
    - Step-by-step manual for legislative outreach

Become a storyteller!

Contact Mabel Terminel, ECHO Program Office mabel.terminel@nih.gov

ECHO Science to Action Symposium
Postponed From May to September 2025

- **Purpose**: Bridge gap between cutting-edge child health research and actionable solutions to enhance kids' growth and development
- **Focus**: How early developmental influences affect children's health
  - Chemical exposures, microplastics, neighborhood factors, social determinants, opioids in newborns
- **Attendee Benefits**:
  - Connect with researchers, policymakers, health professionals, advocates, media
  - Inform programs, policies, practices
  - Discuss enhancing children's health for generations to come

Navigating Challenges

Biospecimen Collection Pause

- No collection kits right now
  - Serious issue
  - Working with Lab Core, Coordinating Center, Biospecimen Operations Task Force to get kits to sites ASAP
- Guidance until then
  - With remaining kits, prioritize collection earlier in life course
    - e.g. if running low on kits to collect blood in pregnancy, prioritize early pregnancy visit
  - Please do <u>not</u> use your own supplies to collect samples
    - Standardization vs. losing out on samples
- Thank you for your patience!

Looking to the future

“Make America Healthy Again”
Executive Order 2.13.25

- “… aggressively combat the critical health challenges facing our citizens, including the rising rates of **mental health disorders, obesity, diabetes, and other chronic diseases**.”
- “… gold-standard **research on the root causes** of why Americans are getting sick”
- “This concern applies urgently to America’s children …”
- “To fully address the growing health crisis in America, we must re-direct our national focus … toward understanding and drastically lowering chronic disease rates and **ending childhood chronic disease**.
  - “This includes fresh thinking on **nutrition, physical activity, healthy lifestyles, over-reliance on medication and treatments, the effects of new technological habits, environmental impacts, and food and drug quality and safety.**”

Make America Healthy Again (MAHA) Commission Areas of Interest

Outcomes	Exposures
Mental illness	Nutrition
Cancer	Physical activities
Asthma	Healthy lifestyles
Autism Spectrum	Technology habits
Autoimmune disease (IBS, psoriasis, MS)	Environmental impacts
Allergies	Food quality and safety
Fatty liver disease	Drug quality and safety
Diabetes	Chemical exposures
Obesity	Electromagnetic radiation
ADHD	Corporate influence

Selected Examples from ECHO Already
8 of ~2000

February 15, 2023

Trends in Screen Time Use Among Children During the COVID-19 Pandemic, July 2019 Through August 2021

Monique M. Hedderson, PhD[1]; Traci A. Bekelman, PhD, MPH[2]; Mingyi Li, MHS[3]; et al

» Author Affiliations | Article Information

JAMA Netw Open. 2023;6(2):e2256157. doi:10.1001/jamanetworkopen.2022.56157

Journal of Adolescent Health
Volume 76, Issue 4, April 2025, Pages 647-656

Original article

Adolescent Social Media Use and Mental Health in the Environmental Influences on Child Health Outcomes Study

Courtney K. Blackwell Ph.D. [a], Maxwell Mansolf Ph.D. [a], Theda Rose Ph.D. [b],

American Journal of Preventive Medicine
Volume 65, Issue 6, December 2023, Pages 1003-1014

Research Article

Childhood Sugar-Sweetened Beverage Consumption: an Agent-Based Model of Context-Specific Reduction Efforts

Matt Kasman PhD [1], Ross A. Hammond PhD [1 2 3], Lydia Reader BS [2], Rob Purcell BS [1],

The American Journal of Clinical Nutrition
Volume 120, Issue 3, September 2024, Pages 583-592

Original Research Article

Association of maternal fish consumption and ω-3 supplement use during pregnancy with child autism-related outcomes: results from a cohort consortium analysis

Kristen Lyall [1], Matt Westlake [2], Rashelle J Musci [3], Kennedy Gachigi [4], Emily S Barrett [5],

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

ORIGINAL ARTICLE

Eat, Sleep, Console Approach or Usual Care for Neonatal Opioid Withdrawal

Authors: Leslie W. Young, M.D., Songthip T. Ounpraseuth, Ph.D., Stephanie L. Merhar, M.D., Zhuopei Hu, M.S., Alan E. Simon, M.D., Andrew A. Bremer, M.D., Ph.D., Jeannette Y. Lee, Ph.D., +35, for the ACT NOW Collaborative* Author Info & Affiliations

Published April 30, 2023 | N Engl J Med 2023;388:2326-2337 | DOI: 10.1056/NEJMoa2214470 | VOL. 388 NO. 25

August 28, 2023

Neighborhood Opportunity and Vulnerability and Incident Asthma Among Children

Izzuddin M. Aris, PhD[1]; Wei Perng, PhD[2,3]; Dana Dabelea, MD, PhD[2,3,4]; et al

Author Affiliations | Article Information

JAMA Pediatr. 2023;177(10):1055-1064. doi:10.1001/jamapediatrics.2023.3133

ECHO Research

ehp Environmental Health Perspectives
ACCEPTED MANUSCRIPTS | ISSUE IN PROGRESS | ARCHIVES | ABOUT THIS JOURNAL | JOURNALS

Research | 7 June 2023

Associations of Gestational Perfluoroalkyl Substances Exposure with Early Childhood BMI *z*-Scores and Risk of Overweight/Obesity: Results from the ECHO Cohorts

This article accompanies INVITED PERSPECTIVE: PFAS AND THE CHILDHOOD OBESITY PHENOTYPE—CHALLENGES AND OPPORTUNITIES.

Authors: Yun Liu, Adaeze C. Wosu, Abby F. Fleisch, Anne L. Dunlop, Anne P. Starling, Assiamira Ferrara, Dana Dabelea, ... SHOW ALL ... , and and the program collaborators for Environmental influences on Child Health Outcomes | AUTHORS INFO & AFFILIATIONS

Publication: Environmental Health Perspectives • Volume 131, Issue 6 • CID: 067001 • https://doi.org/10.1289/EHP11545

ELSEVIER
Environment International
Volume 193, November 2024, 109071

Full length article

Gestational exposure to organophosphate ester flame retardants and risk of childhood obesity in the environmental influences on child health outcomes consortium

Alicia K. Peterson [a] [b], Stacey E. Alexeeff [a], Jennifer L. Ames [a], Juanran Feng [a],

ECHO Cohort and MAHA

- ECHO highly aligned with MAHA priorities
- We’ve already produced high-quality solution-oriented research.
- We’re poised for much more!

Summary

- Amazing progress already in Cycle 2 (2023-2030)
  - Keep up the good work!
- How we are doing overall
  - 10-year evaluation
  - ECHO Program Office Strategic Plan
- Expanding reach of ECHO
  - Ancillary Studies process nearing debut
- New engagement opportunities
  - Become a Storyteller
  - See you at ECHO Science to Action Symposium in September
- New scientific opportunities
  - MAHA priorities

Thank you for the incredible teamwork!

ECHO
Environmental influences on Child Health Outcomes
A program supported by the NIH

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Environmental influences on Child Health Outcomes

A program supported by the NIH

Scientific WG: Obesity

Rachana Singh, MD, MS
(presented by Mike O’Shea, MD, MPH)

April 3, 2025

Background/Rationale

- Prevalence of obesity during pregnancy is increasing; about 50% of pregnant women are overweight or have obesity

- Among children born at term, maternal pre-pregnancy obesity has been associated with greater risk of mid-childhood obesity and abdominal adiposity

- Higher childhood BMI is associated with higher blood pressure

- Children born preterm are more likely to be exposed to perinatal inflammation and socioeconomic disadvantage, which might accentuate associations between higher maternal body mass index (BMI) and higher BMI/blood pressure in the offspring.

Specific Aims & Hypothesis

- **Aim 1**: Estimate the association between maternal pre-pregnancy body mass index (BMI) and BMI and blood pressure in the offspring

  *- **Hypothesis 1**: Higher maternal pre-pregnancy BMI is associated with higher BMI and blood pressure in the offspring.*

- **Aim 2**: Compare these associations for those born at term versus those born preterm

  *- **Hypothesis 2**: Associations are more pronounced for offspring born preterm as compared to born at term.*

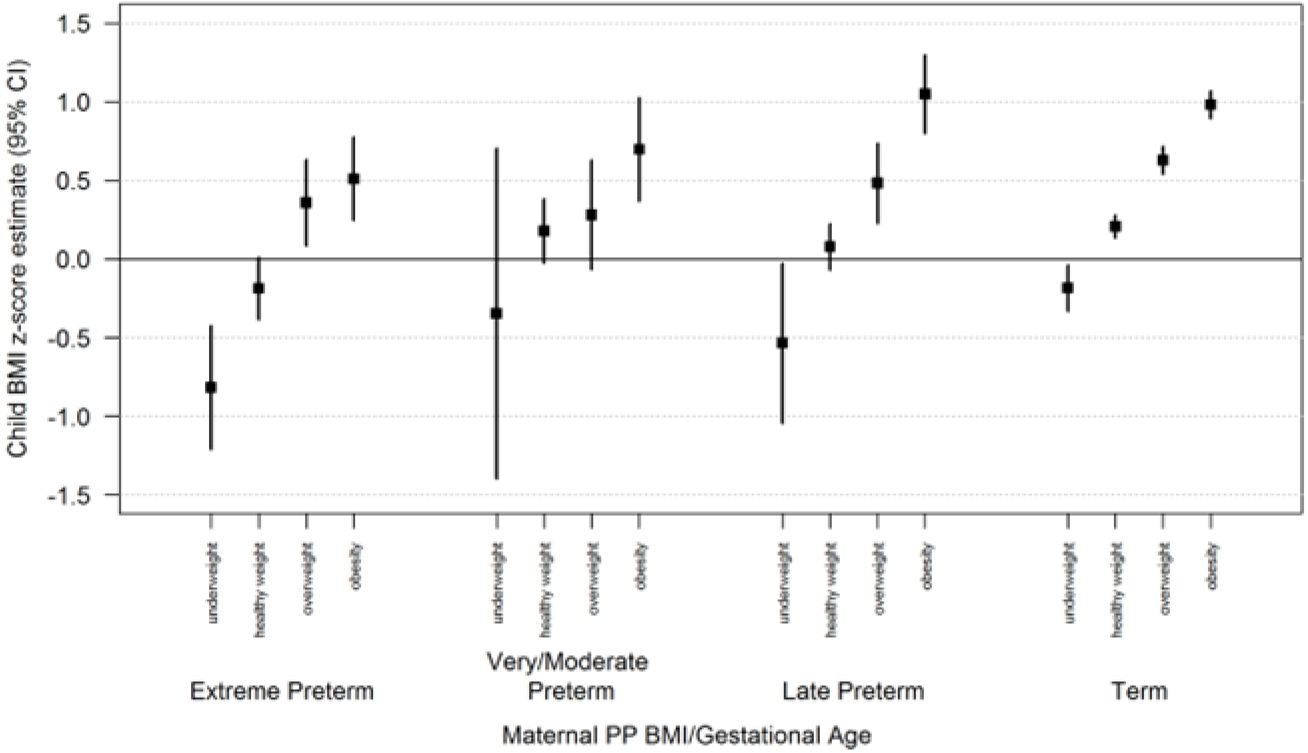
Approach

- Sample: 13,810 mother-child dyads with available pre-pregnancy maternal BMI and at least one child BMI measured during 5-12 years of age, from 44 ECHO cohorts
- A subset (n=9098) had measures of child systolic and diastolic blood pressure harmonized.
- For children with more than one BMI or blood pressure measurement available in this age range, we randomly selected one measurement, giving priority to records with both BMI and blood pressure available.
- For mothers with multiple offspring in the study, we randomly selected one child to be included in the analytical population.

Approach

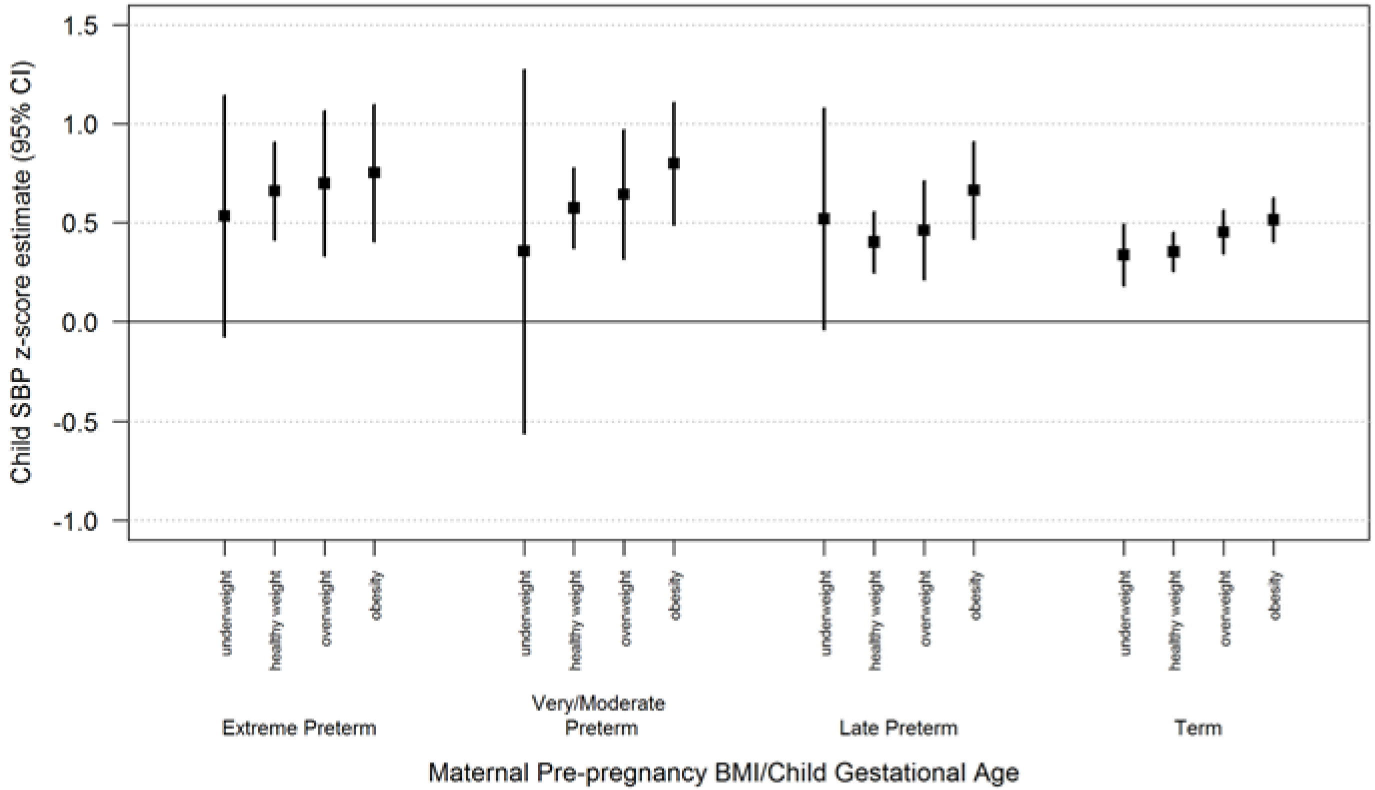
- Maternal pre-pregnancy BMI was either measured at research visit, abstracted from medical record, or self-reported, and categorized as:
  - underweight (<18.5 kg/m^2)
  - healthy weight (18.5 kg/m^2 to <25 kg/m^2)
  - overweight (25 kg/m^2 to 29.9 kg/m^2)
  - obesity (≥30 kg/m^2)
- Age and sex-specific child BMI z-scores were calculated from weight and height measured at the study visit.
- Child systolic and diastolic blood pressure was measured in triplicate and percentiles were derived for age, sex, and height.
  - Elevated blood pressure: (SBP or DBP ≥90th percentile or BP greater than 120/80 mmHg and both measures <95th percentile
  - Stage 1 hypertension: SBP or DBP 95th to <95th + 12mmHg, or 130/80 to 139/89 mmHg, whichever was lower
  - Stage 2 hypertension: SBP or DBP ≥95th percentile + 12mmHg, or ≥ 140/90 mmHg, whichever was lower

Main Results – Mother BMI and Child BMI



Extremely: 987
Very/moderate: 384
Late preterm: 788

Main Results – Mother BMI and Child BP



Extremely: ~ 330
Very/moderate: ~ 335
Late preterm: ~ 555

Conclusions

- After adjustment for maternal education, maternal age, and non-singleton birth, child BMI z-scores followed a monotonic increasing trend with increasing maternal pre-pregnancy BMI levels.

- No such association was demonstrated for offspring blood pressure for both term- and preterm-born offspring.

- Interestingly, children born preterm had lower BMI z-scores yet tended to have elevated blood pressure and hypertension compared to their term counterparts.

Potential Next Steps

- Enrich the sample: larger sample of preterm children; older age children
- Explore renal versus cardio-metabolic factors for blood pressure differences noted between term and preterm-born children.
- Evaluate potential moderators:
  - Maternal sleep in pregnancy
  - Physical activity in pregnancy
  - Neighborhood characteristics in pregnancy
  - Discrimination experienced by mother during pregnancy

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Environmental influences on Child Health Outcomes

A program supported by the NIH

Scientific WG: Airways

Rachel Miller MD, Co-WTL EC0428a
CCCEH Cohort multi-PI
Dr. David and Dorothy Merksamer Professor of Medicine (in Allergy and Immunology)
Icahn School of Medicine at Mount Sinai

April 3, 2025

Rationale

- Environmental exposures and neighborhood-level social determinants of health have been associated with childhood wheeze and asthma.
- The Child Opportunity Index (COI) weighs 29 indicators of neighborhood conditions (via census tracts) that correlate with greater upward economic mobility and better health of children in long-term studies.
- Recent ECHO research has demonstrated that high compared to low COI levels measured at birth are associated with reduced incidence of childhood asthma.

Zanobetti et al. *JAMA Pediatr*. 2022.
Aris et al. *JAMA Pediatr*. 2023.

Specific Aims & Hypothesis

- Determine the impact of prenatal neighborhood conditions as measured by the COI on the development of the more burdensome childhood asthma with recurrent exacerbation (ARE) phenotype.

- **Hypothesis 1:** Lower COI measured using the birth address is associated with higher incidence rates for childhood ARE.
- **Hypothesis 2:** Individually reported race and ethnicity modify the association between COI and ARE.

Approach

Distribution of the study population

Incidence rates (IRs) for ARE

- 6.5 overall incidence per 1000 person-years.
- Highest for children born in very low COI neighborhoods.
- Higher for non-Hispanic Black children compared to non-Hispanic White children across all COI neighborhoods.

IRs of ARE higher for non-Hispanic Black and Hispanic Black children in Very Low COI category

ARE cases highest at very young ages across COI categories

Conclusions

- The IRs of AREs for children born in very low COI neighborhoods were higher than for the other COI categories.
- IRs for non-Hispanic Black children were higher than non-Hispanic White children in every COI category.
- Following adjustment for individual-level characteristics, children born in a very low COI neighborhood demonstrated a higher incidence of ARE among children ages 2-4 years, born in the early 2000s and with a parental history of asthma.

Next Steps

- *The Journal of Allergy and Clinical Immunology.*
- Currently online and print version in press.

- https://www.jacionline.org/article/S0091-6749(25)00273-8/abstract

ECHO

Environmental influences on Child Health Outcomes

A program supported by the NIH

Neurodevelopment Working Group: Prenatal Exposure to Organophosphate Ester Flame Retardants and Behavioral Outcomes in Early Childhood

Jiwon Oh
Postdoctoral Researcher, University of California Davis

April 3, 2025

Background/Rationale

- Organophosphate esters (OPEs) are used as flame retardants and plasticizers
  - Found in consumer and personal care products, including building materials, furniture, textiles, electronics, food packaging, cosmetics, and children's products
  - Increased in use following phase-outs of PBDEs
  - Endocrine disrupting potential
- Exposure to OPEs during gestation, a critical period for neurodevelopment, has been shown to have neurotoxic effects in laboratory animals; however, human studies remain limited and inconclusive
- Neighborhood vulnerability may amplify the adverse impacts of environmental exposures on health outcomes by increasing susceptibility to external stresses

PBDE, polybrominated diphenyl ethers

Specific Aims & Hypothesis

- Specific aims
  - Examine associations between prenatal OPE exposure and internalizing and externalizing behaviors in children 1.5–5 years
  - Assess whether child sex and a measure of social vulnerability modify these associations

- Hypothesis
  - Higher prenatal OPE exposure will be associated with more behavioral problems
  - These associations will vary by child sex and social vulnerability

Methods

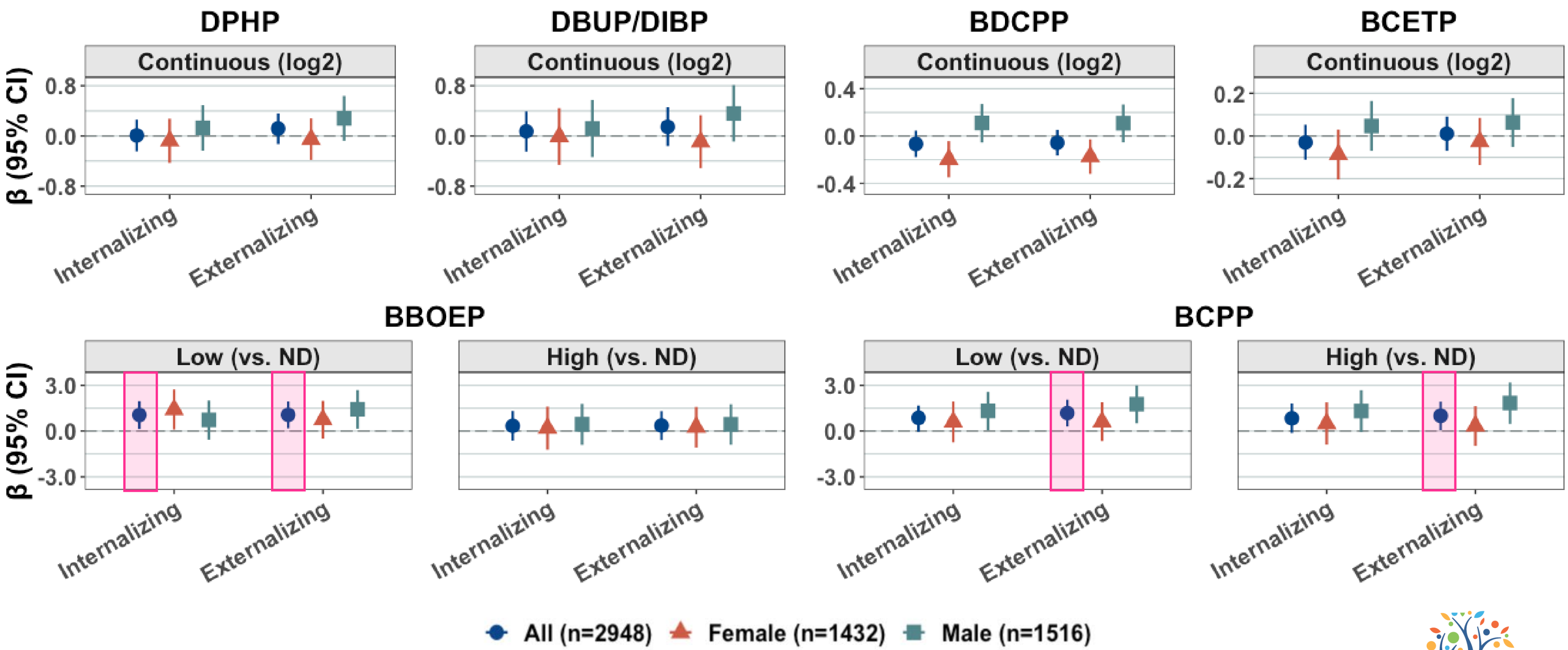
- **Study population:** 2,948 mother-child dyads (singleton births) from 12 cohorts
- **Exposure**
  - Nine OPE biomarkers measured in maternal urine, primarily collected during the 2^{nd} and 3^{rd} trimesters of pregnancy (ECHO-funded bioassay)
  - Modeled based on the detection frequency: continuous (detected >70%), categorical (detected 50-70%), binary (detected 25-50%)
- **Outcome**
  - Child Behavior Checklist (CBCL) for Ages 1.5−5, assessed by caregivers (part of the ECHO-wide protocol)
  - Internalizing and externalizing T-scores normalized by child sex and age were used (higher T-scores indicate more problems)

Statistical Analysis

- Main analysis: **linear mixed-effects models** with a random effect for cohort
  - Covariates: **maternal characteristics** (race/ethnicity, age at delivery, education, marital status, pre-pregnancy body mass index, smoking during pregnancy, parity), **child characteristics** (sex, age at behavior assessment, season of birth)
  - Missing data (<20%) imputed using multiple imputation by chained equations

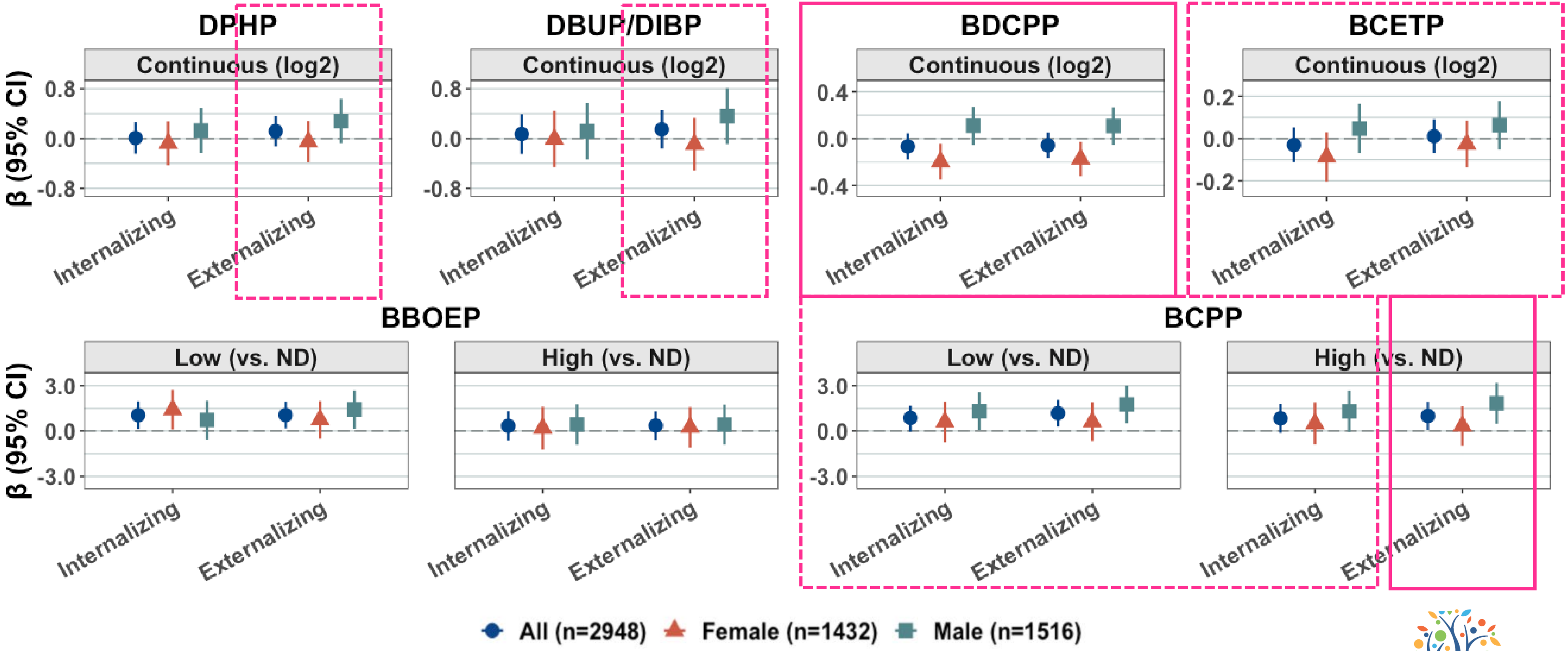
- Effect modification analysis by sex and social vulnerability index (SVI)
  - Present stratified estimates and evaluate interaction terms between sex/SVI and each OPE biomarker

Two OPE Biomarkers Associated with Behaviors



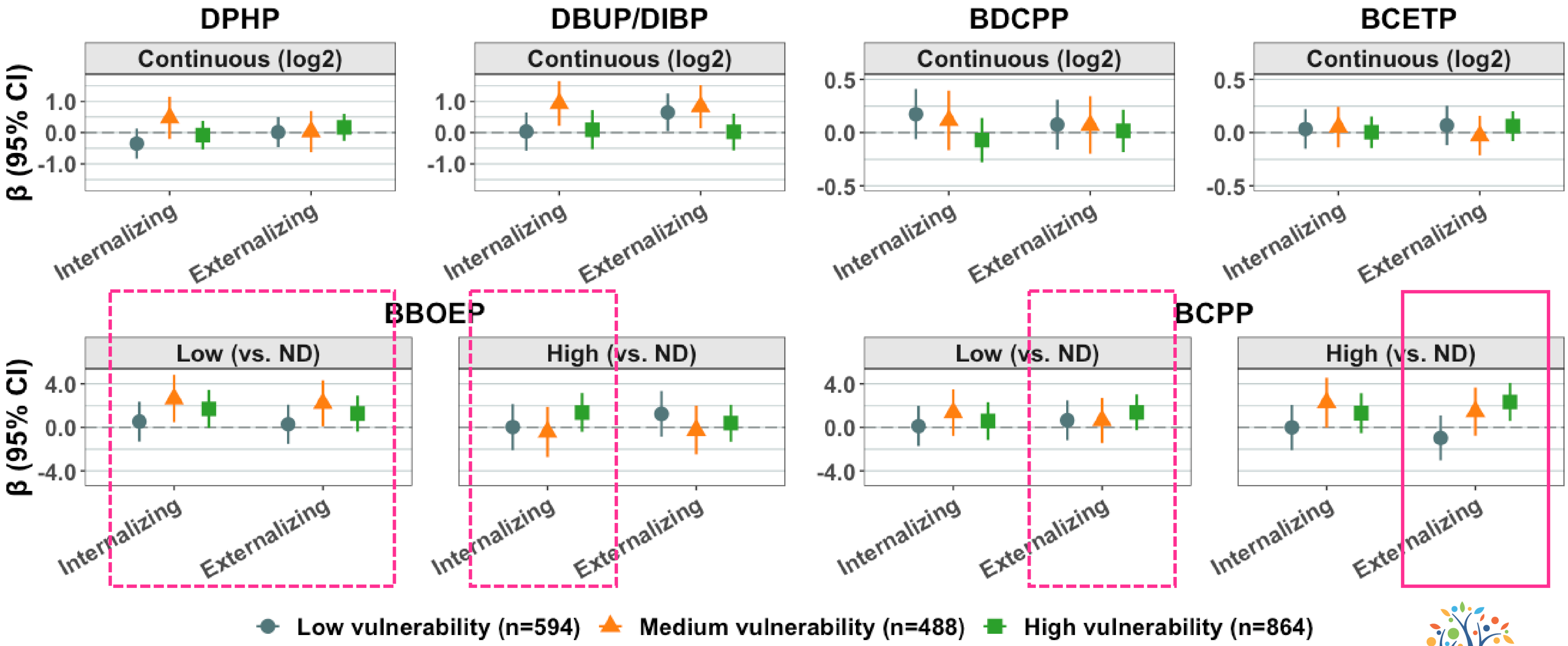
Note: Results for three OPE biomarkers detected <50% are not presented.

Stronger Associations with Higher Scores in Males



Note: Results for three OPE biomarkers detected <50% are not presented. Solid box indicates interaction *p*<0.1.

Joint Effects of an OPE Biomarker and Social Vulnerability on Behavior



Note: Results for three OPE biomarkers detected <50% are not presented. Solid box indicates interaction p<0.1.

Conclusions

- This research benefited from the **ECHO-funded bioassay** and the **ECHO-wide protocol** for assessing children's neurodevelopment
- Gestational exposure to **several OPEs** was associated with **more behavioral and emotional problems** among toddlers and preschoolers
- **Males may be more sensitive** to gestational OPE exposure in relation to behavioral problems
- This research highlights the opportunity to **integrate neighborhood-level factors** (e.g., Social Vulnerability Index, Child Opportunity Index) into epidemiological analyses of chemical exposures and neurodevelopmental outcomes

Note: The manuscript is revised and resubmitted to *Environmental Health Perspectives*.

ECHO

Environmental influences
on Child Health Outcomes

A program supported by the NIH

Scientific WG: PPP

Prenatal stress & depression in relation to placenta morphometry and histopathology (EC0825)

Whitney Cowell, PhD MPH
Assistant Professor, NYU Grossman School of Medicine

April 3, 2025

Background/Rationale

- Maternal stress and depression have been associated with elevated inflammation during pregnancy. *(PMID 17029703, 30447280, 36280180)*

  → Linked with adverse pregnancy outcomes
  (PMID 31529581, 28720162, 16839830, 16046378)

- The placenta is central to the transmission of the maternal milieu to the fetus, yet limited research has considered the influence of stress or depression on the placenta directly. *(PMID 26250599, 22753006, 17536998, 16469781)*

Specific Aims & Hypothesis

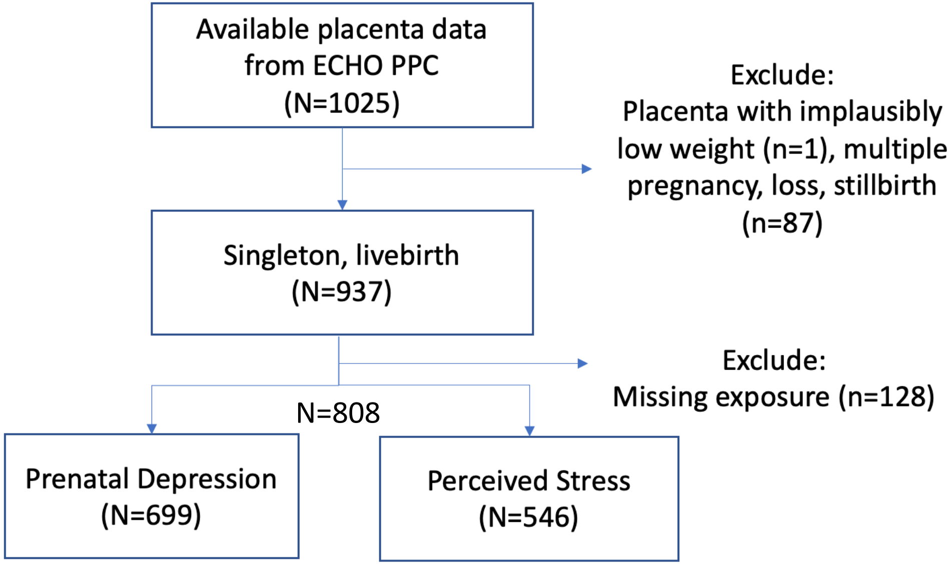
Higher prenatal depressive symptomology and perceived stress will be associated with:

1. Lower birthweight and birthweight to placenta weight ratio, indicative of a less efficient placenta

2. Increased placenta histopathological inflammation

Approach – Analytic sample

- 5 ECHO sites
  - Boricua (2%)
  - Safe Passage (22%)
  - CREW3 (23%)
  - Fair Start (12%)
  - NYU CHES (42%)
- 22 preterm births
- 5 siblings



Approach

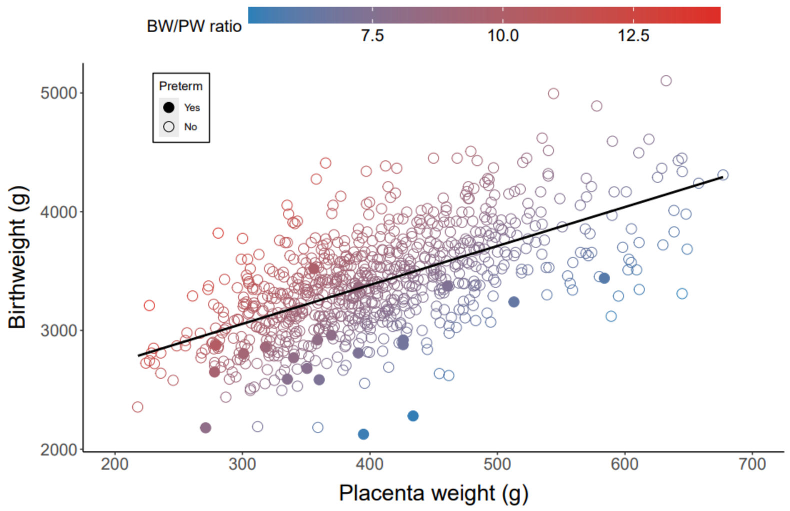
- Exposures
  - Prenatal depressive symptomology
  - Prenatal perceived stress

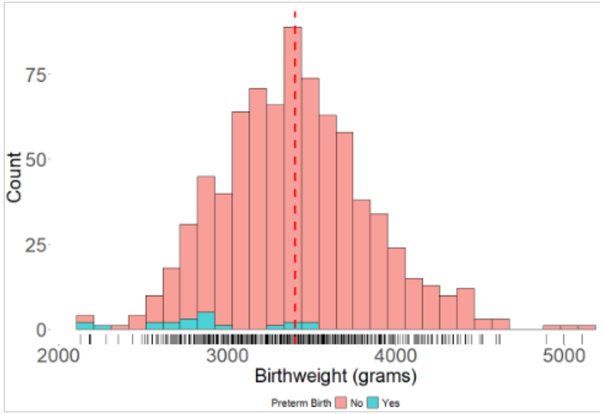
- Outcomes
  - Morphology
    - Birthweight
    - Placenta weight
    - BW:PW ratio

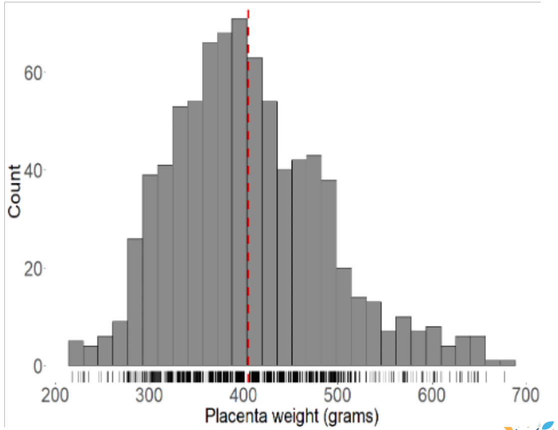
  - Histopathology
    - Chronic placenta inflammation
    - Maternal inflammatory response
    - Fetal inflammatory response
    - Maternal vascular malperfusion
    - Fetal vascular malperfusion

- Models
  - GLM with GEE to account for clustering by site
  - Unadjusted
    - Depression & perceived stress harmonization instrument
  - Adjusted
    - Depression and perceived stress harmonization instrument, maternal age, education, newborn sex, parity, pre-pregnancy BMI, gestational age (2.5% preterm)
    - Multiple imputation for missing covariates

Main Results







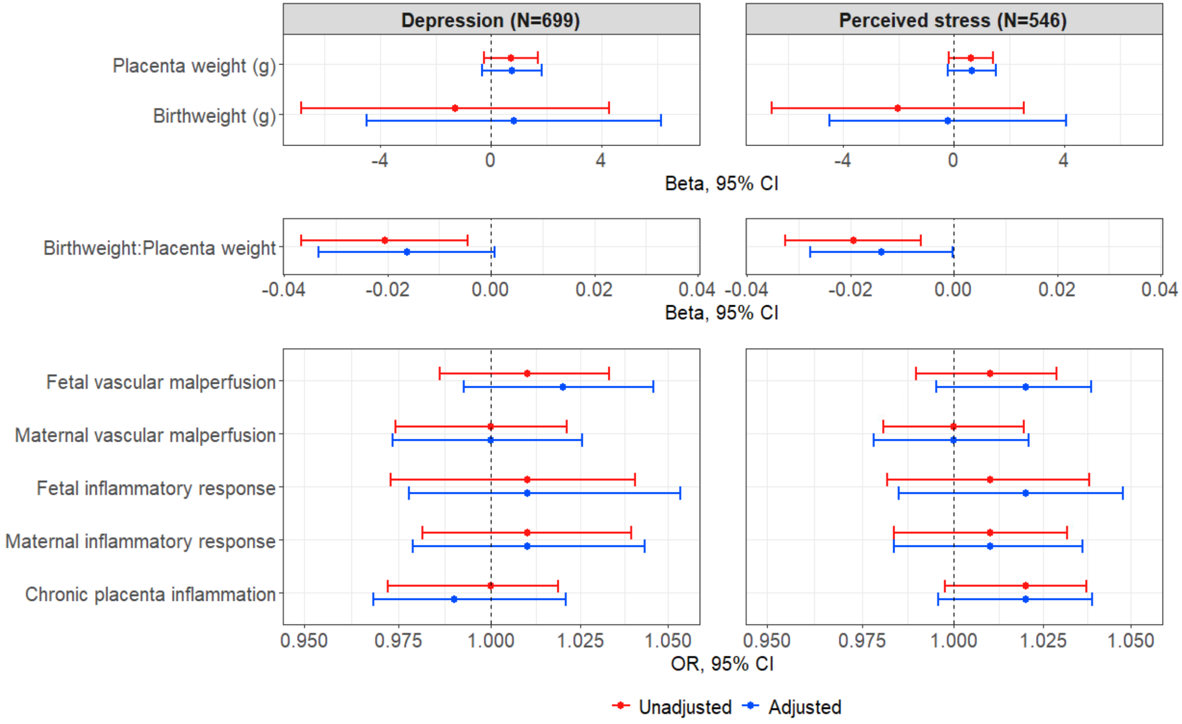
Placenta histopathological characteristics (N, %)	
	All (n = 808)
Chronic placenta inflammation	481 (60%)
Maternal inflammatory response	199 (25%)
Fetal inflammatory response	129 (16%)
Maternal vascular malperfusion	315 (39%)
Fetal vascular malperfusion	459 (57%)

Main Results

- In this sample, prenatal depression and stress are associated with:
  - Decreased BW:PW ratio, driven by an increase in placenta weight
  - Trend toward increased odds of fetal vascular malperfusion and chronic placenta inflammation (stress only)

Placenta lesions indicating reduced blood flow and perfusion

Chronic inflammatory lesions of the placenta



Needs for Next Steps

- BW:PW ratio considerations
  - Assumes relation of BW on PW is linear, but flow and fractal theories suggest that placenta weight may scale to birth weight to the ¾ power
  - Results are consistent when using modified formula ($BW^{0.75}$:PW)
- Placenta size (width, length, thickness)
- Comparison of histopathology prevalence with other samples
- Modification by inflammatory conditions of pregnancy
  - Hypertensive disorders
  - Gestational diabetes
  - Infection

ECHO

Environmental influences
on Child Health Outcomes

A program supported by the NIH

Scientific WG: Positive Health

Courtney K. Blackwell, PhD
ECHO Measurement Core

April 3, 2025

ECHO Environmental influences on Child Health Outcomes

Background/Rationale

… repositories for pediatric studies are rare. Biobanks that span the spectrum of developmental stages are extremely limited.[1]

… clinic-friendly, noninvasive biomarkers could also be used to identify patient-specific response to both stressors and therapeutic interventions.[2]

When employed within a trusted relationship between caregivers and clinicians, selective use of biological measures of stress responses would help address the documented limitations of rating scales of adverse childhood experiences as a primary indicator of individual risk and strengthen the ability to focus on variation in intervention needs, assess their effectiveness, and guide ongoing management.[3]

Background/Rationale

- Biomarker research traditionally focuses on negative health outcomes.[4-11]
- Emerging science in adult samples suggests associations between certain biomarkers and psychological well-being
  - *Neuroendocrine (cortisol,* norepinephrine, DHEA-S)[12-14]
  - *Immune (CRP, IL-2, IL-3, IL-6, IL-10, TNFa)*[12,13,15,16]
  - *Cardiovascular (HDL, LDL)*[12, 13]
  - *DNA methylation (biological aging)*[17]
- Very few studies in pediatric samples
  - E.g., adolescent optimism associated with lower IL-6[18]; positive psychotherapy intervention associated with lower epigenetic age acceleration[19], neonatal inflammation associated with better well-being for adolescents born pre-term[20]
- Limited work evaluating biological substrates of psychological well-being and ill-being *at the same time*
  - E.g., distinct associations of well-being with cortisol, norepinephrine, HDL cholesterol, DHEA-S, TNFα, IL-2, IL-3, and systolic blood pressure[12,14]

Specific Aims & Hypothesis

- **Primary Aim:** To investigate whether subjective measures of well-being, stress, and psychopathology are differentially associated with different immune, cardiovascular (lipid), and epigenetic aging markers.
  - **H1:** Children with higher psychological well-being (life satisfaction, meaning and purpose) will have lower levels of inflammation and LDL; higher levels of anti-inflammatory markers; better HDL; and lower levels of age acceleration compared to children with lower well-being.
  - **H2:** Children with higher psychological "ill-being" (stress, depression, internalizing and externalizing problems) will have higher levels of inflammation and LDL; lower anti-inflammatory levels; worse HDL; and greater age acceleration compared to children with lower ill-being.
  - **RQ1:** Are there differences in associations by child sex?

Approach: *Exploratory cross-sectional study*

- Bivariate correlations between well-being, ill-being, and biomarkers
  - Construct matrix to evaluate distinct associations

- Multiple regression analyses predicting biomarkers from well-being, ill-being, and covariates

- Sex-stratified models to explore different associations in these strata

Reproduced from Ryff et al. 2006[12]

Main Results & Conclusions

- TBD

Needs for Next Steps

- Requires submitting new analysis concept (once open) for investigator-initiated assays for inflammation and lipid assays – currently the only available cytokine samples for children who also have self-reported well-being were collected in infancy
- Waiting for DNAm data to pursue epigenetic age under this analysis proposal EC0789

References

1. Shores DR, Everett AD. Children as biomarker orphans: progress in the field of pediatric biomarkers. The Journal of pediatrics. 2018 Feb 1;193:14-20.
2. Forkey H, Szilagyi M, Kelly ET, Duffee J. Trauma-informed care. *Pediatrics*. 2021;148(2):e2021052580.
3. Shonkoff JP, Boyce WT, Bush NR, et al. Translating the Biology of Adversity and Resilience Into New Measures for Pediatric Practice. *Pediatrics*. Jun 1 2022;149(6).
4. Davis SL, Latimer M, Rice M. Biomarkers of Stress and Inflammation in Children. *Biol Res Nurs*. Oct 2023;25(4):559-570.
5. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain, behavior, and immunity*. 2007;21(7):901-912.
6. Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychol Med*. Sep 2019;49(12):1958-1970.
7. Pantell MS, Silveira PP, de Mendonça Filho EJ, et al. Associations between Social Adversity and Biomarkers of Inflammation, Stress, and Aging in Children. *Pediatric Research*. 2024;95(6):1553-1563.
8. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. *Mol Psychiatry*. 2016;21:642–649.
9. Slopen, N., Kubzansky, L. D., & Koenen, K. C. (2013). Internalizing and externalizing behaviors predict elevated inflammatory markers in childhood. Psychoneuroendocrinology, 38, 2854–2862.
10. Suglia SF, Koenen KC, Boynton-Jarrett R, et al. Childhood and Adolescent Adversity and Cardiometabolic Outcomes: A Scientific Statement From the American Heart Association. *Circulation*. Jan 30 2018;137(5):e15-e28.
11. Copeland WE, Shanahan L, McGinnis EW, Aberg KA, van den Oord EJ. Early adversities accelerate epigenetic aging into adulthood: a 10-year, within-subject analysis. *Journal of Child Psychology and Psychiatry*. 2022;63(11):1308-1315.
12. Ryff CD, Dienberg Love G, Urry HL, et al. Psychological well-being and ill-being: do they have distinct or mirrored biological correlates? *Psychotherapy and psychosomatics*. 2006;75(2):85-95
13. Ryff CD, Singer BH, Dienberg Love G. Positive health: connecting well-being with biology. *Philosophical transactions of the Royal Society of London Series B, Biological sciences*. Sep 29 2004;359(1449):1383-94.
14. Mittwoch-Jaffe T, Shalit F, Srendi B, Yehuda S. Modification of cytokine secretion following mild emotional stimuli. *Neuroreport*. 1995;6(5):789-792.
15. Zuccarella-Hackl C, Princip M, Auschra B, Meister-Langraf RE, Barth J, von Känel R. Association of Positive Psychological Well-Being with circulating inflammatory markers: a systematic review and Meta-analysis. *Neuroscience & Biobehavioral Reviews*. 2023;150:105186.
16. Ironson G, Banerjee N, Fitch C, Krause N. Positive emotional well-being, health behaviors, and inflammation measured by C-Reactive protein. *Social Science & Medicine*. 2018;197:235-243.
17. Kim ES, Nakamura JS, Strecher VJ, Cole SW. Reduced epigenetic age in older adults with high sense of purpose in life. *The Journals of Gerontology: Series A*. 2023;78(7):1092-1099.
18. Oreskovic NM, Goodman E. Association of optimism with cardiometabolic risk in adolescents. *J Adolesc Health*. Apr 2013;52(4):407-12.
19. Sullivan AD, Merrill SM, Konwar C, et al. Intervening After Trauma: Child–Parent Psychotherapy Treatment Is Associated With Lower Pediatric Epigenetic Age Acceleration. *Psychological Science*. 2024:09567976241260247.
20. Lee J, Yanni D, Oran A, Blackwell CK, Taylor G...Santos H, Fry R, O'Shea TM. Associations between neonatal systemic inflammation and health of adolescents born extremely preterm. *In preparation*.

ECHO

Environmental influences on Child Health Outcomes

A program supported by the NIH

Scientific WG: Physical Chemical Working Group

Rose Schrott, PhD, ScM
Johns Hopkins University

April 3, 2025

ECHO Environmental influences on Child Health Outcomes

Prenatal organophosphate ester (OPE) exposure impacts child health

- Prenatal OPE exposure has been associated with several pregnancy and child health outcomes.
  - OPEs cross the placental barrier
  - Preterm birth & low birthweight
  - Adverse neurodevelopment
  - Metabolic dysregulation
  - Thyroid dysfunction
  - Altered immune responses
- Understanding the biology impacted by OPE exposures can help us to identify new therapeutic targets to complement public policy efforts aimed at improving child health.
  - DNA methylation, a regulator of biology, is a high priority process that may act as a mechanism to explain how environmental exposures can influence child health outcomes

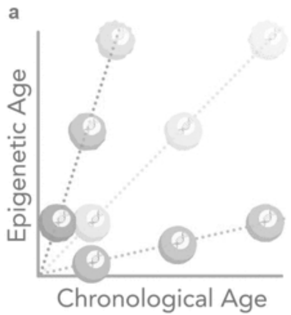
Hypothesis

DNA methylation patterns are associated with increased OPE biomarker levels during pregnancy and these effects may be modified by child sex.

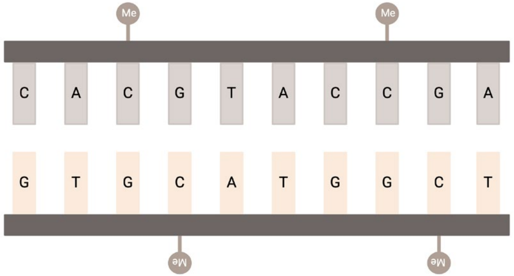
Units of methylation tested

1. Global (aggregate) DNA methylation levels

2. Biologic aging pathway



3. Individual CpGs (EWAS)



Approach

Inclusion criteria

Prenatal OPE biomarkers measured from maternal samples

Cord blood DNA methylation data measured on the 27K, 450K, or EPIC arrays

Exclusion criteria

None

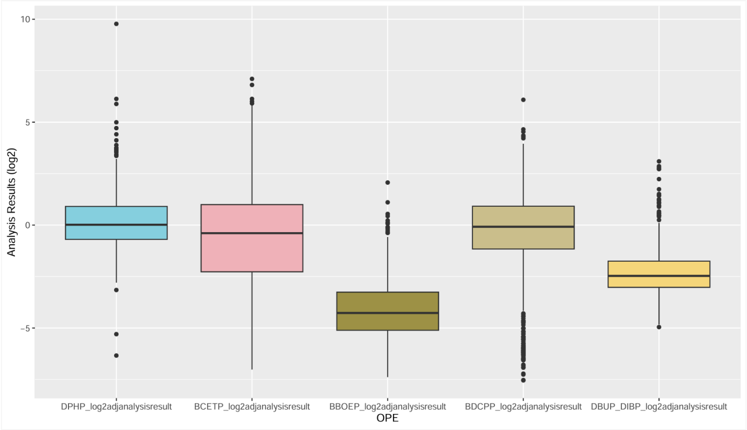
Exposure

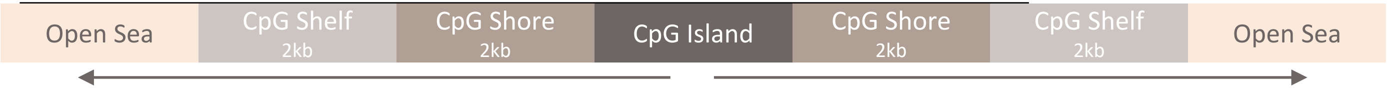
Continuous OPE biomarker levels (BBOEP, BCETP, BDCPP, DBUP_DIBP, DPHP)

Used Boeniger method adjustment to account for urinary hydration status

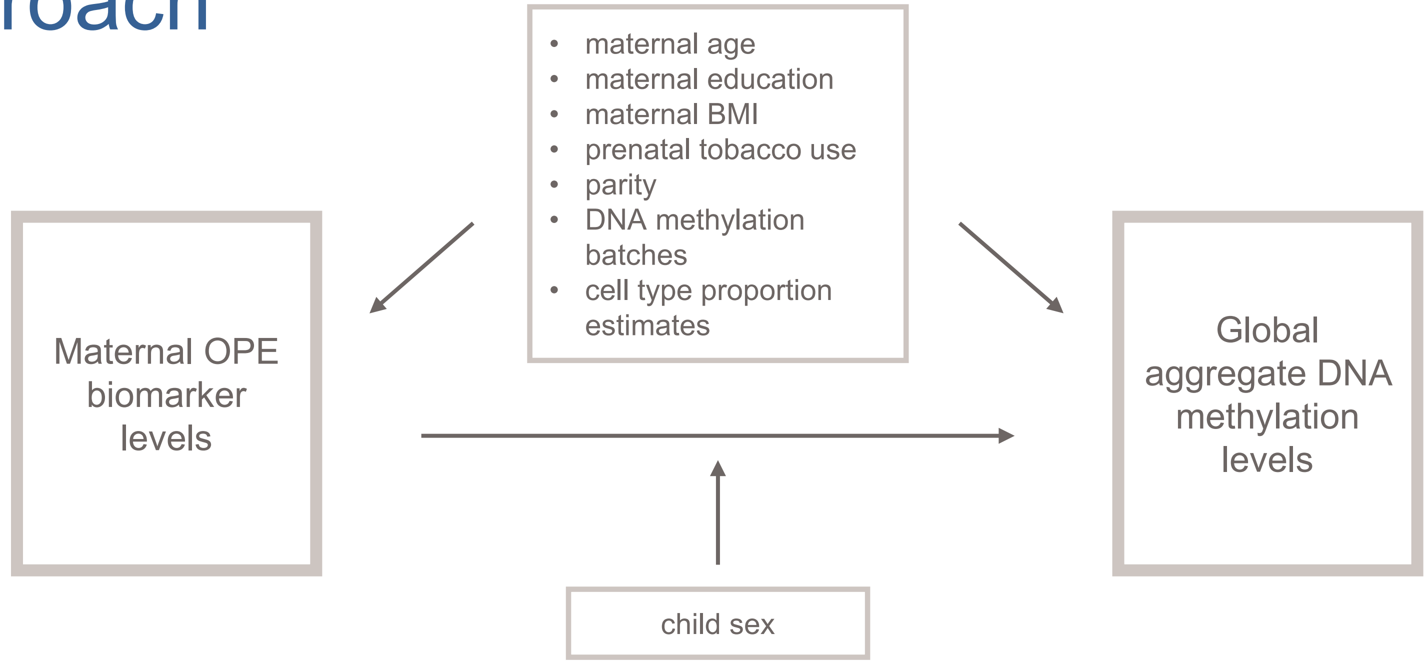
Outcome

Global aggregate DNA methylation measures





Approach



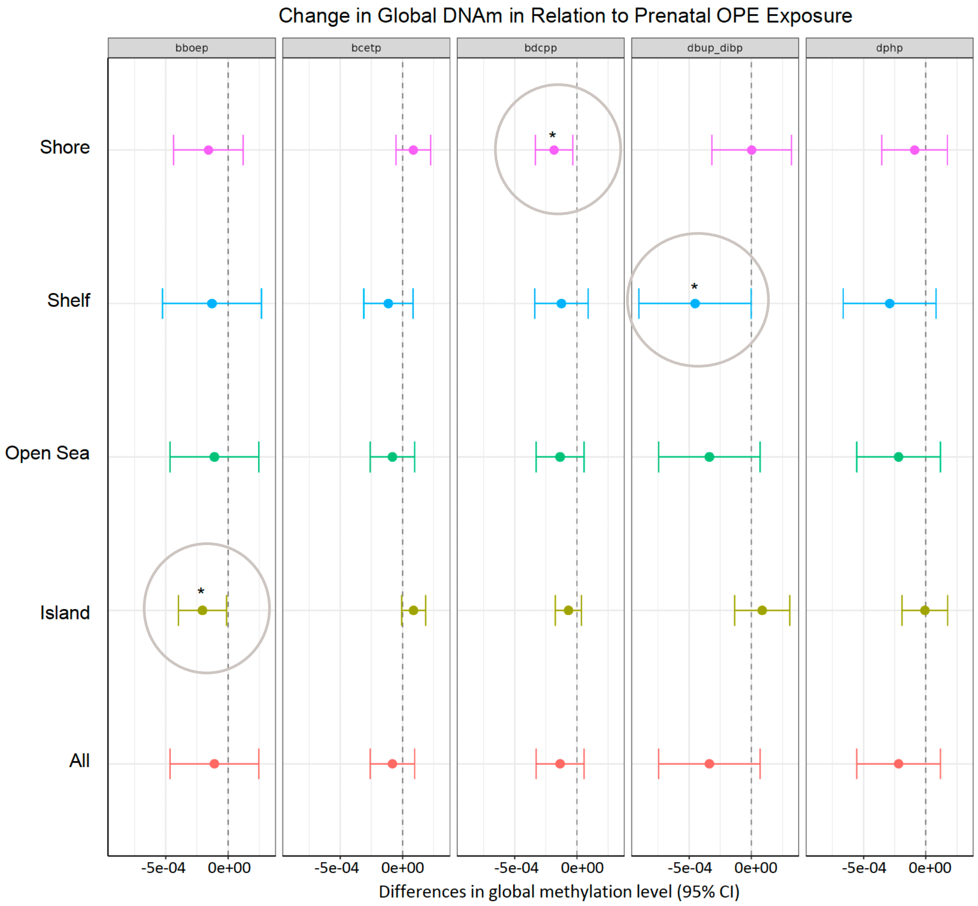
Statistical model: Global DNAm measure ~ OPE + DNA methylation batches + maternal age + maternal education + maternal BMI + prenatal tobacco use + parity + child sex + cell type proportion estimates

Higher levels of OPE biomarkers are associated with less methylation on average at birth

Increased BBOEP biomarker levels were associated with a loss of methylation at *CpG Island* regions

Increased BDCPP biomarker levels were associated with a loss of methylation at *Shore* regions

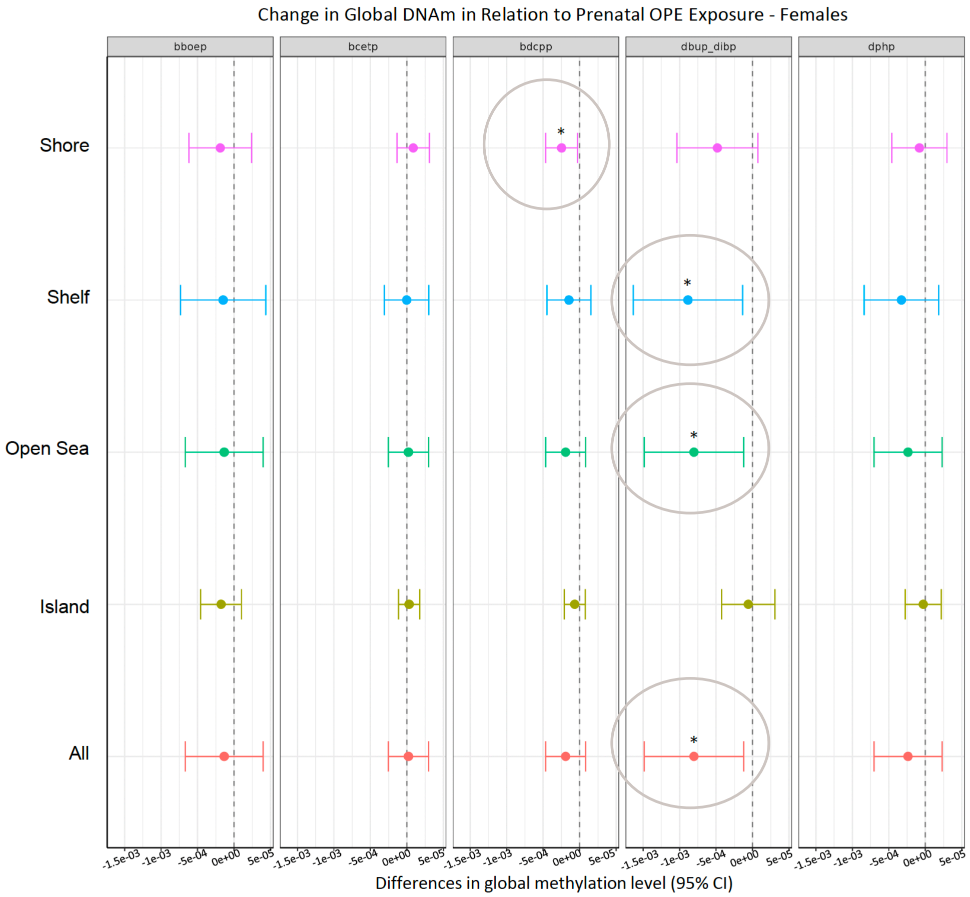
Increased DBUP/DIBP biomarker levels were associated with a loss of methylation at *Shelf* regions



Higher levels of OPE biomarkers are associated with less methylation on average at birth *in females* and not males

Increased BDCPP biomarker levels were associated with a loss of methylation at *Shore* regions

Increased DBUP/DIBP biomarker levels were associated with a loss of methylation at *Shelf, Open Sea,* and *All* regions



Main Results

DNA methylation patterns are associated with increased OPE biomarker levels during pregnancy and these effects may be modified by child sex.

Units of methylation tested

1. **Global (aggregate) DNA methylation levels**
   - High prenatal BBOEP, BDCPP, and DBUP/DIBP biomarker levels were associated with global hypomethylation at birth, with stronger effects detected in *females.*

2. Biologic aging pathway
   - High prenatal BCETP biomarker levels were associated with decelerated gestational epigenetic aging in *females.*

3. Individual CpGs (EWAS)
   - Differentially methylated regions annotated to *PCDHGB1* and *SLC43A2* were associated with BDCPP and DPHP concentrations, respectively (FDR q<0.05).

Conclusions

- First paper that has looked at how OPEs impact child blood DNA methylation at this scale

- Found differences in methylation patterns related to differences in OPE biomarker levels
  - Suggests epigenetics may be a potential mechanism through which OPEs influence underlying cell biology and impact child health outcomes

- Further studies are needed to fully understand how these changes are influencing outcomes at the biologic and phenotypic level.

- Other studies in ECHO have identified associations between prenatal OPE biomarker levels and birth outcomes including preterm birth.
  - Next steps: Examine how the specific methylation changes assessed here are associated with the previously studied child health outcomes in this analytic population and test for mediation

ECHO

Environmental influences on Child Health Outcomes

A program supported by the NIH

Maternal stress during pregnancy and offspring ADHD

Krystin Jones, MSc

April 3, 2025

ECHO Environmental influences on Child Health Outcomes

Background/Rationale

ATTENTION DEFICIT HYPERACTIVITY DISORDER

10.5%

OF CHILDREN 3- 17 YEARS

$31.6 billion

SPENT ANNUALLY

70% - 80%

HERITABILTY

ENVIRONMENTAL RISK FACTORS

- Studies have established associations between maternal stress during pregnancy and externalizing disorders and ADHD symptoms.
- Majority White study populations
  - Racial/ethnic differences in ADHD prevalence and access to care
  - Racial/ethnic differences in experiences of stress among pregnant woman
- Primarily Behavior Scale Measures

Specific Aims & Hypothesis

GOAL: To test the association between maternal perceived stress exposure during pregnancy and offspring ADHD and behavior problems in a racially diverse US-based study population

HYPOTHESIS: Increased prenatal perceived stress will be significantly associated with increased risk of offspring ADHD diagnosis and behavior problems in the ECHO cohort.

Approach

Multilevel regression models to evaluate the relationship between prenatal perceived stress (continuous and categorical) and offspring ADHD diagnosis and ADHD-related Child Behavior Checklist (CBCL) measures, including a random intercept for study site to account for within-site correlations

CRUDE MODEL

Outcome ~ Prenatal Perceived Stress (Continuous and Categorical)

ADJUSTED MODEL

Outcome ~ Prenatal Perceived Stress (Continuous and Categorical) + Maternal Age at Birth + Maternal Prenatal Alcohol Consumption + Maternal Prenatal Tobacco Use + Child’s sex + Child’s Age at Last Visit

Prenatal Perceived Stress

- Continuous
- Categorical: ≤40: Low | >40 & <60: Medium | ≥60: High

Approach

Outcome	ECHO Protocol Measure	Type	Model
ADHD Diagnosis	ADHD Diagnosis	Binary (0: non-cases; 1: cases)	Logistic (OR)
ADHD-DSMV	Preschool & school aged CBCL	Binary (0: <65; 1:≥ 65)	Logistic (OR)
Attention Problems	Preschool & school aged CBCL	Binary (0: <65; 1:≥ 65)	Logistic (OR)
Externalizing Problems	Preschool & school aged CBCL	Continuous	Linear (β)
Total Problems	Preschool & school aged CBCL	Continuous	Linear (β)

Main Results

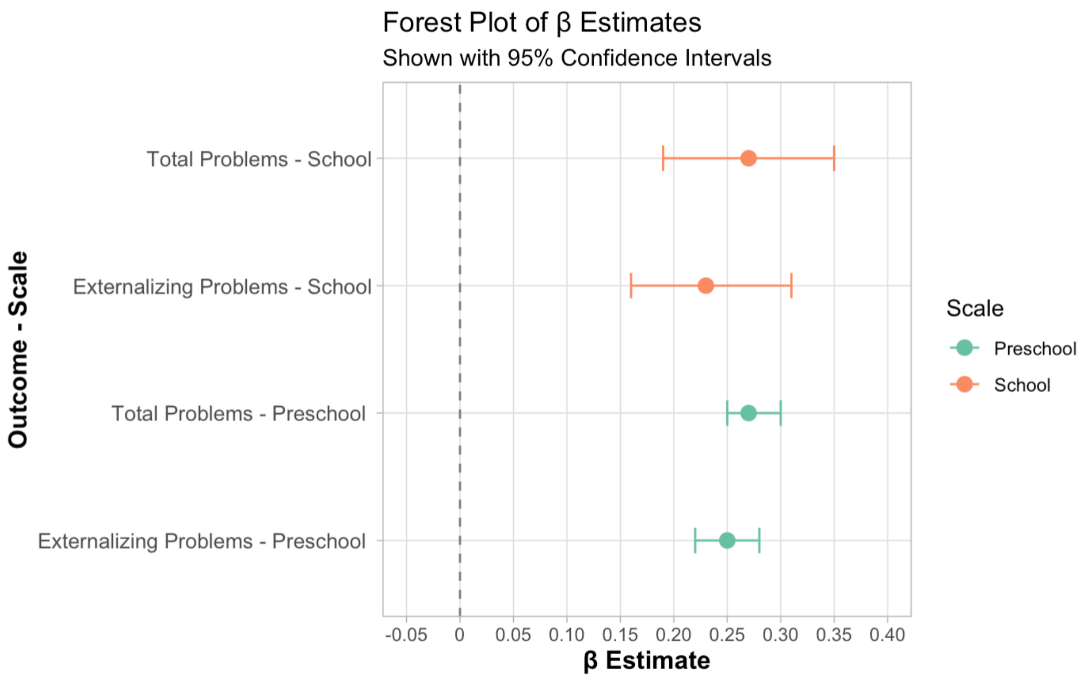
Higher Maternal Perceived Stress During Pregnancy Associated with Higher Risk Offspring ADHD Diagnosis

	Crude		Adjusted*	
Perceived Stress Score	**OR (95% Confidence Interval)**	**P-value**	**OR (95% Confidence Interval)**	**P-value**
Continuous	1.03 (1.01, 1.05)	<0.001	1.03 (1.01, 1.04)	<0.001
Categorical				
Low (<40)	1 (reference)	-	1 (reference)	-
Medium (≥40, ≤60)	1.30 (0.88, 1.92)	0.19	1.26 (0.85, 1.87)	0.26
High (>60)	2.57 (1.53, 4.24)	<0.001	2.46 (1.47, 4.15)	<0.0001

*Adjusted for maternal age at delivery, age of the child at the end of follow up, prenatal tobacco use, prenatal alcohol consumption, maternal education, child's sex; OR: Odds Ratio; aOR: Adjusted Odds Ratio

Main Results

Higher Maternal Perceived Stress During Pregnancy Associated with Higher CBCL Behavior Problems



Conclusions

Key Take Away

- Maternal prenatal stress was associated with offspring ADHD diagnosis and related CBCL symptoms.
- Results are comparable across measures

Clinical & Public Health Significance

- **Appropriate and effective stress management during pregnancy is integral**
  - ~70% of pregnant women experienced a stressful life event in the year prior to their child's birth.
  - Stress screenings or evaluations can be used to understand the source(s) of prenatal stress and make corresponding recommendations for remediation.
  - Improved social support and resources for families
  - Cognitive Behavioral Therapy (CBT)
  - Meditation and mindfulness practices

ECHO

Environmental influences on Child Health Outcomes

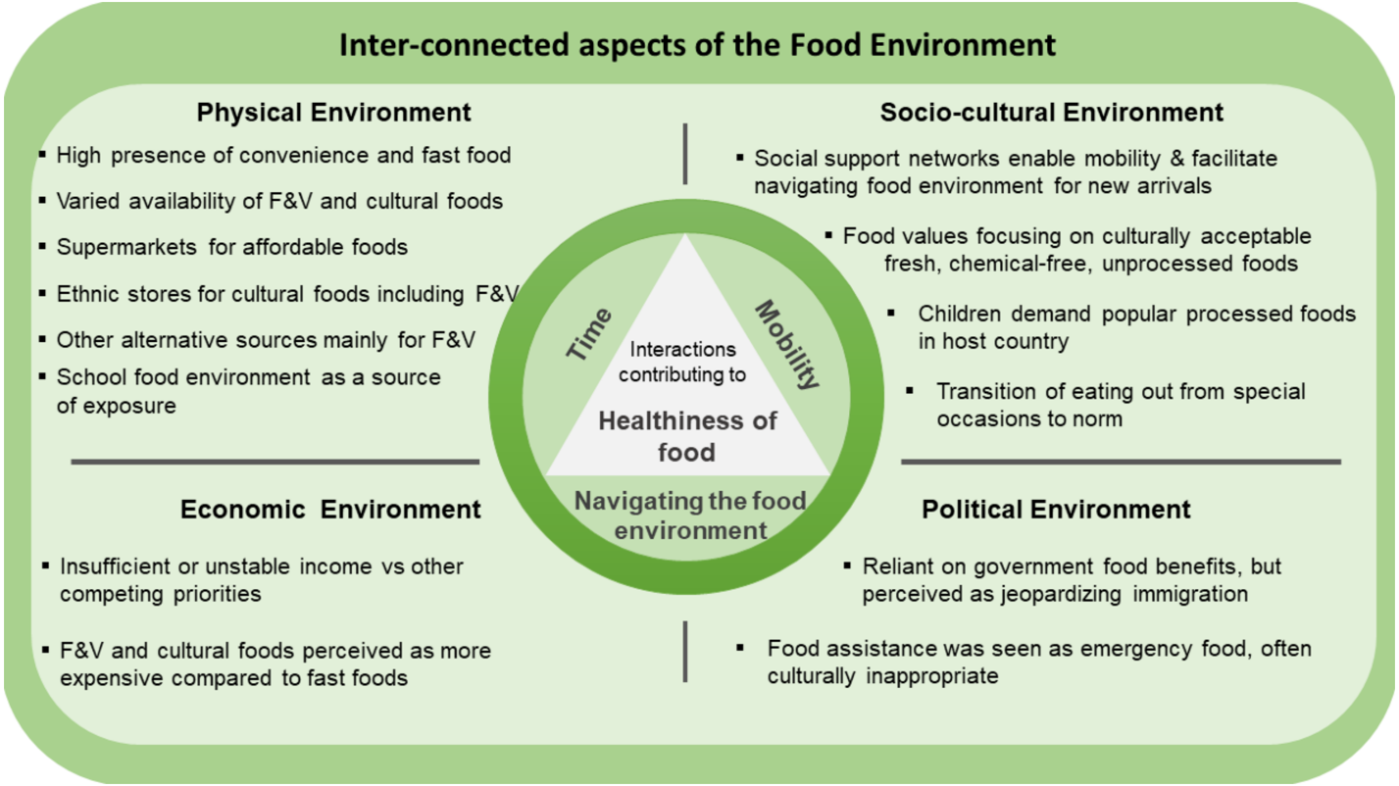
A program supported by the NIH

Lifestyle WG: How does the community food environment and individual-level factors influence fruit and vegetable and sugar-sweetened beverage consumption in children? An ECHO study

Christine Wey Hockett, Ph.D.
Director of Community Research, Research Scientist
Lead of Data Management and Analysis Core
Avera Research Institute
Associate Professor & ARI Division Chief, Department of Pediatrics
University of South Dakota, School of Medicine

April 3, 2025

Background/Rationale



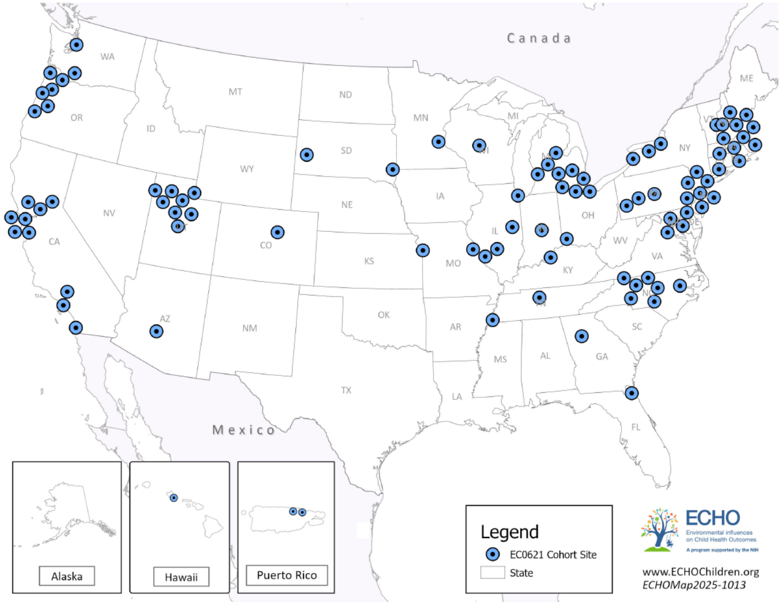
Specific Aims & Hypothesis

- What community food environment and individual level factors are associated with fruit and vegetable and sugar-sweetened beverage consumption in children, and how does rurality status impact these relationships?

Study Sample

- 12,835 children from 69 cohorts
  - ➢ 2-19 years of age
  - ➢ 84% Urban, 11% Suburban/Small Town, 5% Rural

- Inclusion criteria:
  - – Complete diet data related to fruit/vegetable (F/V) and sugar-sweetened beverage (SSB) consumption
  - – Assigned Rural-Urban Continuum Codes (RUCC)
  - – Area-level food factors
    - • USDA Food Environment Index



Methods

- Outcomes: **1) fruit and vegetable and 2.) sugar-sweetened beverage consumption in the child participant**
  - Created dichotomous categories (≥1 serving/day[week] compared to <1 serving/day[week])
- Exposures: **individual- and community-factors**
  - USDA Food Environment Index factors into five domains[4]
    - **Accessibility, Affordability, Availability, Acceptability, and Accommodation[5]**
  - Least Absolute Shrinkage and Selection Operator (LASSO) regression models
- Modifier: **rurality[6]**
  - Urban (RUCC 1-3), Suburban/small town (RUCC 4-6), and Rural (RUCC 7-9)
- Implemented the multiple imputation, multilevel regression models, and pooled analysis

[4]Rhone n.d.; [5]Turner et al. 2018; [6]Sanders and Cromartie n.d.

Results

Fruit & Vegetable Consumption (F/V)

- General food sales tax, retail stores

F/V and SSB (overlap)

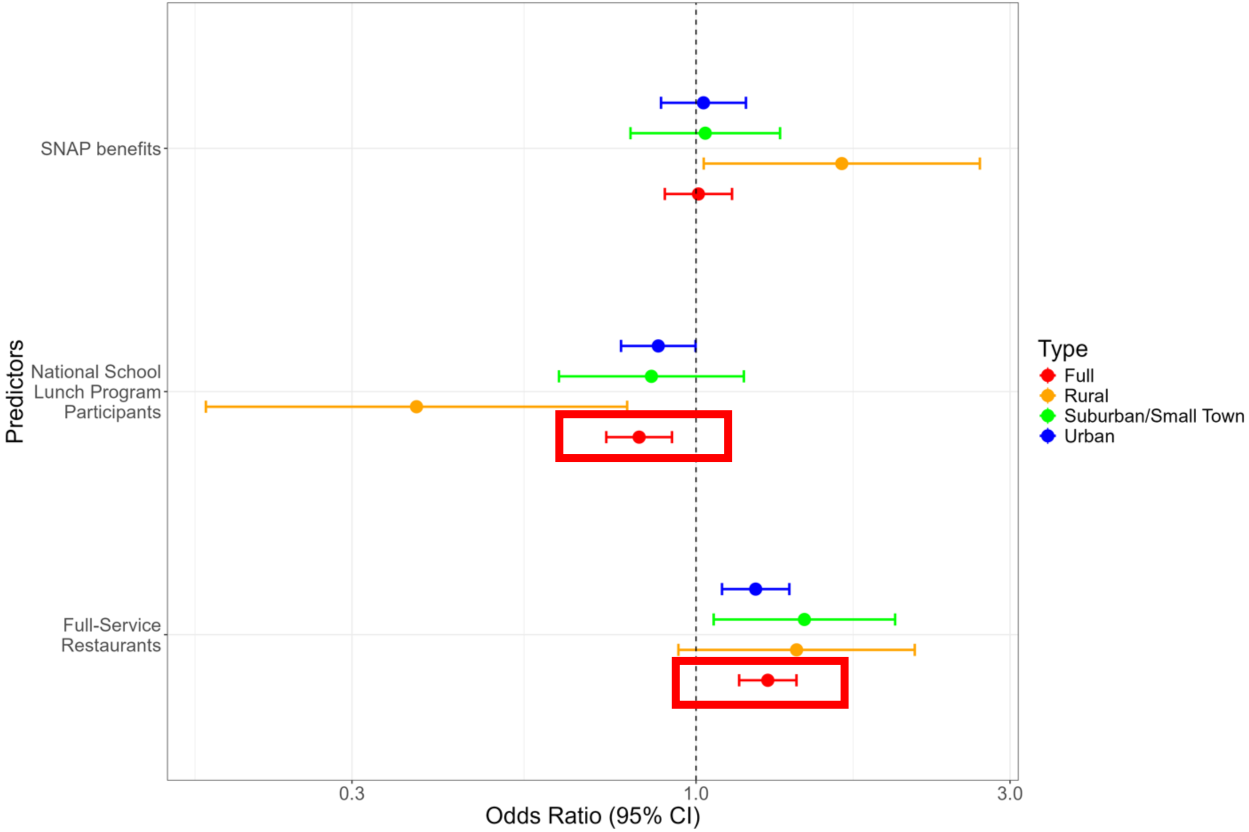
- Household very low food security
- SNAP-authorized stores
- Farmers markets that accept SNAP
- SNAP benefits per capita
- National School Lunch Program participants
- Full-service restaurants

Sugar-sweetened Beverage Consumption (SSB)

- Household food insecurity
- Farmers markets that report selling fruit & vegetables
- Farmers markets that report accepting WIC
- School Breakfast Program participants
- Summer Food Service Program participants
- Child & Adult care
- Grocery stores
- Specialized food stores
- Farmers markets

Fruit & Vegetable Consumption

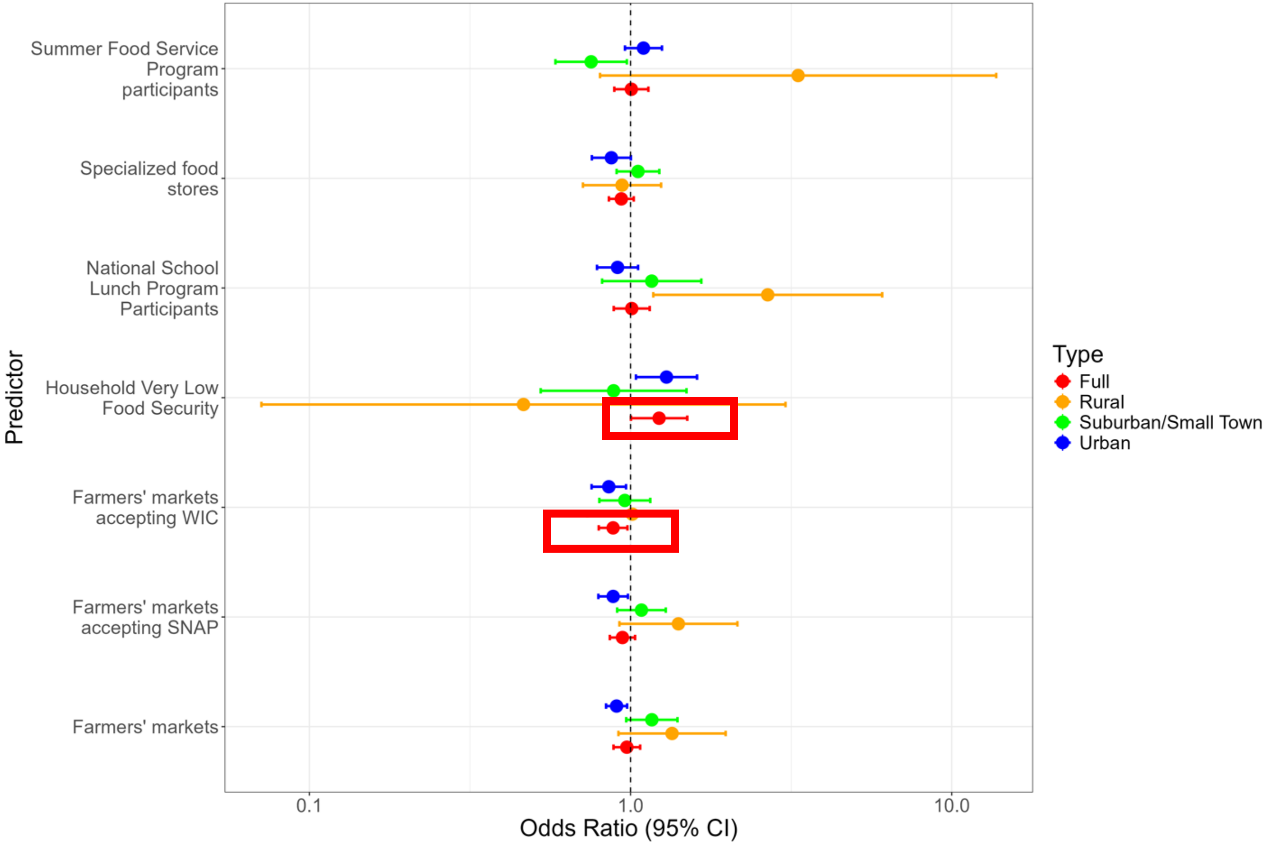
defined as <1 serving/day compared to ≥1 serving/day



Adjusting for child age category, sex, race, ethnicity, maternal education, income, rural category, and census region

Sugar-sweetened Beverage Consumption

defined as ≥1 serving/week compared to <1 serving/week



Adjusting for child age category, sex, race, ethnicity, maternal education, income, rural category, and census region:

Results

F/V consumption

Variables	Full	Urban	Suburan / Small Town	Rural
SNAP benefits				+
National school lunch program	-	-		-
Full-service restaurants	+	+	+	
Child Age, 11-17 yrs (Ref: 2-5yrs)	-	-	-	-
Child Age, 18-21 yrs (Ref: 2-5yrs)	-	-	-	
Child Sex (Female, Ref: Male)	+	+		
Child's Race (Black, Ref: White)	-			
Child Hispanic (Ref: non-Hispanic)	-	-		
Education (Ref: Less than High School)				
Some College, Associate's degree	+	+		
Bachelor's degree	+	+		
Master's degree	+	+		
Income (Ref: <$30,000)				
$100,000+	+	+		
Region (Ref: Northeast)				
Midwest (Ref: Northeast)	+	+		
South (Ref: Northeast)	+	+		
West (Ref: Northeast)	+	+		

Results

SSB consumption

Variables	Full	Urban	Suburan / Small Town	Rural
Very low food security	+	+		
Farmers' Markets accepting SNAP		-		
Farmers' Markets accepting WIC	-	-		
National school lunch program				+
Summer food service program			+	
Farmers' Markets selling F/V		-		
Child Age, 5-10 yrs (Ref. 2-5yrs)	+	+	+	+
Child Age, 11-17 yrs (Ref. 2-5yrs)	+	+	+	+
Child Age, 18-21 yrs (Ref. 2-5yrs)	+	+	+	+
Child's Race (Black, Ref: White)		+		
Child Hispanic (Ref: non-Hispanic)	+	+	+	+
Education (Ref: Less than High School)				
Bachelor's degree	-	-		
Master's degree	-	-		
Income (Ref: <$30,000)				
$30,000-$49,999		-		
$50,000-$74,999	-	-		
$75,000-$99,999	-	-		
$100,000+	-	-	-	

Conclusions

- Community-level food factors that are associated with healthy food consumption in children are different in rural and urban communities.

- Hypothesis-generating analysis
  - Provides direction to where more research is needed to better understand why and how these community-level factors may influence individual-level consumption of F/V and SSB

- More research is needed to better understand multi-level relationships
  - Rurality needs to be considered

Acknowledgements

- ECHO Program and Centers and Cores
- ECHO site study staff and participants

- Emily Knapp, Lead DAC Analyst
- Co-Authors
  - Aschner J, Camargo C, Dabelea D, Dunlop, A, Elliott A, Ferrara A, Zhu Y, Chehab R, Santaroosa S, Karagas M, Melough M, Ganiban J, MacKenzie D, McEvoy C, Lyall K, O'Conner T, Thompson A, Kerver J, Strakovsky R, Zeigler K, McCormack L.

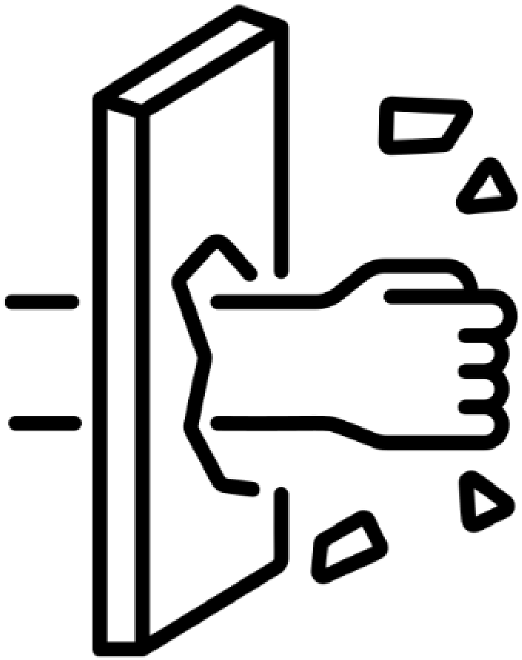
You Can't Ask That!

ECHO Participant Action Board

April 3, 2025

Breaking Barriers Between Participants & Researchers

This session is about **transparency**, **honesty**, and **breaking down barriers** between us



ECHO PAB – Who are We?

MISSION

To foster ECHO partnerships by providing real life experiences as ambassadors for participants in all areas

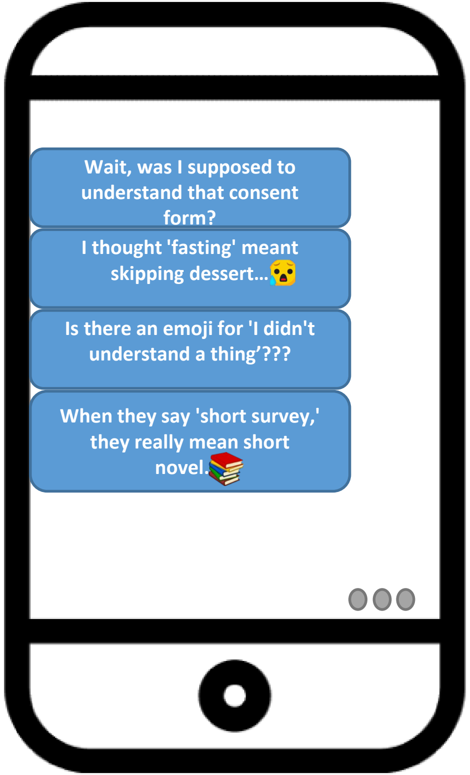
VISION

To create a space where participants' voices and lived experiences shape research

VALUES

Real Talk: The Good, The Awkward, & The Unexpected!

Personal Experiences



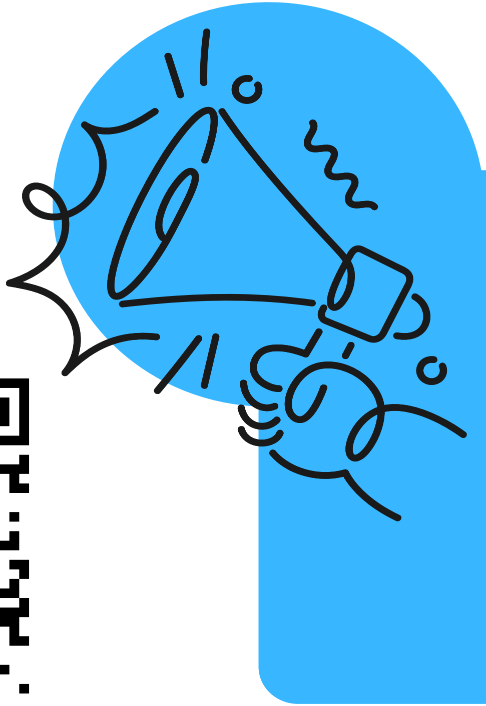
Moving ECHO Science Forward

Let’s Talk!

The Floor is open – No questions are off-limits!

Our ECHO, Our Health Facebook Live Events

Our ECHO, Our Health is a space where ECHO participants, investigators, and community members come together to learn about the latest findings from the ECHO Cohort, share insights, and discuss health research. We will host live events to facilitate direct communication between researchers and participants, creating opportunities for mutual learning and collaboration.



Join our Facebook Group!

Step 1: Scan the QR code or search “Our ECHO, Our Health” on Facebook.

Step 2: Request to join the group and answer 2 very short membership questions, and accept group rules/disclaimer

Pdf flyer can be found on sharepoint

FACEBOOK LIVE EVENT

Our ECHO, Our Health

CHILDHOOD WELLBEING

ECHO
Environmental influences on Child Health Outcomes
A program supported by the NIH

WHY ATTEND?

Join us for an engaging live discussion exploring the latest ECHO findings on childhood wellbeing. Learn how factors like supportive parenting, sleep quality, and meaningful social connections shape children's wellbeing, even in challenging circumstances. This interactive event offers a special chance to connect directly with ECHO investigators, ask your most pressing questions, and participate in a conversation that highlights the experiences and insights of the ECHO community.

GET INVOLVED

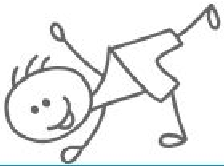
Have questions about childhood wellbeing or positive health practices? Share them with us in the Facebook group using **#ECHOwellbeing.** We'll answer them during our live event.

EVENT DETAILS

OUR ECHO, OUR HEALTH FACEBOOK GROUP

MAY 7 , 2025

6:30 - 7 PM EST



COURTNEY BLACKWELL, PhD
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SID RATKIEWICZ
ELGAN Participant
Engagement Coordinator

TO ENHANCE THE HEALTH OF CHILDREN FOR GENERATIONS TO COME

ECHO

Environmental influences on Child Health Outcomes

A program supported by the NIH

The 1-0-1 on Cycle 2 Data Elements

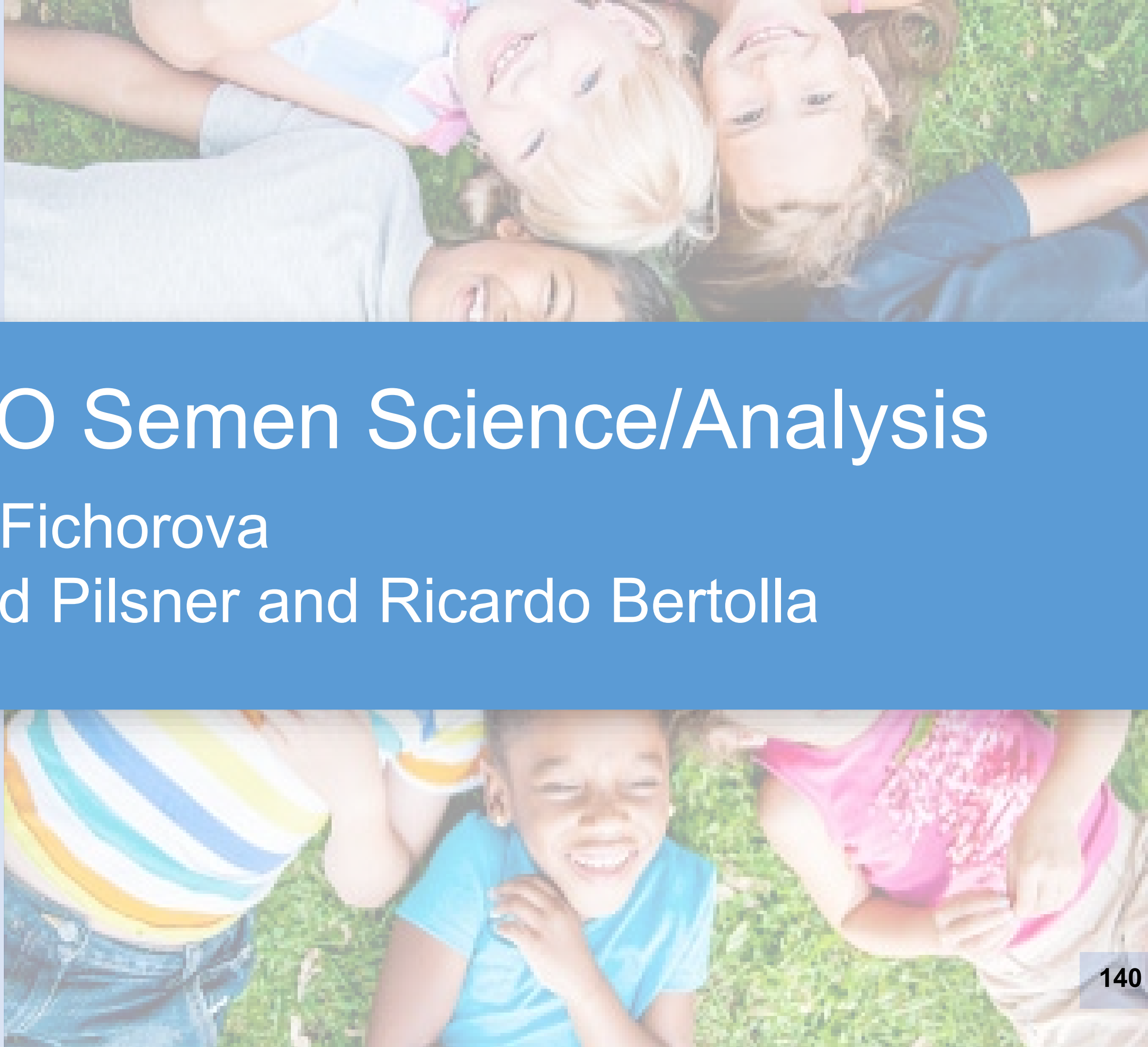
Raina Fichorova, Richard Pilsner/Ricardo Bertolla, Roz Wright

April 3, 2025

ECHO Environmental influences on Child Health Outcomes

ECHO Semen Science/Analysis

Raina Fichorova
Richard Pilsner and Ricardo Bertolla



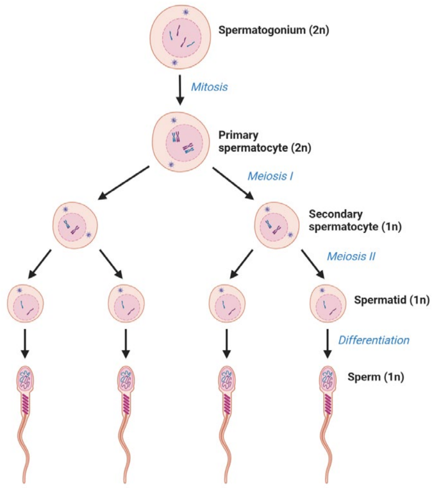
Leading concept

The content of semen has phenotypic effects on child health outcomes well beyond its donation of genetic material.

Learning Objective: **Why** and **how** we should incorporate semen collection in ECHO science

~3 months

Paternal exposures during spermatogenesis & maturation

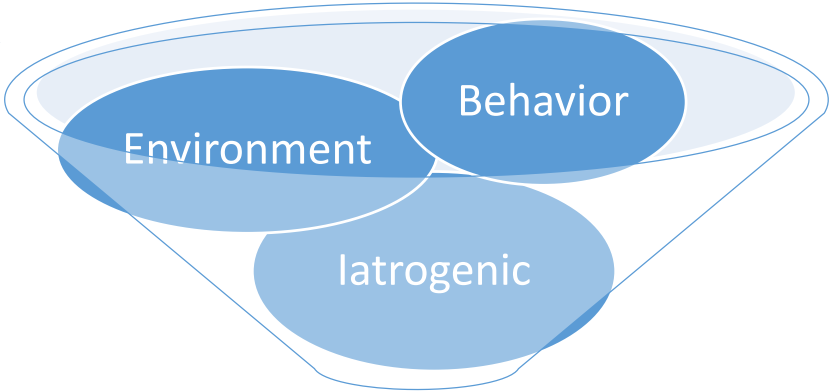


~15 days maturation in epididymis

Sperm health, genetics, epigenetics

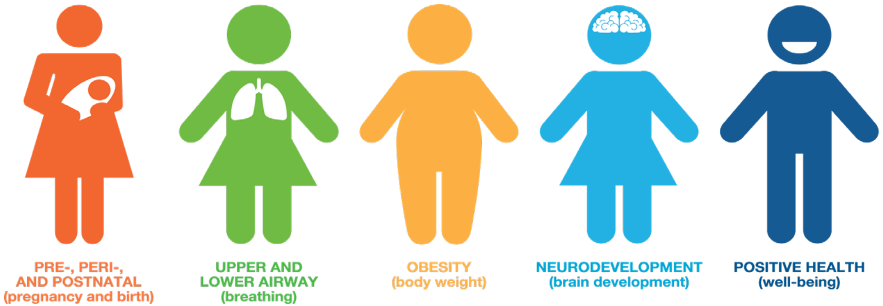
- How may data obtained from multiple types of semen analyses help us advance the health of children
  - What type of data can and should we collect
- What types of exposures can we consider/assess in semen?
- What type of research questions can we ask based on our specific interests and priorities for PPP and pediatric outcomes

ECHO Epicenter Concepts



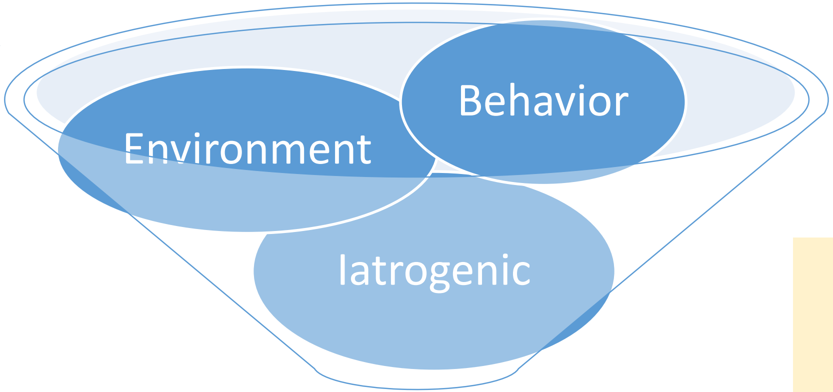
Semen: cellular, molecular and biochemical parameters

Child Health



ECHO Epicenter Concepts

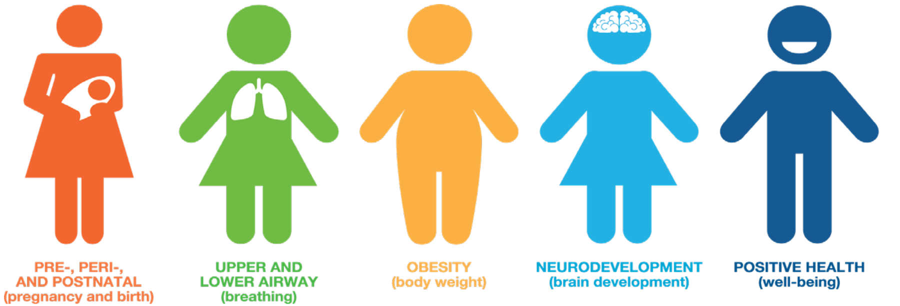
IDeA States Pediatric Clinical Trials Network (ISPCTN)



Semen: cellular, molecular and biochemical parameters

Modifiable Resilience & Risk

Child Health



What types of environmental exposures can we consider/assess in semen?

- Seminal fluid → direct measure of within testis exposures to chemicals, e. g. endocrine disrupting chemicals while urine is a measure of total body burdens, although levels may be lower in semen than in urine, overall low correlation between semen and urine
  - Buck Louise et al, Environ Res 2018, 163, 64 (**n=501**)
- While some pollutants are present in both peripheral blood and semen, others (Li and Mn) have been found at higher concentrations in semen, suggesting that semen may be an internal site of bioaccumulation.
  - Int J Environ Res Public Health. 2022 Sep 15;19(18):11635.
- Measurement of metals / metalloids in semen may be more predictable of semen quality than conventional blood measurements
  - Calogero Ecotoxicology and Environmental Safety 2021, 215, 112165 (**n=179**)
- Phthalates can break the blood-testis barrier through ferroptosis
  - Tiwary & Richburg, Toxicological Sciences 2024, 197, 147–154
  - Zhao Y, et al. Redox Biol. 2023;59:102584.

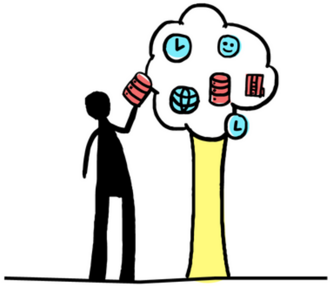
What types of environmental exposures can we consider/assess in semen?

- Semen quality correlates better with levels of phthalate metabolites in semen than in blood
    - Song et al, Emerging Contaminants 2022, 6, 39 (**n=112**)
- Heavy metals and plasticizers directly impact sperm epigenetics with causative proof from animal studies:
    - Zhang et al, Reprod Toxicol 2025, 132
- Air pollution → sperm epigenome (EARLI, n=38)
    - Scrott et al. Environmental Epigenetics, 2024, 10 dvae003
- Dioxines, phthalates, heat → sperm DNA fragmentation
    - Kumar and Singh, Environmental Sciences Europe, 2022, 34:6

Biomarkers of child outcomes: paternal programming

- **Ejaculate / spermatogram**
  - Semen volume & sperm count
  - Sperm motility & morphology
  - Leukocytospermia
- **Genomic / epigenetics traits**
  - Sperm epigenome: DNA methylation, histone modification, ncRNA
  - Sperm DNA damage / fragmentation
  - Microbial DNA / metagenome
  - Sperm epigenetic clock
- **Seminal plasma content**
  - Environmental contaminants /disruption of the blood testis barrier / semen-specific bioacumulation
  - Protein / Immune biomarkers e.g. cytokines, prostaglandins
  - Soluble markers of oxidative stress
  - Metabolome (human and microbial)
  - Extracellular vesicles (EV) (human and microbial) – stably encapsulated DNA, RNA, proteins, lipids, lipoproteins

Maternal environment



Lowest hanging fruit based on stability

- Stable DNA patterns (human and microbial)
- Stable environmental chemicals
- EV cargo

Semen Relevance to ECHO Outcomes: The Premise

What has been studied?

PRE-, PERI- AND POSTNATAL

- **Sperm DNA fragmentation → small for gestational age / low birth weight**
  - Li et al. Sci Rep 2024 Jan 3;14(1):356.
  - Boeri et al. World J Mens Health 2024 Apr;42(2):384-393. (**ART, n=1063**)
- **Cytokine levels in the seminal plasma → sperm DNA integrity and embryo development**
  - Yang et al, Front Immunol 2021, 21, 699181
- **Seminal microbiota** with Lactobacillus dominance → ↑**semen health**
  - Weng et al, Plos One 2014, 9, e110152 (**n=96**)
- **Seminal microbiota → vaginal microbiome, maternal T_{regs}, embryo quality**
  - Štšepetova, Reprod Biol Endocrinol 2020; 18, 3 (**n=50**)
  - Altmae at al, Nature Rev/Urology, 2019, 16, 703
- **Seminal microbiota → preeclampsia**
  - Kenny & Kell, Frontiers in medicine 2018; 4, 239
- **Seminal fluid proteins → maternal, egg and embryo epigenetics**
  - Patlar, Int J Mol Sci 23, 14533
- **Somatic tissue-based clocks cannot predict epigenetic aging in germ cells**
  - Dutta et al, Genes 2024, 15, 16
- **Sperm epigenetic clock → ↓fecundability and shorter gestational age**
  - Pilsner et al. Hum Reprod. 2022 Jun 30;37(7):1581-1593

Semen Relevance to ECHO Outcomes: The Premise

What has been studied?

OBESITY

- **Paternal nutrition→ sperm & seminal plasma changes**, **sperm miRNA → offspring lipid metabolism, adiposity**
  - Furse et al, Metabolomics 2022, 18:13
  - Fullston et al, FASEB J, 2013, 27, 4226
- Paternal **obesogene exposure →Transgenerational obesity phenotype**
  - Chamorro-Garcia et al, Nat Commun 2017, 8, 2012
- **Sperm DNA fragmentation → Postnatal weight gain**
  - Fernandez-Gonzalez et al. Biol Reprod 2008, 78, 761
- **Paternal semen quality → Childhood obesity**
  - Rumbold et al, 2019, Fertil Steril 111, 1047
- **Transgenerational reprograming of metabolic syndrome-related genes** (glucose, lipid and cholesterol metabolism)
  - Carone et al, Cell, 2010, 143, 1084
- **Sperm DNA methylation → Genetic markers of Type II diabetes and obesity**
  - Katari et al, Hum Mol Genet 2009, 18, 3769

Semen Relevance to ECHO Outcomes: The Premise

What has been studied?

NEURO-DEVELOPMENT

- Transmission of intergenerational stress and neurodevelopment program through epididymosomes (eEV)

  ♂ **Stress → eEV (proteome&miRNA) → mRNA offspring brain**

  - Chan et al. Nature Commun 2020; 11:1499

- **Sperm DNA methylome → autism** risk
  - *Feinberg et al, Int J. Epidemiol 2015, 44 (**n=44**), 1199* (EARLI)
  - *Feinberg er al, Mol Psychiatry 2023:1-11 (**n=45**)* (EARLI)
  - *Garrido et al, Clin Epigenet 2021 13, 6 (**n=26**)*

- Single-cell sperm transcriptomes and variants (**Sperm-seq**) → offspring **autism spectrum disorder**
  - *Genom. Med. 2020, **5**, 14 .*

- **Male germline DNA methylation → behavior, autism, schizophrenia**
  - Milekic et al. Mol Psychiatry 2015 Aug;20(8):995-1001

- **Sperm DNA fragmentation** → Offspring behavior, anxiety
  - Fernandez-Gonzalez et al. Biol Reprod 2008, 78, 761 (mouse model)

Semen Relevance to ECHO Outcomes: The Premise

What has been studied?

UPPER AND LOWER AIRWAY

– Preconception paternal smoking → **sperm DNA methylation** → ↑ risk of **offspring non-allergic asthma** by 7 years of age
  - Liu et al, European Respiratory Journal 2022 60(4): 2200257

POSITIVE HEALTH

– **Sperm DNA methylation → offspring biological aging**
  - Dutta S, Goodrich JM, Dolinoy DC, Ruden DM. Biological Aging Acceleration Due to Environmental Exposures: An Exciting New Direction in Toxicogenomics Research. Genes (Basel). 2023 Dec 21;15(1):16.

What can ECHO add?

- Human data
- Larger sample size
- Complete exposome data
- More maternal health outcomes
- Placental health
- More newborn outcome measures
- More childhood outcome measures
- Explore feasibility of novel sperm bioassays/biomarkers – sperm methylome, sperm epigenetic clock, seminal microbiome, epididymosome cargo, Sperm-seq

Validate mechanistic semen biomarkers of paternal programming, identify risk factors and modifiable determinants of child health

ECHO Semen Processing/Analysis

Richard Pilsner/Ricardo Bertolla

Best practices for collection/storage of semen to accommodate science

- **Site burden/Costs:**
  - **Need to measure general semen parameters (sperm count, morphology, motility)**
  - Requires andrology lab training and proficiency testing
  - Capex: microscope/Computer Assisted Semen Analyses (CASA)

- **Engage participants/Report backs:**
  - Offer basic/advanced semen quality results
  - CLIA-certified andrology lab for report backs

- **What can be analyzed:**
  - **Sperm DNA methylation**
  - **Seminal plasma exposomics/metabolomics**
  - Proteomics (sperm and seminal plasma)
  - Seminal plasma extracellular vesicles

Best practices for collection/storage of semen to accommodate science

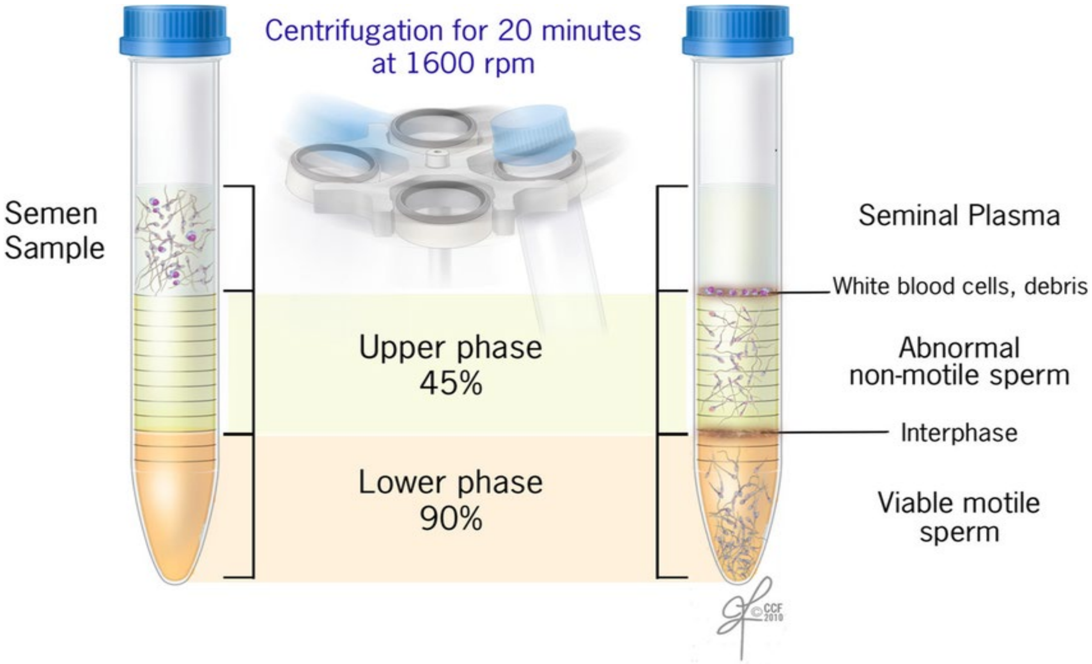
Recommendation

1) Home collection
2) Overnight shipping to andrology/centralized lab
3) Semen parameters assessed
4) Process fresh (unfrozen) semen

Centralized processing

1. Receive samples – QC for transport conditions and chain of custody;
2. Perform Computer Assisted Semen Analysis (CASA);
3. Separate cells and seminal plasma;
    1. Centrifuge seminal plasma to remove debris,
    2. Freeze in 100 uL aliquots + two 0.5 mL aliquots (example);
4. Process sperm pellet to remove contaminating immature germ cells and somatic cells;
5. Extract DNA/RNA/Protein from 15-20 million sperm and freeze;
6. Freeze remaining sperm in 10-15 million sperm aliquots;
7. Add data into Biotrak.

Gradient centrifugation



Clinical report example – report back

WSU Andrology Laboratory

275 E. Hancock St., Rm. 033, Detroit, MI 48201

Semen Analysis Report

Report Number	SA-001-25	Patient Name	XXXXXXXXXX

Analysis Results

Parameter	Result	Reference Range	Indicator
Liquefaction Time (min)	25	–	
pH	8	–	
Volume (mL)	3	≥ 1.4	
Concentration (million/mL)	50	≥ 16	
Total Sperm Count (millions/ejaculate)	150	≥ 39	
Progressive (%)	50	≥ 30	
Total Motility (%)	84	≥ 42	
Immotile (%)	16	≤ 20	
Morphology (%)	5	≥ 4	
Vitality (%)	60	≥ 54	
Round Cell Count (million/mL)	2	< 5	
WBC Count (million/mL)	1	< 1	

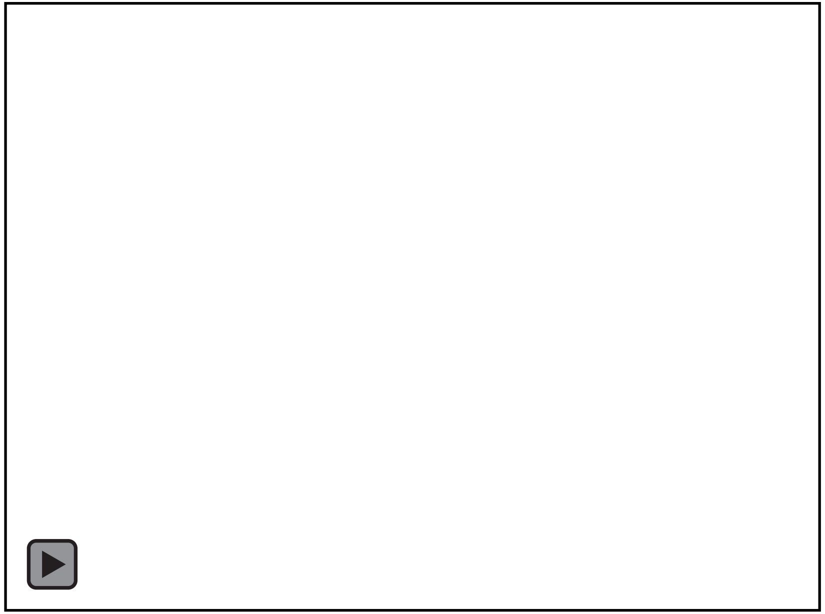
Cut points based on 2021WHO guidelines

How to ship semen overnight?

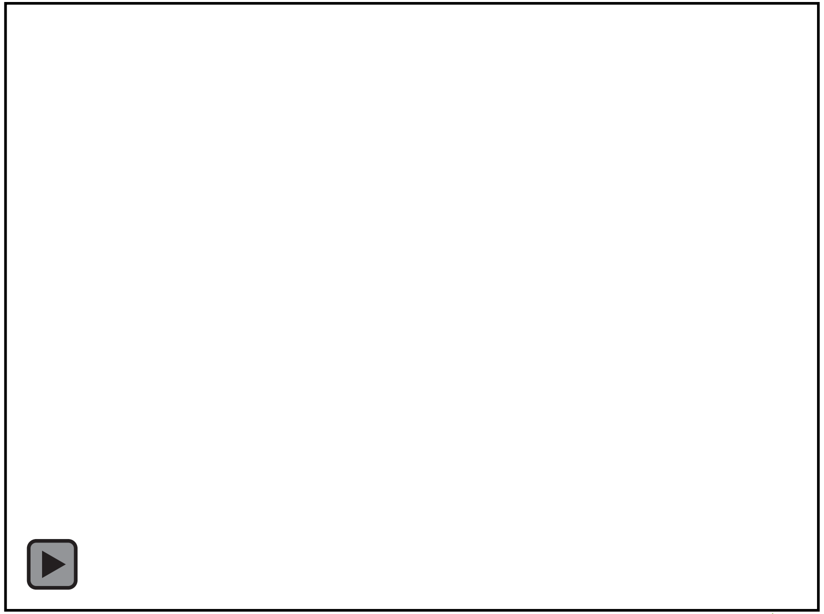
- Crude semen
  - Ship at 4ºC
- Semen with sperm preservation media
  - Ship at R/T

Semen shipment with media

- CASA fresh



- CASA 24-hour with media



CASA = computer-assisted semen analysis

Semen shipment without media

- CASA fresh
- CASA 24-hour without media

CASA = computer-assisted semen analysis

Proposed pilot (n=50)

- Home collection and overnight shipment to WSU andrology lab
  - With (n=25) and without (n=25) sperm preservation media
- Basic and advanced semen analyses
  - Sperm count, concentration, motility, and morphology
  - DNA fragmentation index, High DNA stainability
- Semen processing
  - Seminal plasma metabolomics/exposomics
  - Sperm DNA methylation (Epic array V2)
  - Sperm proteomics
- Surveys for participant feedback, burden, etc.

ECHO

Environmental influences
on Child Health Outcomes

A program supported by the NIH

Respiratory Health Across Lifespan – When Does the Story Begin?

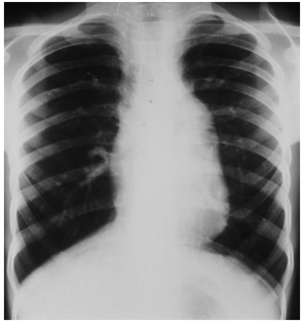
Rosalind J. Wright, MD, MPH
Dean for Public Health, Icahn School of Medicine at Mount Sinai

April 3, 2025

ECHO Environmental influences on Child Health Outcomes

Early experiences influence later-life health & disease

Life Course Framework

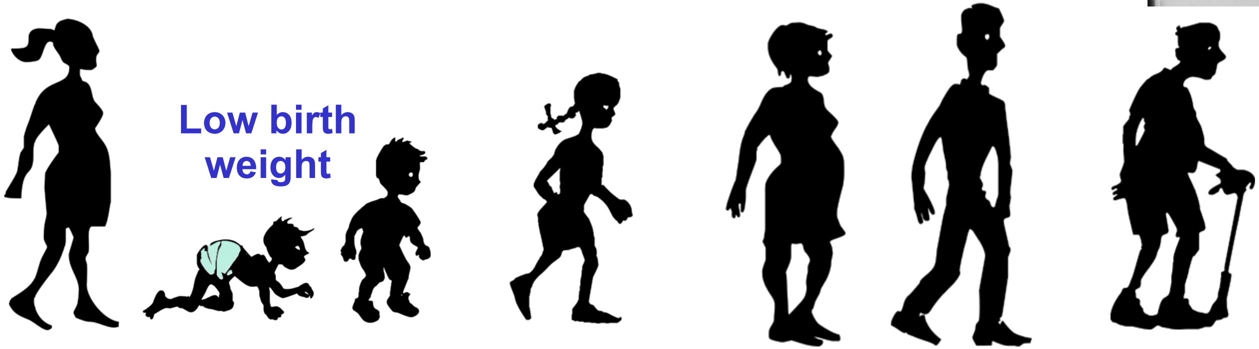


Toxic exposures

Obesity, hypertension, CNS, cardiovascular/pulmonary disease, diabetes

COPD

Low birth weight



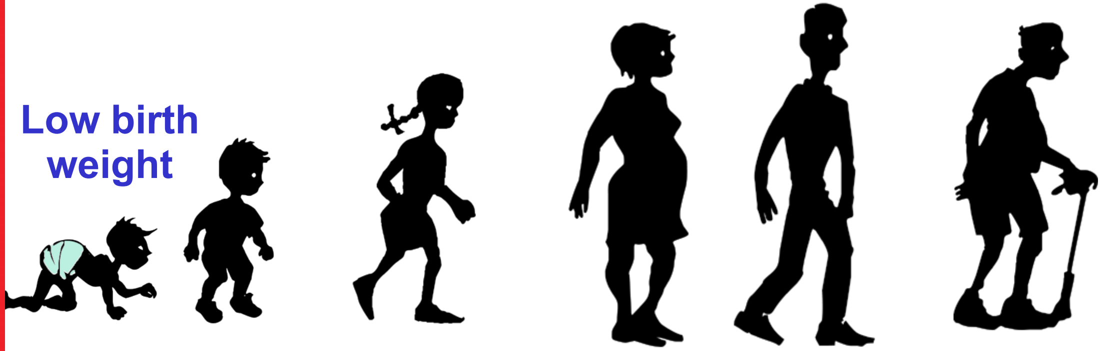
How environmental exposures in early life influence health and development in childhood and across the life span.

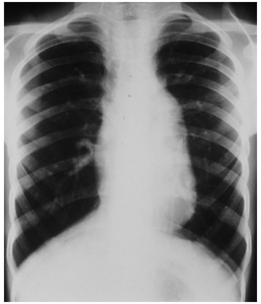
Life Course Framework

Toxic exposures

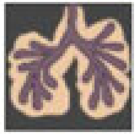
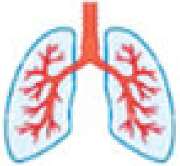
Low birth weight

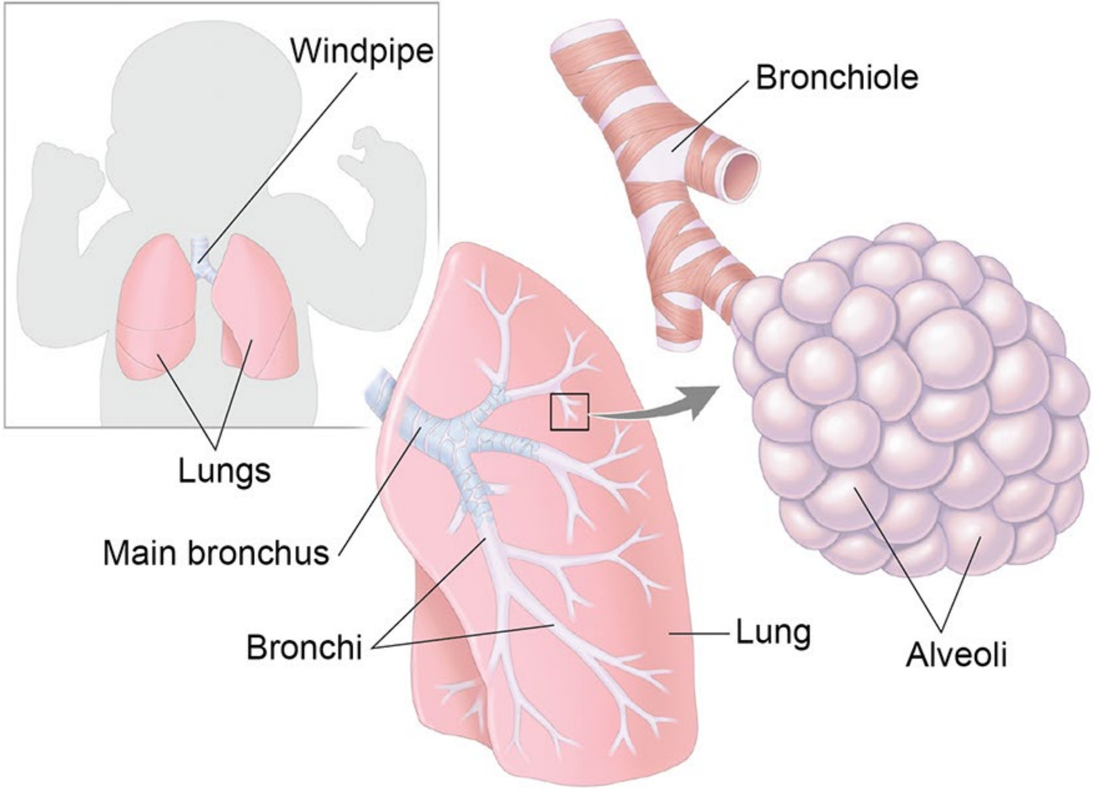
Obesity, hypertension, CNS, cardiovascular/pulmonary disease, diabetes





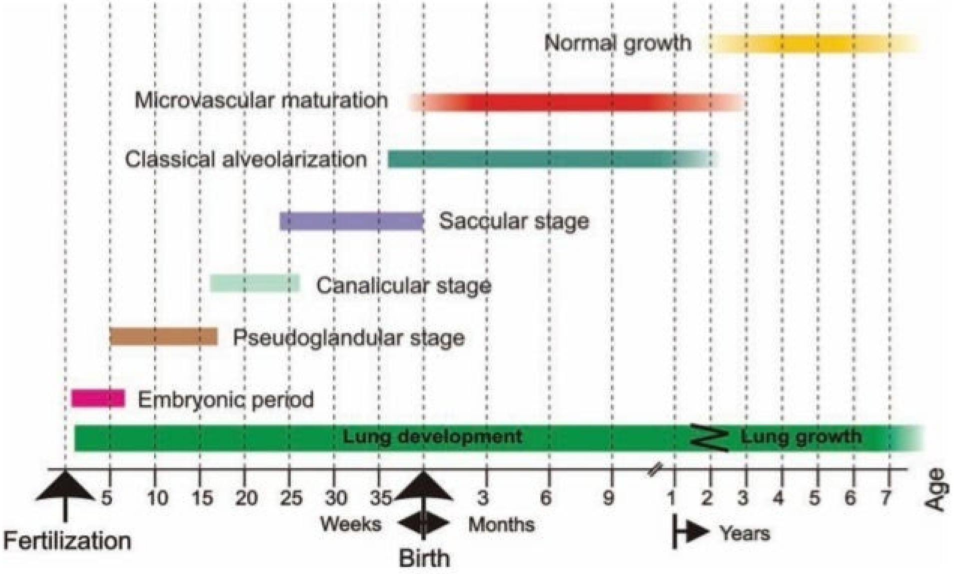
Stages of Lung Development

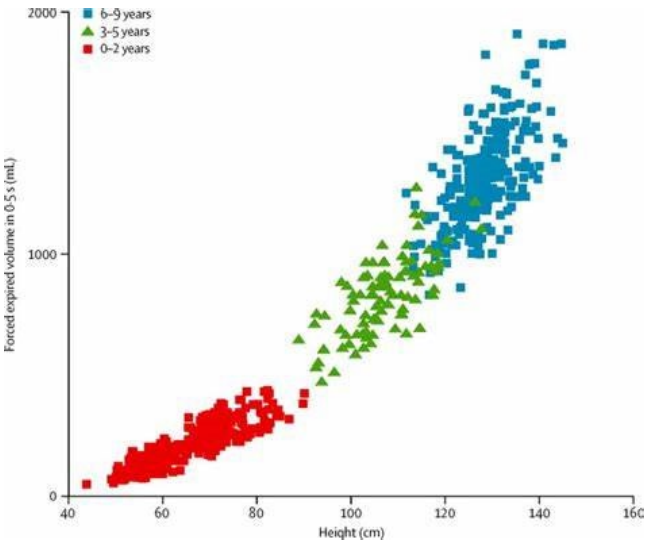
	Embryonic stage	Pseudoglandular stage	Canalicular stage	Saccular stage	Alveolar stage
Distal lung Airways					
	5-7 Weeks	7-17 Weeks	17-26 Weeks	26-36 Weeks	36-3 Weeks
Conducting and respiratory airways	Trachea, right and left bronhus	Bronchial tree	Ventilatory unit	Alveolar sac	Secondary septation
Distal epithellium	Lung endoderm progenitor cell	Proximal progenitor cell	Neuro-endocrine cells	Basal cell	


Windpipe
Lungs
Bronchiole
Main bronchus
Bronchi
Lung
Alveoli

babycentre

Stages of human lung development and their timing

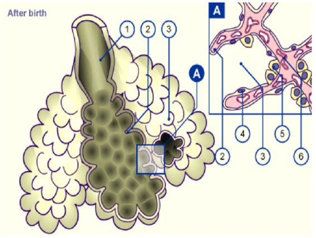




Postnatal Lung Growth

Birth - 8 years

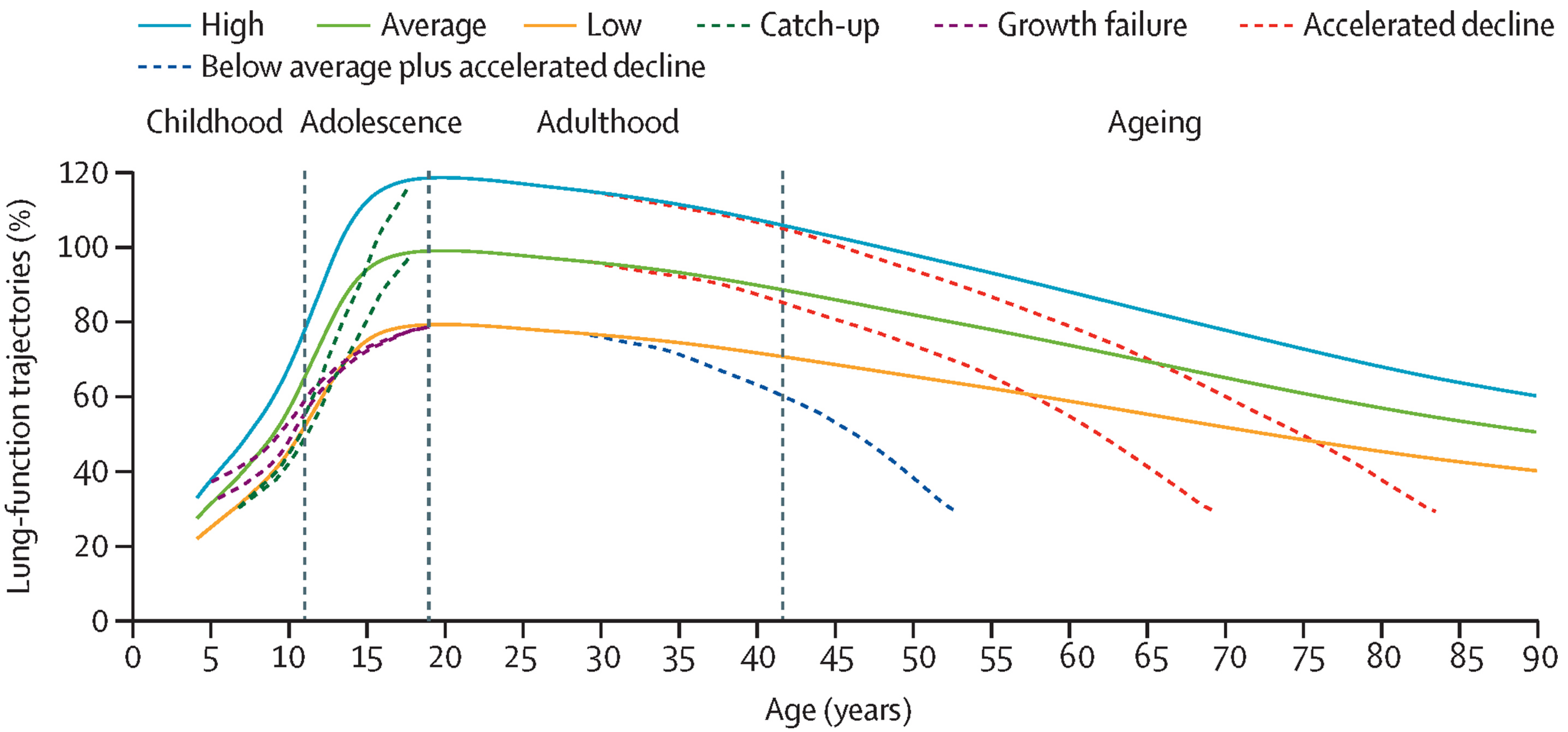
- Alveoli continue to increase in number and size, paralleled by arterial development



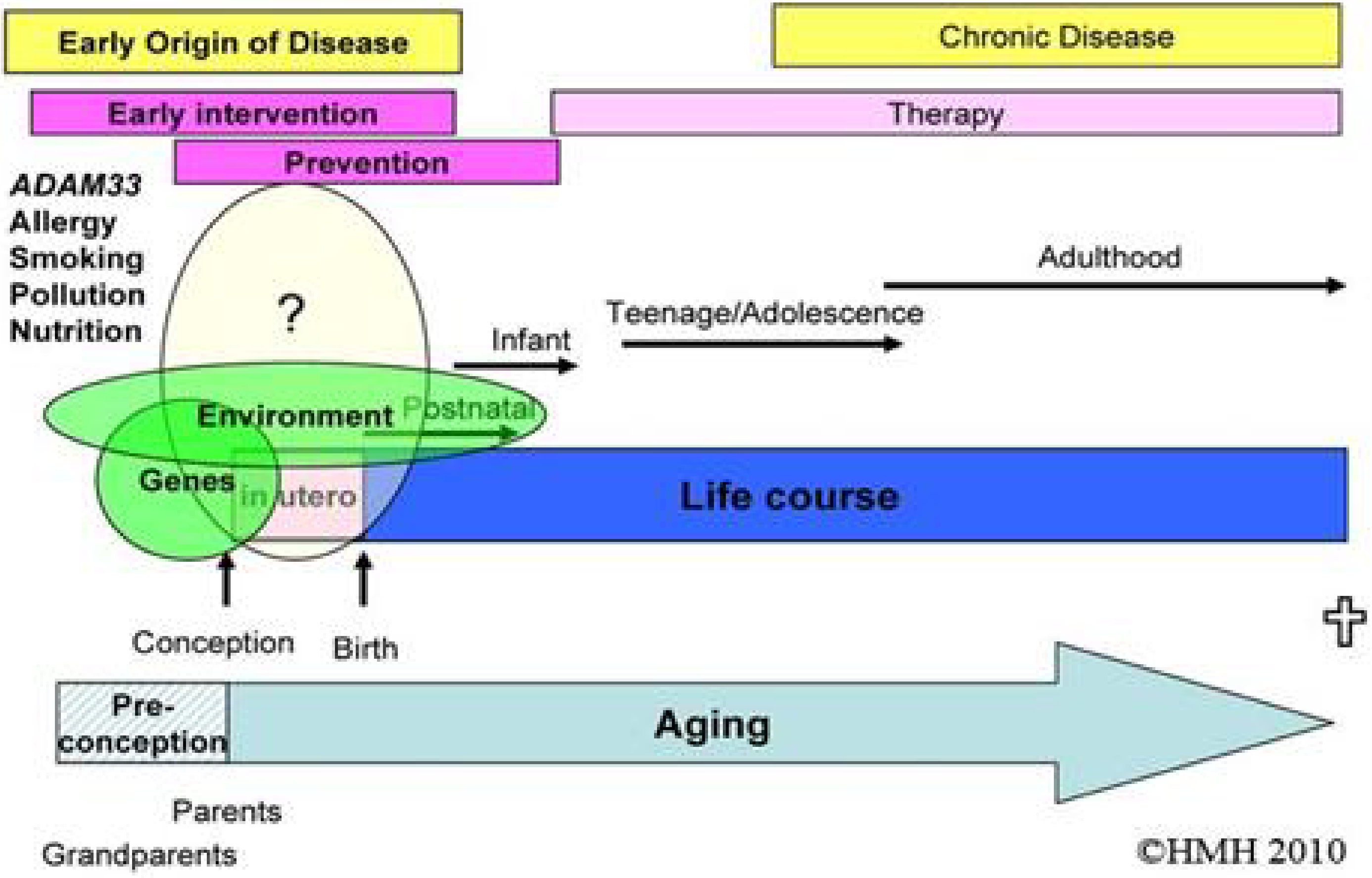
1 – Alveolar duct
2 – Primary septum
3 – Alveoli
4 – Type I pneumocytes
5 – Type II pneumocytes
6 – Capillaries

Lung function trajectories

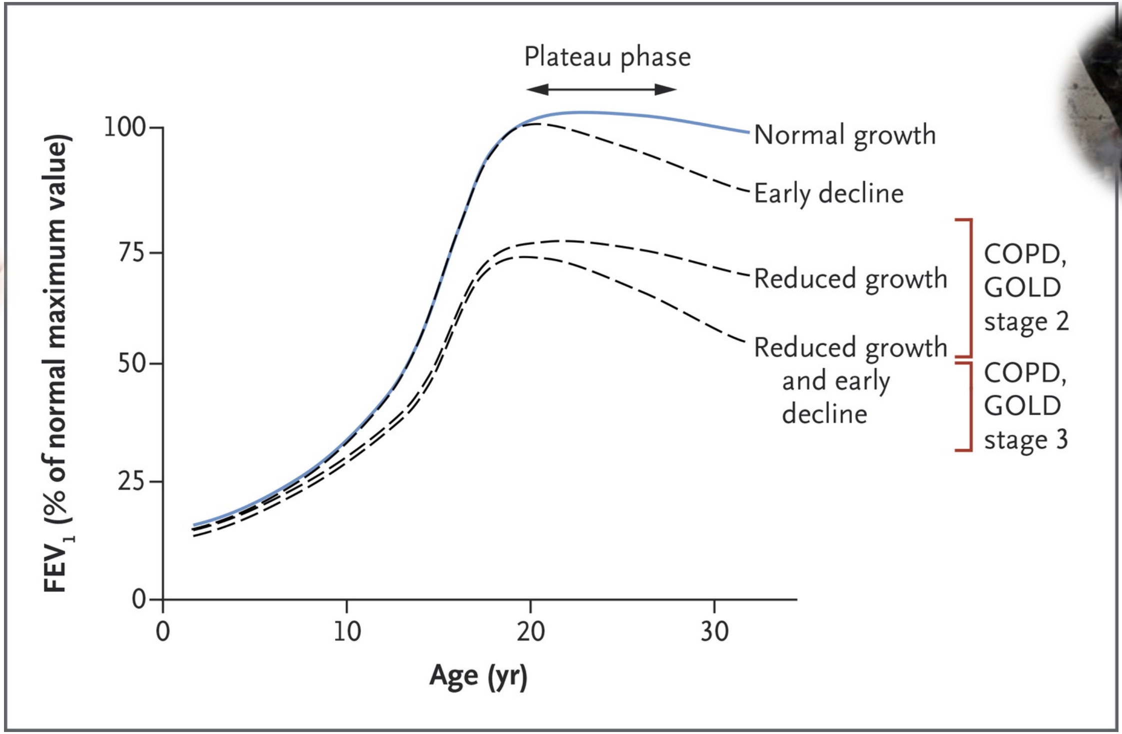
Melén E, et al., Lancet 2024; 403 (10435): 1494



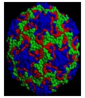
Life course approach to respiratory health



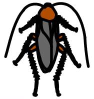
Time-dimension: Lung-function trajectories from birth to death



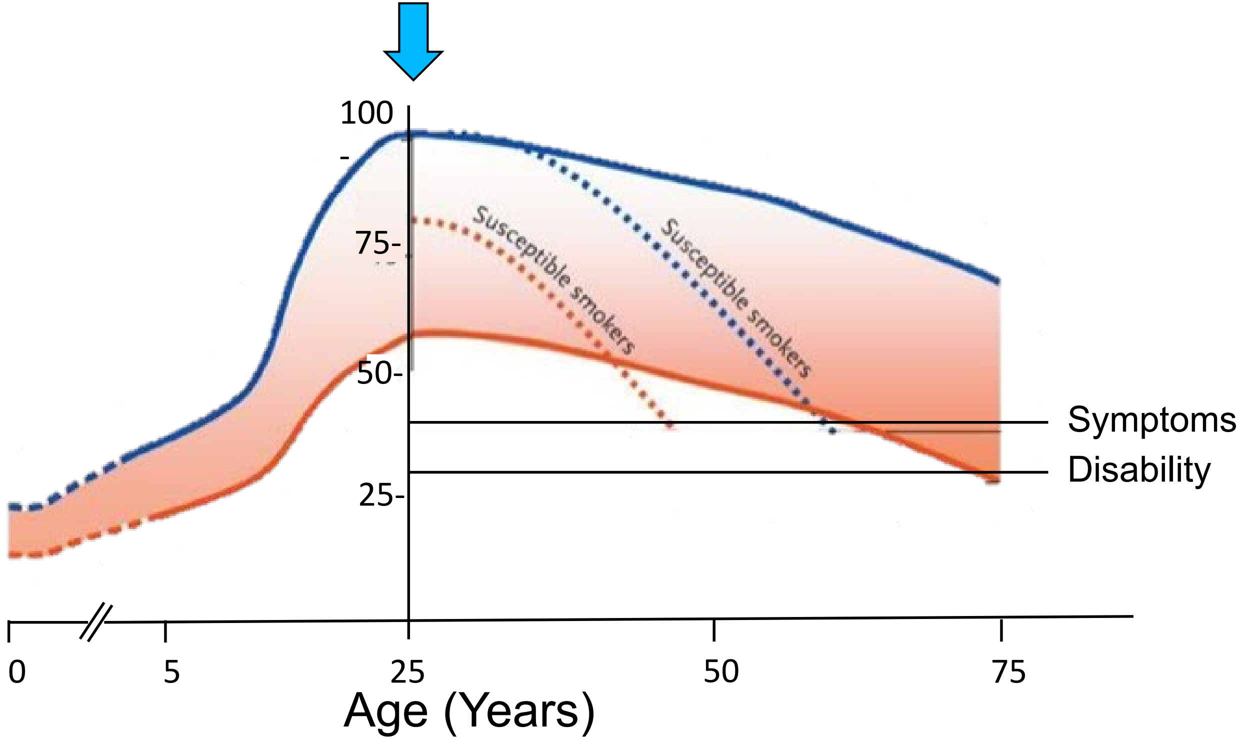
Lange P, et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. N Engl J Med 2015 Jul 9;373(2):111-122.



Viruses



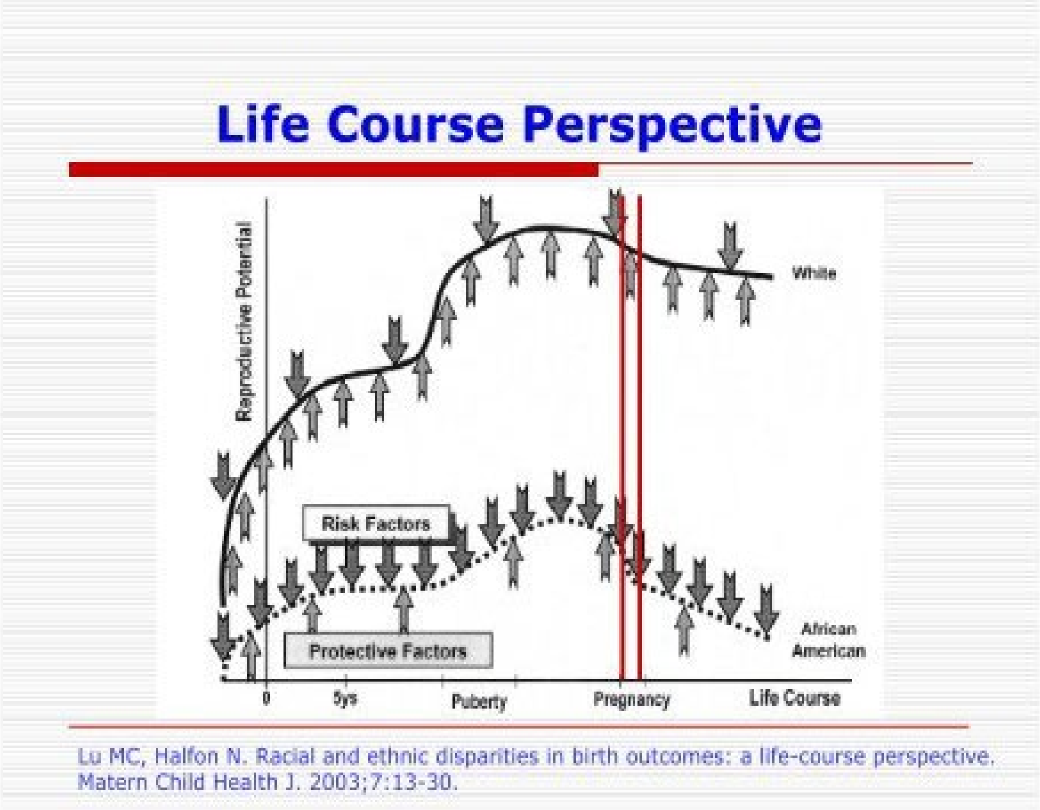
Maximal Level of FEV_1 (%)



Lung function (FEV1) over the lifecourse

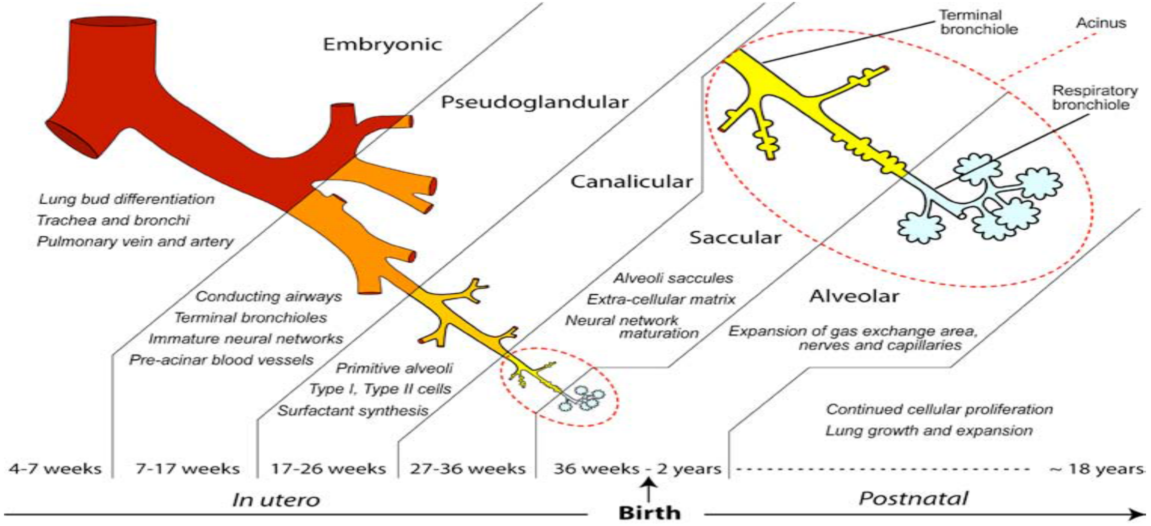
Lung function "tracks" throughout childhood, therefore impaired early life lung function results in reduced maximally attainable FEV1, a strong risk factor for the development of subsequent respiratory disease such as COPD, early mortality, CVD, etc.

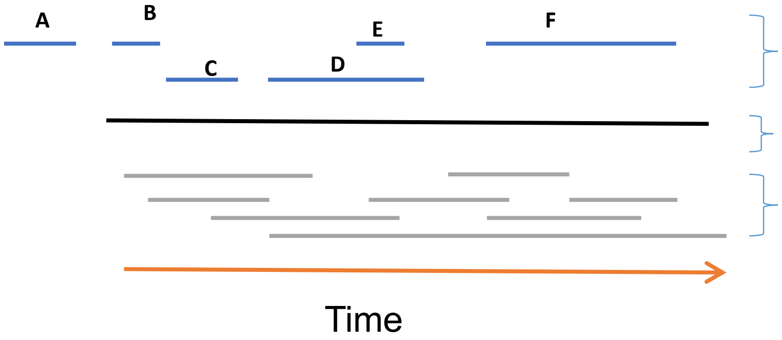
Balance between risk and resiliency factors



- How risk reduction and health promotion strategies influence trajectories.
- Mitigate effects of risk factors.
- Without these balancing effects building resilience, trajectories are suboptimal.

Critical Windows – Pregnancy and Early Life



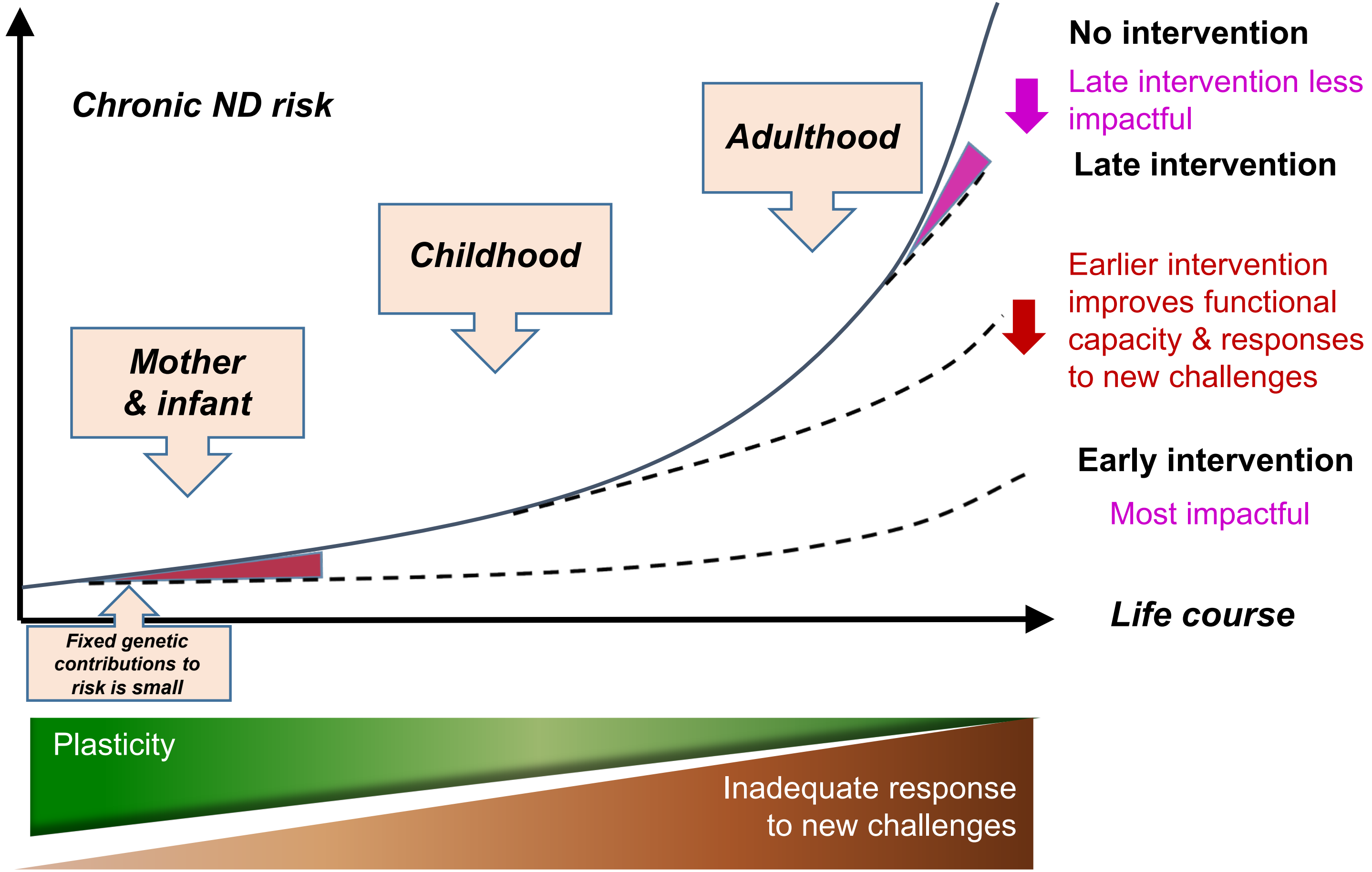


Environment Specific Exposure windows

Phenotype Developmental window

Biological Cell/tissue processes

Lifecourse strategy for lung development



Gluckman, Hanson, Cooper et al New Engl J Med 2008; 359: 61-73 Hanson M , Godfrey K et al Prog Biophys Molec Biol 2011; 106: 272-280

ECHO Protocol Spirometry Specifications

Spirometry is a core measure in the following years / age bands.
Time to complete is ~15-20 minutes.

- 2025, 2028: 7*-10yr and 11-17yr
- 2026, 2029: 18-20yr

***Notes:**

- The ECHO Cohort Protocol age band is 6-10 years, but spirometry collection starts at age 7
- Children who are 6 turning 7 in the calendar year and have a visit before their 7th birthday ***will not*** complete spirometry
- Sites do not need to re-contact the child after they turn 7 to complete spirometry – there will be missing data for that participant
- To the extent possible, try to schedule visits after the child's birthday to maximize spirometry data collection

Spirometry – Lung Function Testing

- Spirometry is used to check how well your lungs work
- Measures how much air you breathe in, how much you breathe out (volume) and how quickly you breathe out (flow)
- Spirometry is one component of a Pulmonary Function Test (PFT)
- Spirometry patterns help to identify diseases (obstructive vs. restrictive)
- Spirometry can track healthy/suboptimal lung growth over childhood

Spirometry – Lung Function Testing

- The two most common parameters that spirometry records are FVC and FEV1
  - Forced Vital Capacity (FVC): The maximum amount of air that can be forcefully exhaled after a deep breath filling your lungs, measured in liters
  - Forced Expiratory Volume over 1 Second (FEV1): The amount of air exhaled in the first second of the forced exhalation, also measured in liters

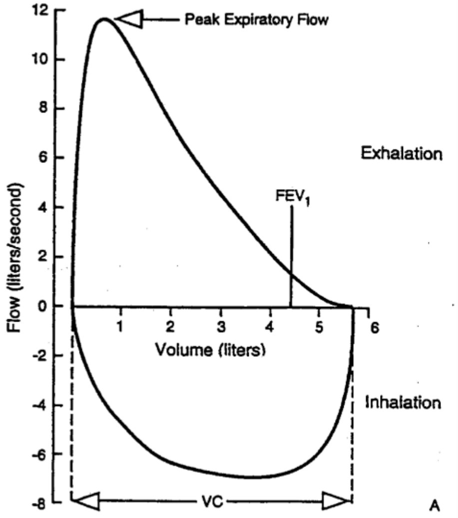
- ECHO participants can complete spirometry at in-person visits or remotely
  - Regardless of location, all participants receive live coaching, feedback, and support from site staff

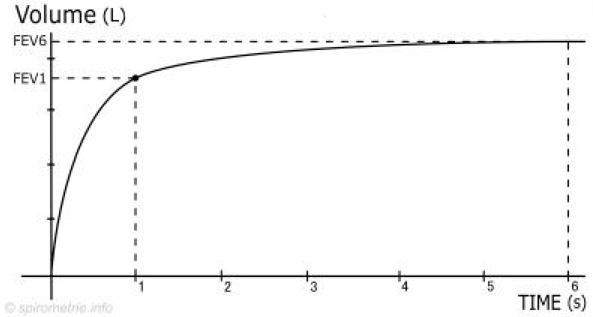
Equipment and Supplies

1. ECHO equipment to measure height and weight
2. Spirometer
   – Device differs for in-person or remote collection
3. Disposable mouthpiece and turbine
   – Single-participant-use
4. Nose clip
   – Reduces air escaping the nose (source of error)
5. Smartphones/tablets/computers
   – With camera, microphone, speakers
6. ZEPHYRx software
   – Kiosk (for in-person testing) or Breathy Easy App (for remote testing)

ECHO Spirometry Data

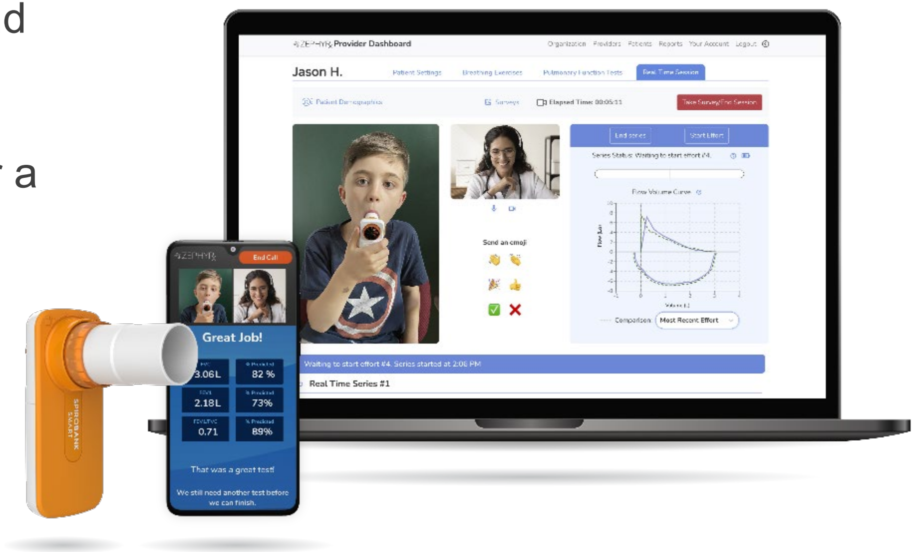
- Enter into ZEPHYRx software
  - Height and weight
  - Sex, date of birth, ethnicity
  - Body position (sitting)
- Spirometry results
  - Forced vital capacity (FVC)
  - Forced expiratory volume in 1 second (FEV1)
  - And more…
- Data Collection Form (DCF)
  - Current infection
  - Medications
  - Reasons activity not completed
  - Nose clip use





ZEPHYRx Remote Spirometry System

- The ZEPHYRx Home Spirometry System uses a handheld Spirometer (MIR Spirobank Smart) and the ZEPHYRx Breathe Easy app
- Can be run on a participant's phone or tablet, or a clinic provided phone or tablet
- Participants do spirometry through an in-app virtual coaching call with the study team
- Sites can view all results on the ZEPHYRx Provider Dashboard

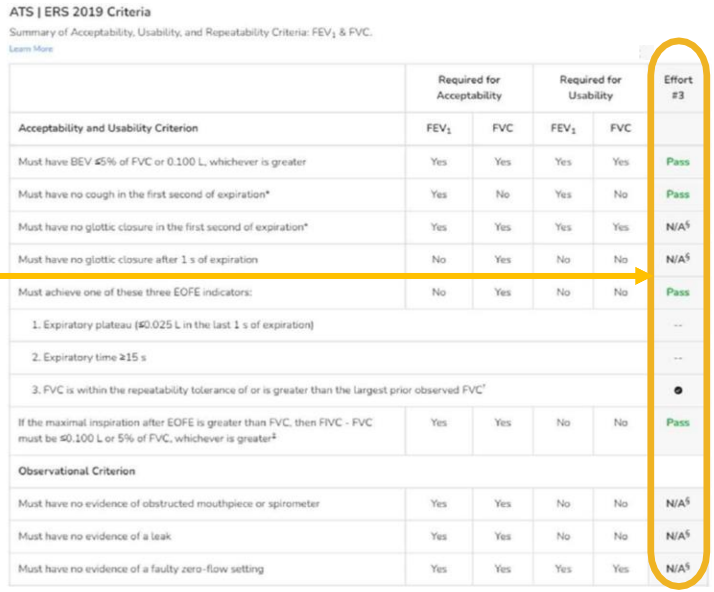


Quality Assurance with ArtiQ

Real Time Quality Feedback

- Each effort is assessed for acceptability and usability
- Receive a green check if all criterion are passed
- **Items with N/A require staff input to assess**

ZEPHYRx Kiosk View



ATS | ERS 2019 Criteria

Summary of Acceptability, Usability, and Repeatability Criteria: FEV_1 & FVC.

Learn More

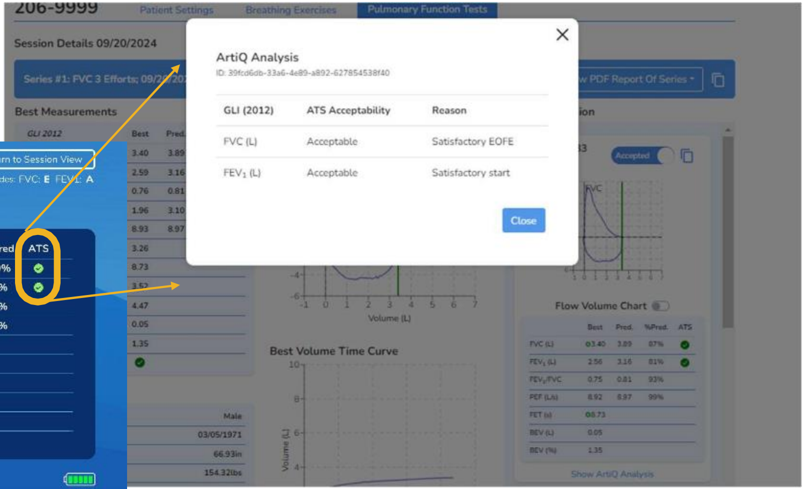
	Required for Acceptability		Required for Usability		Effort #3
Acceptability and Usability Criterion	FEV_1	FVC	FEV_1	FVC	
Must have BEV ≤5% of FVC or 0.100 L, whichever is greater	Yes	Yes	Yes	Yes	Pass
Must have no cough in the first second of expiration*	Yes	No	Yes	No	Pass
Must have no glottic closure in the first second of expiration*	Yes	Yes	Yes	Yes	N/A§
Must have no glottic closure after 1 s of expiration	No	Yes	No	No	N/A§
Must achieve one of these three EOFE indicators:	No	Yes	No	No	Pass
1. Expiratory plateau (≤0.025 L in the last 1 s of expiration)					--
2. Expiratory time ≥15 s					--
3. FVC is within the repeatability tolerance of or is greater than the largest prior observed FVC†					●
If the maximal inspiration after EOFE is greater than FVC, then FIVC - FVC must be ≤0.100 L or 5% of FVC, whichever is greater‡	Yes	Yes	No	No	Pass
Observational Criterion					
Must have no evidence of obstructed mouthpiece or spirometer	Yes	Yes	No	No	N/A§
Must have no evidence of a leak	Yes	Yes	No	No	N/A§
Must have no evidence of a faulty zero-flow setting	Yes	Yes	Yes	Yes	N/A§

ZEPHYRx Kiosk criteria display from Session View

Quality Feedback with ArtiQ – AI Overreading

- Each effort is accessed with an AI algorithm
- Reviews the curve and checks the parameters like Glottic Closure that cannot be assessed by the ZEPHYRx software

ZEPHYRx Kiosk View



ZEPHYRx Kiosk criteria display from Session View

ECHO Environmental influences on Child Health Outcomes. A program supported by the NIH

Spirometry

ECHO Cohort Version 03.20 / February 17, 2025

COHORT SITE ID	PARTICIPANT ID	PIN	FORM COMPLETED
__ __ __ __ __ __ __ __ __	______________	__ __ __	__ __/__ __/__ __ __ __ (mm dd yyyy)

VISIT GROUP (age at time of visit)				RESPONDENT
☐01 Prenatal	☐02 Age 0 to 35 mos.	☐03 Age 3 to 20 yrs.	VISIT YEAR	
☐01 2nd Trimester ☐02 3rd Trimester __ __ Gestational age in weeks	☐01 0 to 5 mos. ☐02 6 to 11 mos. ☐03 12 to 23 mos. ☐04 24 to 35 mos. __ __ Age in months	☐01 3 to 5 yrs. ☐02 6 to 10 yrs. ☐03 11 to 17 yrs. ☐04 18 to 20 yrs. __ __ Age in years	__ __ __ __	☐01 Participant ☐02 Biological Mother ☐03 Biological Father ☐04 Other Respondent → Code: ___

STUDY STAFF INSTRUCTION: This form is completed by Cohort Study Site staff to record child spirometry metadata, using the Child ID. Child height and weight should be measured immediately before completing spirometry. Study staff should complete Section A before the child begins the measure, and Section B after the child completes the measure. Study staff should administer this form to the caregiver or the child; the form should not be self-administered by participants or caregivers. If the respondent is the child, study staff may phrase the questions using "you" instead of "the child."

Section A. Pre-Assessment Questions – *Information provided in this section may affect the interpretation of results. Complete these questions before beginning the test.*

1. Is the child ill with an upper or lower respiratory infection today?
   - ☐01 Yes ➔ ***If yes, reschedule the spirometry test and do not complete the rest of this form***
   - ☐02 No
   - ☐-8 Don't know

2. Did the child use an inhaler, nebulizer, or other medication to treat asthma, recurrent wheezing, or recurrent cough today?
   - ☐01 Yes ➔ ***If yes, continue Question 3***
   - ☐02 No
   - ☐-8 Don't know } ***If no or don't know, skip to Section B***

3. Which medications has the child used today?	If yes, what time did the child use this today?
3.a. Bronchodilator inhaler and/or nebs (for example, Albuterol, Proventil, Proair) ☐01 Yes ☐02 No	**3.a.1.** |__|__| : |__|__| *(24 hour clock)* hh mm
3.b. Inhaled steroid inhaler (for example, Fluticasone, Flovent, Arnuity Ellipta, Pulmicort, Asmanex, Qvar, Alvesco) ☐01 Yes ☐02 No	**3.b.1.** |__|__| : |__|__| *(24 hour clock)* hh mm
3.c. Combination inhaled steroid and long-acting beta agonist inhaler (for example, Advair, Airduo, Dulera, Symbicort, Breo Ellipta) ☐01 Yes ☐02 No	**3.c.1** |__|__| : |__|__| *(24 hour clock)* hh mm

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Spirometry

ECHO Cohort Version 03.20 / February 17, 2025

PARTICIPANT ID ______________

3. Which medications has the child used today?	If yes, what time did the child use this today?
3.d. Oral asthma medication (for example, Singulair, Montelukast) ☐01 Yes ☐02 No	**3.d.1.** |__|__| : |__|__| *(24 hour clock)* hh mm
3.e. Monoclonals or biologic injections for asthma (for example, Xolair, Nucala, Fasenra, Dupixent, Tezspire) ☐01 Yes ☐02 No	**3.e.1.** |__|__| : |__|__| *(24 hour clock)* hh mm
3.f. Other (specify): ______________________ ☐01 Yes ☐02 No	**3.f.1.** |__|__| : |__|__| *(24 hour clock)* hh mm

Section B. Post-Assessment Questions. *Complete these questions after completing the test.*

1. Was the child able to complete the measurements?
   - ☐01 Yes ➔ ***Skip to question 2***
   - ☐02 No

   1a. Why was the child unable to complete the measurements?
   - ☐01 Participant refusal to cooperate during test
   - ☐02 Child became tired or frustrated
   - ☐03 Other, specify ______________________
   - ☐-8 Don't know

2. Did the child use the nose clip?
   - ☐01 Yes
   - ☐02 No
   - ☐-8 Don't know

Setting				Mode	
☐01 Clinic or site	☐02 Phone	☐03 Other location	☐04 Video	☐01 Self-administered	☐02 Staff-administered

Developing Rapport and Coaching Participants is Key

Provide a brief explanation

- This is a spirometer
- It measures how much air you can blow out and how fast you can blow it out
- You are the one who makes it run
- Optional: point out parts of equipment to participant to demystify the spirometer

Prepare the child for what's to come – instruct and demonstrate

- Sitting with straight posture with head slightly elevated
- Feet flat on floor
- Place nose clip on your nose
- **Inhale** completely taking the biggest breath, then…
- **Exhale** with maximal force (as hard and fast as you can) until I tell you to stop (you may want to stop early)
- Avoid bending forward at the waist when blowing out
- Demonstrate after instructing

Developing Rapport and Coaching Participants

Explain how to perform the activity well

- Use the mouthpiece and nose clip
- Make sure that the tongue is underneath the mouthpiece
- Lips create a tight seal around mouthpiece
- Hold onto the mouthpiece with teeth to make sure it doesn’t come out
- Nose clip on
- Take a big, deep, full breath in (the biggest breath the participant can)
- As soon as participant cannot get any more air into their lungs, have them blow out as hard and as fast as they can
- Keep blowing out with all their strength until told to stop
- Example: “Really blast hard and keep squeezing air out for at least five seconds because it takes that long to ‘empty’ your lungs. It might seem as if you are ‘empty,’ but keep squeezing out as long as you possibly can. It is very important for you to give a maximum effort.”

Developing Rapport and Coaching Participants

Coaching and motivation may be needed

- Think of yourself trying to blow out 100 candles on a birthday cake
- Blow out like you are trying to blow a huge spit wad across the room through a large straw

Things That Impact Spirometry Quality, Effort, and Technique

- Coughing
- Poor understanding of the activity
- Refusal/inability to cooperate

Spirometry Completion Criteria

- The activity ends if one of these three things happens
  - The participant completes three or more acceptable and reproducible efforts (series score is A, B, C, D, or E)
  - The participant completes eight efforts
  - The participant is unable to continue
- After the series ends, complete Spirometry Data Collection Form (DCF), Section B
  - Did participant complete activity?
    - If not, why not?
  - Did participant use nose clips?

ECHO

Environmental influences
on Child Health Outcomes

A program supported by the NIH