

REVIEW ARTICLE


Environmental influences on child health outcomes: cohorts of individuals born very preterm

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The National Institutes of Health's Environmental influences on Child Health Outcomes (ECHO) Program was designed to address solution-oriented research questions about the links between children's early life environment and their risks of pre-, peri-, and post-natal complications, asthma, obesity, neurodevelopmental disorders, and positive health. Children born very preterm are at increased risk for many of the outcomes on which ECHO focuses, but the contributions of environmental factors to this risk are not well characterized. Three ECHO cohorts consist almost exclusively of individuals born very preterm. Data provided to ECHO from cohorts can be used to address hypotheses about (1) differential risks of chronic health and developmental conditions between individuals born very preterm and those born at term; (2) health disparities across social determinants of health; and (3) mechanisms linking early-life exposures and later-life outcomes among individuals born very preterm.

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IMPACT:

- The National Institutes of Health's Environmental Influences on Child Health Outcomes Program is conducting solution-oriented research on the links between children's environment and health.
- Three ECHO cohorts comprise study participants born very preterm; these cohorts have enrolled, to date, 1751 individuals born in 14 states in the U.S. in between April 2002 and March 2020.
- Extensive data are available on early-life environmental exposures and child outcomes related to neurodevelopment, asthma, obesity, and positive health.
- Data from ECHO preterm cohorts can be used to address questions about the combined effects of preterm birth and environmental exposures on child health outcomes.

INTRODUCTION

The National Institutes of Health-funded Environmental influences on Child Health Outcomes (ECHO) Program seeks to promote the health and well-being of children in the United States (U.S.) through solution-oriented research. Its overarching goal is to characterize relationships between the environment and children's health.¹ The ECHO Program focuses on pre-, peri-, and postnatal outcomes; neurodevelopmental disorders; asthma; obesity; and positive health. The ECHO Program interprets the environment broadly as including psychosocial factors, chemical exposures, the physical environment, and home and community

resources. The ECHO-wide cohort comprises 69 existing cohorts of children and their parents or guardian. Cohorts differ in age and inclusion criteria at enrollment, current life stage, race and ethnic distribution, and geographic region of residence. These differences provide opportunities for harmonizing large datasets, thereby allowing examination of specific questions amongst subgroups of children who may have unique susceptibilities.

Children who are born very preterm (before 32 weeks of gestation) or extremely preterm (before 28 weeks of gestation) are at increased risk for multiple adverse health outcomes. For

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example, in the Extremely Low Gestational Age Newborn (ELGAN) Study,² one of the largest research cohorts of individuals born extremely preterm, the frequencies of asthma,³ attention deficit hyperactivity disorder,⁴ epilepsy,⁵ autism spectrum disorder,⁶ and cognitive impairment⁷ were at least four times the frequencies found in population-based estimates of prevalence among children born at term in the U.S. Thus, ECHO cohorts comprising children born very preterm or extremely preterm will enhance the statistical power of studies of neurodevelopmental disorders and asthma.

The ELGAN cohort is one of three ECHO cohorts composed almost entirely of individuals born very preterm; the other two are the Neonatal Neurobehavior and Outcomes in Very Preterm Infants (NOVI) cohort and the Developmental Impact of Neonatal Intensive Care Unit Exposures (DINE) cohort. In addition to these three cohorts, other cohorts in ECHO that are not composed exclusively of individuals born very preterm have enrolled individuals born very preterm.

Our rationale for focusing this article on the potential contributions of the three ECHO cohorts composed exclusively of individuals born preterm is twofold. First, all three of these cohorts collected detailed data on neonatal morbidities, such as bronchopulmonary dysplasia (BPD) and brain abnormalities identified with neonatal ultrasound, conditions that often are important covariates in analyses of child health outcomes. Second, these three ECHO cohorts account for 97% of very preterm individuals who have consented to participate in ECHO. This subgroup of ECHO participants is at very high risk for health disorders.⁸

Our goal is to serve as a “roadmap” to aid child health researchers in their efforts to apply data from the ECHO preterm cohorts toward the broad goals of the ECHO program. First, we describe the initial research goals, selection criteria, and key exposures and outcomes for the three preterm infant ECHO cohorts. The rich extant data (data available prior to the start of the ECHO Program) from these cohorts, coupled with new data collected on study participants using the ECHO-wide data collection protocol, is creating a rich and unique dataset to address critical and impactful research questions regarding children born preterm; thus we will describe ways to access data from the ECHO Program. Second, we outline four areas of child health research where data from these preterm infant cohorts are likely to be particularly valuable: (1) identification of modifiable risk factors for adverse child health outcomes, (2) developmental origins of health, (3) health disparities across social class, and (4) resiliency factors that moderate the long-term effects of early-life adversity.

COHORTS OF INDIVIDUALS BORN VERY PRETERM

Table 1 summarizes demographic and neonatal characteristics of the three ECHO cohorts of individuals born very preterm. Tables 2–4 summarize follow-up assessments that have been completed or are ongoing in the three cohorts. Information about other variables that are being collected from ECHO study participants can be found in the ECHO-wide Cohort Data Collection Protocol, using this link: <https://echochildren.org/echo-program-protocol/>. The following three sections provide additional background and details about the three ECHO cohorts of individuals born very preterm.

NOVI

The aim of the NOVI Study was to determine whether neurobehavioral abnormalities at discharge can identify infants with impairment at 2 years corrected age and whether cumulative medical risk and the post-discharge caregiving environment modify associations between neurodevelopmental status at discharge and at 2 years corrected age. The NOVI Study cohort

was enrolled from April 2014 through June 2016 at nine university-affiliated neonatal intensive care units (NICUs) in seven U.S. cities: Providence, Rhode Island; Grand Rapids, Michigan; Kansas City, Missouri; Honolulu, Hawaii; Winston-Salem, North Carolina; and Torrance and Long Beach, California. These NICUs were also participating in the Vermont Oxford Network for quality improvement, and the database for that network was used as a source of data for neonatal morbidities. Eligibility was determined based on the following inclusion criteria: (1) birth at <30 weeks postmenstrual age (PMA); (2) parental ability to read and speak English or Spanish; and (3) residence within 3 h of the NICU and follow-up clinic. Exclusion criteria included maternal age <18 years, maternal cognitive impairment, maternal or infant death, and major congenital anomalies. Parents of eligible infants were invited to participate in the study when survival to discharge was determined to be likely by the attending neonatologist. Of 709 infants consented, 704 enrolled, and 679 (96% of those enrolled) had complete neurobehavioral assessment data and 624 (88% of enrollees) had buccal cells collected for epigenomic screening. At the time of the follow-up assessment at 2 years corrected age, 566 infants participated (80% of enrollees). With additional funding from ECHO, 495 (70% of enrollees) children and 440 (62% of enrollees) children participated at 3 and 4 years, respectively. Currently, visits are being completed when NOVI participants are 4.5 and 5 years of age using the ECHO-wide Cohort Protocol. The major findings from NOVI, thus far, relate to associations between infant atypical neurobehavior and specific medical problems such as infant sepsis⁹ and brain injury.¹⁰ These infants also displayed unique epigenetic changes¹¹ and were born to mothers with adverse medical and psychosocial conditions.¹² Longitudinal collection of buccal cells, which has provided insight into DNA methylation changes related to neurobehavior and medical health,^{12–14} will allow for deeper understanding of epigenetic changes over time.

DINE

The DINE study unites participants previously enrolled in one of the four NICU-based NIH-supported studies into a single harmonized study cohort. These four studies include the Prematurity and Respiratory Outcomes Program (PROP),¹⁵ the Trial of Late Surfactant (TOLSURF) study,¹⁶ the Preterm Erythropoietin Neuroprotection Trial (PENUT),¹⁷ and the Neonatal Intensive Care Unit Hospital Exposures and Long-Term Health (NICU-HEALTH) study.¹⁸ Between January 2010 and March 2020, DINE participants were recruited into their parent study based on enrollment criteria at one of the eight university-affiliated NICUs in New York, New York; Rochester, New York; Buffalo, New York; Nashville, Tennessee; Cincinnati, Ohio; Winston-Salem, North Carolina; Minneapolis, Minnesota; and Jacksonville, Florida. Each parent cohort collected detailed clinical, demographic, and developmental data as well as a rich repository of biospecimens during their initial enrollment period.

PROP was a multi-center, observational, prospective cohort study of 835 preterm infants born at 23–28 completed weeks of gestation between August 2011 and November 2013 (ClinicalTrials.gov NCT01435187).^{15,19–22} PROP was a U01 collaboration between the National Heart, Lung, and Blood Institute (NHLBI), a data coordinating center, and 6 clinical centers, with NICUs at 13 hospitals. Of the original NICUs in PROP, 34 clinical centers with 6 recruitment hospitals currently participate in ECHO-DINE. A key aim of PROP was to identify clinical, physiologic, and biochemical markers during NICU hospitalization that predict respiratory morbidity through 1 year of age. Each PROP center participated in multiple hypothesis-driven, biomarker-based studies investigating mechanistic pathways associated with BPD (chronic lung disease of prematurity) and respiratory morbidity one year after hospital discharge. Post-NICU discharge data were obtained at 3, 6, 9, and 12 months corrected age. A diagnosis of BPD at 36 weeks

Table 1. Characteristics of ECHO preterm cohorts and ECHO-wide participants born very preterm.

Characteristic	PROP ^a	ToISurf ^a	NICU-Health	PENUT ^a	NOVI	ELGAN	ECHO-wide very preterm infants (<32 weeks) ^b
Number enrolled	835 ^c	511 ^c	320	941 ^c	704 ^d	1506	3371
Number survived to NICU discharge (%)	346 (91%)	N/A	318 (99.4%)	N/A	695 (98.7%)	1200 (80%)	N/A
Consented to ECHO participation	276	65	130	78	499	703	1817
Location of recruitment of ECHO participants	New York, Ohio, Tennessee	Florida, Minnesota, North Carolina	New York	Florida, Minnesota, North Carolina	California, Hawaii, Michigan, Missouri, North Carolina, Rhode Island	Massachusetts, Connecticut, Michigan, Illinois, North Carolina	N/A
Years of recruitment	2011–2013	2010–2013	2011–2020	2011–2017	2014–2016	2002–2004	2002–2017
Gestational age	23–28 6/7 weeks	≤28 0/7 weeks	<33 weeks	24–27 6/7 weeks	22–29 weeks	23–27 weeks	22–31 weeks
Race							
White	223 (65.6%)	50 (61.7%)	172 (55.3%)	67 (69.8%)	313 (44.5%)	878 (58.3%)	1844 (54.7%)
Black	78 (22.9%)	29 (35.8%)	62 (19.4%)	23 (24%)	135 (19.2%)	428 (28.4%)	805 (23.9%)
Asian	<5	0 (0%)	27 (8.4%)	<5	29 (4.1%)	35 (2.3%)	103 (3.1%)
Native Hawaiian or other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (1.3%)	0 (0%)	10 (0.3%)
American Indian or Alaska Native	0 (0%)	0 (0%)	<5	0 (0%)	<5	14 (0.9%)	33 (1%)
Multiple race	13 (3.8%)	<5	17 (5.3%)	<5	159 (22.6%)	49 (3.3%)	303 (9%)
Other race	<5	<5	29 (12.1%)	0 (0%)	48 (6.8%)	7 (0.5%)	72 (2%)
Unknown or missing	18 (5.3%)	<5	<5	0 (0%)	<10	95 (6.3%)	201 (6%)
Ethnicity							
Non-Hispanic	304 (89.4%)	78 (96.3%)	283 (88.4%)	85 (88.5%)	533 (75.7%)	1315 (87.3%)	2727 (81%)
Hispanic	26 (7.6%)	<5	37 (11.6%)	11 (11.5%)	162 (23%)	179 (11.9%)	579 (17%)
Unknown or missing	10 (2.9%)	<5	0 (0%)	0 (0%)	9 (1.3%)	12 (0.8%)	65 (2.0%)
Neonatal characteristics and complications							
% females/% males	46.2/53.8	45.7/54.3	49.4/50.6	46.9/53.1	44.6/55.4	47.0/53.1	46.8/52.4
Mean (SD) gestational age, weeks	27.9 (3.5)	25.1 (1.4)	30.3 (1.9)	25.5 (1.2)	26.6 (1.9)	25.8 (1.3)	25.6 (5.6)
Mean (SD) birth weight, g	1119.2 (643.5)	743.5 (181.7)	1371.2 (359.1)	777.5 (208.3)	947.3 (281)	803.2 (201.4)	945 (424)
N (% birth weight z-score < -2) ^{b,e}	14 (4.5%)	8 (9.9%)	70 (21.9)	11 (11.5%)	12 (1.7%)	31 (2.1)	2.1
Bronchopulmonary dysplasia, (%) ^f	114 (36.8%)	54 (65.9%)	59 (18.4)	52 (54.2%)	357 (50.7)	644 (51.9)	1215 (36.0)
Necrotizing enterocolitis (%)	12 (4.2%)	8 (9.9%)	8 (2.5)	3 (3.1%)	51 (7.2)	(6.4)	N/A
Sepsis ^g (%)	187 (59.7%)	51 (65.4%)	26 (8.1)	53 (55.2%)	92 (13.1)	(29.2)	N/A

Table 1. continued

	PROP ^a	ToISurf ^a	NICU-Health	PENUT ^a	NOVI	ELGAN	ECHO-wide very preterm infants (<32 weeks) ^b
Cerebral white matter injury ^h (%)	N/A	N/A	6 (2.6)	5 (5.2%)	80 (11.4)	(15.8)	N/A
Intraventricular hemorrhage (%)	32 (15%)	33 (40.2%)	47 (20.4)	27 (23.3%)	124 (17.6)	(24.1)	N/A

Note: Data for NICU-Health, NOVI, and ELGAN are from cohort-specific databases; all other data are provided by the ECHO Data Analysis Center. PROP Prematurity and Respiratory Outcomes Program, ToISurf Trial of Late Surfactant, NICU Neonatal Intensive Care Unit, PENUT Preterm Erythropoietin Neuroprotection Trial, ELGAN Extremely Low Gestational Age Newborn, NOVI Neonatal neurobehavioral Outcome of Very preterm Infants, ECHO Environmental Influences on Child Health Outcomes.

^aOnly a subset of sites that enrolled participants in PROP, TOLSURF, and PENUT are participating sites in ECHO-DINE.

^bData from the ECHO Data Analysis Center; other data from cohort analysts.

^cTotal enrolled in PROP, ToISurf, and PENUT at all sites.

^dAlthough 709 study participants were enrolled in NOVI, 5 participants withdrew, and data from these individuals will not be available in ECHO.

^eBirth weight z-score derived based on Aris et al.¹¹⁰

^fUse of supplemental oxygen at 36 weeks post-menstrual age; for ELGAN cohort, BPD is missing for infants who died prior to 36 weeks (denominator is 1241).

^gSepsis defined as positive blood culture.

^hPersistent ventriculomegaly or cerebral echolucency.

PMA was made in 41% of the cohort; 68% of the cohort experienced respiratory morbidity through 1 year of age.

TOLSURF was an NHLBI-supported masked, randomized, sham-controlled trial conducted in 25 U.S. hospitals to determine the effect of late doses of surfactant on BPD at 36 weeks PMA in preterm infants receiving inhaled nitric oxide (U01HL094338; PI: Roberta Ballard, MD; ClinicalTrials.gov NCT01022580).^{16,23} Preterm infants were eligible for TOLSURF if they were <28 weeks gestation and required intubation and mechanical ventilation between 7 and 14 days of age. TOLSURF enrolled 511 infants across 25 sites between January 2010 and September 2013. Compared with PROP, infants in TOLSURF had a lower mean birth weight and lower gestational age and were enrolled in week 2 of life rather than week 1. Exclusion criteria were life-threatening congenital abnormalities or airway anomalies, clinical instability, or low likelihood of being available for long-term follow-up. TOLSURF reported that survival without BPD did not differ between the surfactant-treated group and the control group at 36 weeks PMA (31.3 vs 31.7%; 95% CI, 0.75–1.28; $P=0.89$).¹⁶ TOLSURF infants were followed via pulmonary questionnaires every 3–6 months through 24 months and underwent assessment of neurodevelopmental outcomes at 24 months. Three of the highest enrolling TOLSURF sites participate in the ECHO DINE study.

PENUT was a randomized, multi-center, placebo-controlled trial funded by the National Institute of Neurological Disorders and Stroke (NINDS) to assess whether early high-dose erythropoietin improved survival without neurodevelopmental impairment in infants born between 24 and 28 weeks' gestational age at 19 centers across the U.S. between December 2013 and September 2016 (U01NS077953; PI: Sandra Juul, MD, PhD; ClinicalTrials.gov NCT01378273).^{24–26} Infants in PENUT were enrolled at <24 h of age. Infants underwent neurodevelopmental assessment at 2 years of age. Exclusion criteria and data collection elements in PENUT closely resemble those in TOLSURF and PROP. Three PENUT sites, which also participated in TOLSURF, participate in the ECHO DINE study. PENUT investigators recently reported that high-dose erythropoietin treatment administered to extremely preterm infants from 24 h after birth through 32 weeks PMA did not result in a lower risk of severe neurodevelopmental impairment or death at 2 years of age.²⁴

NICU-HEALTH was designed from its inception as an environmental health birth cohort study of preterm infants (K23ES022268; PI: Annemarie Stroustrup, MD; ClinicalTrials.gov NCT01420029, NCT01963065).^{18,27–30} Funded by the National Institute of Environmental Health Sciences (NIEHS), NICU-HEALTH enrolled 320 infants born at <33 weeks' gestational age at Mount Sinai Hospital in New York City in two phases between September 2011 and March 2020. NICU-HEALTH collected comprehensive information about both chemical and non-chemical exposures during NICU hospitalization and evaluated the impact of the NICU environment on neurobehavioral outcomes through early childhood. Comprehensive clinical and exposure data, questionnaire information, and biospecimens were collected through the NICU stay and then following discharge to 2 years of age. Longitudinal follow-up included multiple objective and survey assessments of temperament and cognitive, motor, and behavioral performance; questionnaires about home-based environmental exposures and medical comorbidities, including pulmonary outcomes; and biospecimen collection at 3, 6, 12, and 24 months corrected age (age corrected for degree of prematurity). Participants from a subset of parent study sites were re-recruited into DINE with the goal of identifying and quantifying the impact of hospital-based exposures early in life on the long-term development of children born preterm.

Thus far, DINE has re-recruited 549 participants to the ECHO Program with a target enrollment of 655. DINE participants complete annual follow-up visits under the ECHO-Wide Cohort Protocol.

Table 2. Follow-up assessments in the ECHO-DINE preterm cohort.

Domain	Age at assessment			
	Birth to 24 months ^a	24–36 months	3–5 years	6+ years
Cognitive				
PROP	N/A	Bayley Scales of Infant and Toddler Development—third edition	NIH Toolbox—Early Cognition, Strengths and Difficulties Questionnaire, Ages and Stages Questionnaire, Modified Checklist for Autism in Toddlers Revised (age 3 only), Rothbart Childhood Behavior Questionnaire Very Short Form (age 3 only), Social Responsiveness Scale	NIH Toolbox—Cognition, Strengths and Difficulties Questionnaire, Social Responsiveness Scale
PENUT	Bayley Scales of Infant and Toddler Development—third edition, and Child Behavioral Checklist at 24 months	N/A	See above	See above
TolSurf	Bayley Scales of Infant and Toddler Development—third edition at 24 months	N/A	See above	See above
NICU-Health	Bayley Scales of Infant and Toddler Development—third edition at 24 months	N/A	See above	See above
Motor				
PROP	N/A	N/A	NIH Toolbox—Motor	NIH Toolbox—Motor
PENUT	Standardized neuromotor examination; Gross Motor Function Classification System at 24 months	N/A	See above	See above
TolSurf	Standardized neuromotor examination; Gross Motor Function Classification System at 12 and 24 months	N/A	See above	See above
NICU-Health	NICU Network Neurobehavioral Scale; Bayley Scales of Infant and Toddler Development—third edition at 24 months	N/A	See above	See above
Vision and hearing				
PROP	Ophthalmologic events during hospitalization after birth	Parent-reported vision and hearing problems at 3 years (Rochester site only)	Parent-reported problems with seeing and hearing	Parent-reported problems with seeing and hearing
PENUT	Parent-reported vision and hearing problems at 12 months	N/A	See above	See above
TolSurf	Parent-reported vision and hearing problems at 12 and 24 months	N/A	See above	See above
NICU-Health	Parent-reported vision and hearing problems at 12 and 24 months	N/A	See above	See above
Behavior/psychiatric				
PROP	N/A	N/A	Strengths and Difficulties Questionnaire, Ages and Stages Questionnaire, PROMIS Depressive Symptoms—Early Childhood, PROMIS Anxiety—Early Childhood, PROMIS Positive Affect—Early Childhood	Strengths and Difficulties Questionnaire, PROMIS Psychological Stress Experiences, PROMIS Anxiety, PROMIS Depressive Symptoms, PROMIS Positive Affect

Table 2. continued

Domain	Age at assessment	24–36 months	3–5 years	6+ years
	Birth to 24 months^a			
PENUT	Modified Checklist for Autism in Toddlers; Child Behavior Checklist at 24 months	N/A	Same as above	Same as above
ToiSurf	Modified Checklist for Autism in Toddlers at 24 months	N/A	Same as above	Same as above
NICU-Health	NICU Network Neurobehavioral Scale; Rothbart Infant Behavior Questionnaire; Ages and Stages Questionnaire; Modified Checklist for Autism in Toddlers; Child Behavior Checklist	N/A	Same as above	Same as above
Anthropometrics				
PROP	Weight, recumbent height, head circumference (3, 6, 9, 12 months)	Weight, height, head circumference (18–36 months, 3 years)	Weight, height, head circumference, waist circumference, skinfold thickness (triceps, subscapular)	Weight, bioimpedance, height, head circumference, waist circumference, skinfold thickness (triceps, subscapular)
PENUT	Weight, length, head circumference	N/A	Same as above	Same as above
ToiSurf	Weight, length, head circumference at 12 and 24 months	N/A	Same as above	Same as above
NICU-Health	Anthropometric Measures—Medical Record Abstraction; weight, length, head circumference at 24 months	N/A	Same as above	Same as above
Respiratory system				
PROP	Parent-reported wheeze/hospitalizations due to wheeze (3, 6, 9, 12 months); Daily respiratory assessments and medication use (during hospitalization after birth); Respiratory assessments (36 weeks PMA); Infant Pulmonary Function Testing (12 months)	Parent-reported wheeze/cough/asthma dx/hospitalization or ED visit due to wheeze/hospitalization or ED visit due to pneumonia/allergies (18–36 months, 3 years)	ECHO Airways Questionnaire	PROMIS Asthma, ECHO Airways Questionnaire
PENUT	Parent-reported respiratory support and resuscitation and medications (birth); Respiratory status and support at discharge; Parent report of respiratory medications, on oxygen, using ventilator (12 and 18 months).	N/A	Same as above	Same as above
ToiSurf	Pulmonary Breathing Outcomes Questionnaires at 3, 6, 9, 12, and 18 months	N/A	Same as above	Same as above
NICU-Health	Parent-report of respiratory diagnoses and medications	N/A	Same as above	Same as above

Table 2. continued

Domain	Age at assessment	24–36 months	3–5 years	6+ years
Birth to 24 months^a				
Sleep health				
PROP	N/A	N/A	ECHO Sleep of Children and Adolescents Questionnaire, PROMIS Sleep-related impairment, PROMIS Sleep disturbance	ECHO Sleep of Children and Adolescents Questionnaire, PROMIS Sleep-related impairment, PROMIS Sleep disturbance
PENUT	Child Behavior Checklist—Sleep Problems at 24 months	N/A	Same as above	Same as above
ToSurf	N/A	N/A	Same as above	Same as above
NICU-Health	Child Behavior Checklist Sleep Problems	N/A	Same as above	Same as above
Quality of life				
PROP	N/A	N/A	PROMIS Global Health Scale—Early Childhood, PROMIS Life Satisfaction, PROMIS Meaning and Purpose	PROMIS Global Health Scale 7 + 2, PROMIS Life Satisfaction, PROMIS Meaning and Purpose
PENUT	N/A	N/A	Same as above	Same as above
ToSurf	N/A	N/A	Same as above	Same as above
NICU-Health	N/A	N/A	Same as above	Same as above
COVID related				
PROP	N/A	N/A	ECHO COVID-19 Questionnaire and ECHO COVID-19 Vaccination Questionnaires	ECHO COVID-19 Questionnaire and ECHO COVID-19 Vaccination Questionnaires
PENUT	N/A	N/A	Same as above	Same as above
ToSurf	N/A	N/A	Same as above	Same as above
NICU-Health	N/A	N/A	Same as above	Same as above

Note: Distinctions between PENUT, PROP, and TOLSURF are relevant from birth to <3 years of age. DINE visits began at 3 years old, at which point the data collection for participants from these three extant cohorts would have been the same.

^aIn the first 2 years, schedule of assessments was typically based on adjusted age (rather than actual age).

Table 3. Follow-up assessments in the ECHO-NOVI preterm cohort.

Domain	Assessments used				
	Age range				
	24 months corrected age	3–4 years	4.5–5 years	5.5–6 years	6.5–7 years
Cognitive	Bayley Scales of Infant and Toddler Development-III (BSID-III)	Bayley Scales of Infant and Toddler Development-III (BSID-III); Clinical Evaluation of Language Fundamentals Preschool Second Edition (CELF-P2)	NIH Toolbox Early Cognition Battery	NIH Toolbox Early Cognition Battery; Wechsler Preschool and Primary Scale of Intelligence—Fourth Edition (WPPSI - IV)	NIH Toolbox Cognition Battery; Wechsler Preschool and Primary Scale of Intelligence—Fourth Edition (WPPSI - IV)
Motor	Standardized neurological evaluation; Gross Motor Function Classification System	Standardized neurological evaluation; Gross Motor Function Classification System; Beery-Buktenica Developmental Test of Visual-Motor Integration (6 th edition)	NIH Toolbox Motor Battery; Medical History—Early Childhood- Problems with fine and gross motor development	NIH Toolbox Motor Battery; Medical History—Middle Childhood- Section A: Problems with fine and gross motor development	NIH Toolbox Motor Battery; Medical History—Middle Childhood—Problems with fine and gross motor development
Vision and hearing	Parent-reported outcomes—Vision: blindness, corrective lenses, cataract, ROP; Hearing: impairment, amplification, implant; Standardized neurological evaluation (strabismus; nystagmus; roving eye movements)	Parent-reported outcomes—Vision: blindness, corrective lenses, cataract, ROP; Hearing: impairment, amplification, implant; Standardized neurological evaluation (strabismus; nystagmus; roving eye movements)	Parent-reported outcomes—Vision: impairment (includes blindness), Eye surgery (including for strabismus, cataract, retinopathy of prematurity); Hearing: impairment (includes deafness)	Parent-reported outcomes—Vision: impairment (includes blindness), Eye surgery (including for strabismus, cataract, retinopathy of prematurity); Hearing: impairment (includes deafness)	Parent-reported outcomes—Vision: impairment (includes blindness), Eye surgery (including for strabismus, cataract, retinopathy of prematurity); Hearing: impairment (includes deafness)
Behavior/psychiatric	Child Behavior Checklist; Modified Checklist for Autism in Toddlers	Child Behavior Checklist; Modified Checklist for Autism in Toddlers; Behavior Assessment System for Children (BASC-3); Social Communications Questionnaire	Rothbart Childhood Behavior Questionnaire Very Short Form (Ages 3–5 Years); Behavior Assessment System for Children (BASC-3)—Full Scale; Autism Diagnostic Interview-Revised (ADI-R); PROMIS Anxiety 8a—Parent Proxy; Social Communication Questionnaire (SCQ); Social Responsiveness Scale—Second Edition (SRS-2)	Autism Diagnostic Interview-Revised (ADI-R); PROMIS Psychological Stress Experiences 4a—Parent Proxy; Social Communication Questionnaire (SCQ); Social Responsiveness Scale—Second Edition (SRS-2) School Age; Conners Kiddie Continuous Performance Test Second Edition (Conners K-CPT 2); Medical History—Middle Childhood Anxiety, Depression, ASD, ADD, behavioral or conduct problems	Behavior Assessment System for Children (BASC-3)—Full Scale; Autism Diagnostic Interview- Revised (ADI-R); Social Communication Questionnaire (SCQ); Social Responsiveness Scale—Second Edition (SRS-2) School Age; Conners Kiddie Continuous Performance Test Second Edition (Conners K-CPT 2); Medical History—Middle Childhood Anxiety, Depression, ASD, ADD, behavioral or conduct problems
Anthropometrics	Measurement of weight, length, and head circumference	Measurement of weight, height, and head circumference; blood pressure	Measurement of weight, height, and head circumference; subscapular skinfold, bicep skinfold, and waist circumference; blood pressure	Measurement of weight, height, and head circumference; subscapular skinfold, bicep skinfold, and waist circumference; blood pressure	Measurement of weight, height, and head circumference; subscapular skinfold, bicep skinfold, and waist circumference; blood pressure

Table 3. continued

Domain	Assessments used				
	Age range				
Respiratory system	24 months corrected age	3–4 years	4.5–5 years	5.5–6 years	6.5–7 years
	Parent-reported outcomes (asthma; bronchopulmonary dysplasia; supplemental oxygen)	Parent-reported outcomes (asthma; bronchopulmonary dysplasia; supplemental oxygen)	Medical History—Early Childhood- Section A Q1: Breathing or other respiratory problems, Section C Q6b: other respiratory	Airways Questionnaire—Early Childhood; Medical History—Middle Childhood —Section A: Breathing or other respiratory problems, Section C: other respiratory	Airways Questionnaire—Middle Childhood; PROMIS Asthma Impact: 8a—Parent Proxy; Medical History—Middle Childhood—Section A: Breathing or other respiratory problems, Section C: other respiratory
Sleep health					
Quality of life					
		PROMIS Global Health Scale—Parent Proxy		Sleep Health of Children and Adolescents—Parent Report; PROMIS Sleep-Related Impairment 4a—Parent Proxy; PROMIS Sleep disturbance 4a—Parent Proxy	Sleep Health of Children and Adolescents—Parent Report; PROMIS Sleep-Related Impairment 4a—Parent Proxy; PROMIS Sleep disturbance 4a—Parent Proxy
COVID related					
			COVID-19 Questionnaire—Child Parent-Report Version; COVID-19 Vaccination—Parent Report	PROMIS Global Health Scale 7 + 2—Parent Proxy; Child Global Health	PROMIS Global Health Scale 7 + 2—Parent Proxy; PROMIS Life Satisfaction 8b—Parent Proxy

Table 4. Follow-up assessments in the ECHO-ELGAN preterm cohort.

Domain	Assessments used			
	Age range	15 years	17 years	
Cognitive	12 months corrected age N/A	10 years Differential Ability Scales-II; A Developmental NeuroPsychological Assessment (NEPSY)	15 years Wechsler Abbreviated Scale of Intelligence—second edition; NIH Toolbox Cognitive Battery	17 years NIH Toolbox Cognitive Battery
Motor	24 months corrected age Standardized neurological evaluation; Gross Motor Function Classification System	Gross Motor Function Classification System; Manual Ability Classification System	Gross Motor Function Classification System	NIH Toolbox Motor Battery
Vision and hearing	Parent-reported outcomes (legal blindness; corrective lenses; strabismus); visual tracking and visual fields	Parent-reported outcomes (legal blindness; corrective lenses; strabismus)	Parent-reported outcomes (legal blindness; corrective lenses; strabismus)	Parent-reported outcomes (legal blindness; corrective lenses; strabismus)
Behavior/psychiatric	N/A Child Behavior Checklist; Modified Checklist for Autism in Toddlers	Child Symptom Inventory, Social Communication Questionnaire, Social Responsiveness Scale, Autism Diagnostic Interview-Revised, Autism Diagnostic Observation Scales	Child Behavior Checklist; Youth self-Report; Mini International Neuropsychiatric Interview for Children and Adolescents, Behavior Rating Inventory of Executive Function; Patient-reported Outcomes Measurement Information System (PROMIS) Anxiety and Depression; Affective Reactivity Index	Child Behavior Checklist; Youth self-Report; Affective Reactivity Index; Conners 3 Attention-Deficit/Hyperactivity Disorder Index from parent and child; Affective Reactivity Index; Youth Risk Behavior—Sexual Behavior; Youth Risk Behavior—Substance use
Anthropometrics	Measurement of weight, length, and head circumference	Measurement of weight, length, and head circumference	Measurement of weight, length, and head circumference	Measurement of weight; length; waist circumference; triceps and subscapular skin-fold thickness
Respiratory system	Parent report of rehospitalization for respiratory symptoms; use of bronchodilator, supplemental oxygen, diuretic	Parent report of rehospitalization for respiratory symptoms; use of supplemental oxygen, diuretic	Patient-reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance	ECHO Airways Questionnaire
Sleep health	Child Behavior Checklist Sleep Problems	Patient-reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance	Patient-reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance	Patient-reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance
Quality of life		Pediatric Quality of Life Inventory	Patient-reported Outcomes Measurement Information System (PROMIS) Global Health, Meaning and Purpose, Life Satisfaction	Patient-reported Outcomes Measurement Information System (PROMIS) Global Health, Meaning and Purpose, Life Satisfaction
COVID related				ECHO COVID-19 Questionnaires; Covid-19 School and Social Distancing Practices Questionnaire-Child Self Report and Parent Report

ELGAN

Neonates were enrolled at 14 hospitals in five U.S. states between April 2002 and August 2004. The only inclusion criterion was birth before 28 weeks' gestational age. The only exclusion criterion was anencephaly. ELGAN enrolled 1506 infants, of whom 1200 survived to discharge from the NICU. At the time of the first comprehensive neurodevelopmental assessment at 2 years of age adjusted for prematurity, a total of 1086 infants participated (91% of those surviving to 2 years of age); at the time of the second assessment at 10 years of age, 889 children participated (74% of those surviving to 10 years of age); and at the time of the third assessment at 15 years of age (completed with funding from ECHO), 694 adolescents participated (58% of those surviving to 15 years of age). The overarching hypothesis of the ELGAN Study is that perinatal inflammation is associated with brain structural and functional disorders. To address this hypothesis, placentae were examined for microbes and histological evidence of inflammation. Protein biomarkers of inflammation were measured in neonatal blood, and neonatal and maternal medical records were reviewed for clinical complications and therapies indicative of infection or inflammation. Abundant support for the ELGAN Study's central hypothesis has been described.^{31–45} While the initial focus of the ELGAN Study was inflammation in the neonate and neurodevelopment, the cohort has also been characterized in terms of placental inflammation,^{46–48} placental epigenetic modification and gene expression,^{49–57} obesity,^{58,59} asthma,³ and positive health.⁶⁰

The strengths of the ELGAN Study include longitudinal assessments of cognition, behavior, body mass index/obesity, and asthma (at 2, 10, and 15 years of age); placental microbiology, histology, CpG methylation, miRNAs, transcriptome, and proteomics; and brain magnetic resonance at 15 years of age.

ACCESSING ECHO PROGRAM DATA

The ECHO Program provides support for 39 cohort awards, a coordinating center, a data analysis center, a Participant-Reported

Outcomes Measurement Information System core, and Human Health Exposure Analysis Research core. Investigators who receive funding support from ECHO or who are designated as affiliate investigators may propose analyses of data and publications to the ECHO Publications Committee for review. The URL for the ECHO Publications website is <https://echochildren.org/echo-program-publications/>. Thus one pathway by which investigators who are not currently affiliated with ECHO can gain access to ECHO data is identify a ECHO Award principal investigator to sponsor the investigator as an affiliate ECHO investigator. A list of ECHO Award principal investigators can be found at <https://echochildren.org/map-echo-cohorts-observational-study-sites/>. Investigators may contact the ECHO-wide Cohort (ECHO-DAC@rti.org) to collaborate with an ECHO investigator.

Investigators who wish to analyze data outside of a collaboration with ECHO investigators can obtain a public use dataset that is expected to be available in July 2022. A limitation of the public use dataset is that it will contain records only for individuals who have consented to ECHO participation at level 2 participation level (defined as consent to share residential address and exact dates, such as date of birth). In contrast, by collaborating with an ECHO investigator, a researcher can gain access to all of the extant data stored at the ECHO Data Analysis Center.

RESEARCH PRIORITIES FOR PRETERM ECHO COHORTS

While not an exhaustive list of prioritized projects, this section presents a high-level view of research opportunities using data from the DINE, NOVI, and ELGAN ECHO cohorts; Table 5 lists selected examples of ongoing projects involving ECHO very preterm cohorts. Exposures in these projects include community-level factors such as air pollution and the built environment, maternal factors such as maternal illnesses and medications, neonatal therapies such as acid suppression medications, and post-NICU exposures such as infant weight gain and the COVID pandemic. Outcomes under study include placenta CpG DNA

Table 5. Selected examples of ECHO Projects utilizing data from ECHO very preterm cohorts.

Hypothesis/objective	Exposure(s)	Outcome(s)	Mediators/moderators
Evaluation of sex-based differences in placental DNA methylation profiles related to gestational age	Gestational age	CpG DNA methylation	Moderator: sex assigned at birth
Maternal infections are associated with an increased risk of child behavioral dysregulation	Maternal infections	Child Behavior Checklist dysregulation profile	Moderator: sex assigned at birth
Synthetic oxytocin is associated with an increased risk of autism and ADHD	Synthetic oxytocin	Autism; ADHD	Maternal pre-pregnancy BMI
Describe the impact of air pollution, neighborhoods, and the built environment on the epidemiology of chronic lung disease in children born prematurely	Air pollution, neighborhoods, and the built environment	Bronchopulmonary dysplasia	
High infant post-NICU weight gain improves neurodevelopmental outcome and increases risk of overweight/obese	Change in Infant weight z-score after NICU discharge	Bayley Scales of Infant and Toddler Development; Child Behavior Checklist; Modified Checklist for Autism in Toddlers; BMI	
Acid suppressive medications during infancy increase risk of overweight/obesity	Acid-suppression medications in NICU and after discharge	BMI	
Evaluate prenatal and perinatal factors associated with neurobehavior in preterm and full-term infants	Medical conditions, sociodemographic, substance use	NICU Network Neurobehavioral Scales	
Worsening of positive health and sleep health during the COVID-19 pandemic will be accentuated among children and adolescents born preterm	COVID pandemic	Positive health and sleep health	Moderator: preterm birth

methylation, BPD, neonatal neurobehavior, behavioral dysregulation, early cognitive functioning, autism, attention deficit hyperactivity disorder, body mass index, sleep health, and positive health.

Identification of modifiable risk factors for adverse child health outcomes

An overarching goal of the ECHO Program is to identify modifiable risk factors for obesity, asthma, and neurodevelopmental impairments, as well as factors associated with positive health, which will be discussed below in the section on resiliency. Except for obesity, the adverse outcomes on which ECHO focuses are more frequent among individuals born very preterm, increasing statistical power when analyzing associations between early life risk factors and child health outcomes.

Few studies have followed extremely preterm children starting at birth and extending through childhood, and few have the extensive biological and developmental data, and data on environment and exposures during childhood, that are needed to support rigorous investigations on etiology. Further, environmental health studies often exclude participants born very preterm. This lack of understanding about etiology and environment presents a critical barrier to progress toward preventing adverse outcomes and promoting positive child health among individuals born preterm. To help address this knowledge gap, the ECHO very preterm cohorts have collected data on early life exposures that are potentially related to child health outcomes; examples include placental pathology (ELGAN), maternal postpartum depression and substance use (NOVI), high-reliability cranial ultrasound interpretations (ELGAN, DINE, and NOVI), details of pulmonary course and outcomes (DINE), phthalate exposures in the NICU (DINE), and clinical markers of acute neonatal kidney injury (DINE).

For the identification of modifiable risk factors, ECHO cohorts composed primarily of individuals not born very preterm provide a large number of controls (individuals born at term). By comparing early childhood environmental exposures for very preterm infants and controls, ECHO is poised to increase understanding of the relative contribution of pre- and post-NICU factors in the development of adverse child health outcomes for which very preterm children are at higher risk. Studies of this type can inform priorities and the design of programs to improve the health of individuals born very preterm.

Developmental origins of health

A priority of ECHO very preterm cohorts is to increase understanding of potential mediators of preterm birth-outcome associations, such as parental stress, social determinants of health, and epigenetic variation. This priority aligns with the burgeoning field of the developmental origins of health, which hypothesizes that early-life exposures can program metabolic, immunologic, epigenetic, or physiologic responses that have persisting effects on health.^{61,62} To facilitate mechanistic studies of the developmental origins of health, ECHO preterm cohorts have collected data on biomarkers of potential mechanisms linking early-life exposures and later-life outcomes, such as epigenetic markers in the placenta^{52,53,63} and neonatal tissues,¹² biomarkers of neonatal inflammation,^{64,65} and chemical exposures during neonatal intensive care in the first several postnatal months.¹⁸ Like the "canary in the coal mine," it seems likely that at least some of the findings from mechanistic studies will pertain not just to individuals born preterm but also to those born at term.⁶⁶

Understanding disparities across social determinants of health

In the U.S., child health outcomes on which the ECHO Program concentrates (preterm and low birth weight birth, asthma, obesity, and neurodevelopmental disorders), are more prevalent among

non-Hispanic Black children than among non-Hispanic White children.^{67–71} Identifying factors that contribute to health disparities across race, as well as factors that promote health equity, is an essential step in improving the health of children in the U.S.

Recent epidemiological studies of health disparity across race have focused on social determinants of health, including such factors as systemic racism, environmental pollution, and poverty. Black families, as compared to White families, are more likely to have indicators of socioeconomic disadvantage, such as lower quality housing, and psychological stress,^{69,70} and have greater exposure to air pollution, lead exposure,^{72–74} neighborhood violence,^{75,76} racial segregation and discrimination,^{75,77} and adverse life events. Conversely, Black families are less likely to have access to high-quality daycare⁷⁸ and nutritious foods during pregnancy. Maternal diet can influence the risks of preterm birth and fetal growth restriction,⁷⁹ and iron deficiency during pregnancy is associated with worse neurodevelopmental outcomes in the offspring.⁷⁹

The ECHO-wide cohort protocol includes collection of data across multiple domains related to social determinants of health. Residential address history is being used to derive indicators of structural racism, including neighborhood-level measures of deprivation, segregation, and urbanicity. The Everyday Discrimination Scale⁸⁰ is being collected to capture self-perceived racism. Family-level markers of economic resources include household income and source of the family's medical insurance. At the level of mothers and caregivers, data are being collected on educational attainment and occupation, as well as diet, sleep, substance use, and environmental exposures during pregnancy. Data from DINE, NOVI, and ELGAN cohorts are an important resource in analyses of preterm birth as both an outcome of social determinants of health as well as a mediator between social determinants of health and adverse child health outcomes.

Health disparities during the infant's hospitalization in NICUs^{81–87} include nurse understaffing and higher rates of infection,^{82,83,85,88} mortality,^{81,84,86,89–91} and neonatal morbidities.⁹² Notably, in NICUs rated as higher quality, differences in morbidity between Black and White infants are smaller.^{90,93}

Disparities across race/ethnicity also have been found among hospital patients. Compared with Black and Hispanic infants, White infants were more likely to receive appropriately timed retinal examinations, antenatal steroid therapy, and breastfeeding education.^{82,85} Parents and healthcare providers report that less attention and education was provided to families of color compared with White families.⁸² Following discharge from the NICU, families with fewer financial resources have greater difficulty accessing health care.⁹⁴ Families in rural communities, which typically are farther from regional medical centers, face a larger challenge attending follow-up appointments.⁹⁵ Thus, health disparities across race are present in the pre-conception interval, and continue during pregnancy and neonatal intensive care hospitalization, and after discharge of infants into the community.⁸¹

The coronavirus disease 2019 (COVID-19) pandemic has accentuated health disparities across social class. Given the association between preterm birth and lower socioeconomic status (SES), disparities across indicators of SES in COVID-related health outcomes,^{96,97} and COVID-19-related disruptions to educational support, we expect that pandemic effects on health and educational outcomes will be larger among children born preterm compared with those born at term.^{98,99} In the spring of 2020, the ECHO Program modified its study protocol to include the collection of data on disruptions in children's education, stress, and coping during the COVID-19 pandemic. In the three ECHO cohorts of individuals born very preterm, 1096 individuals have completed questionnaires about the impact of the COVID-19 pandemic on their lives. These ECHO data, combined with data

from ECHO cohorts born predominantly at term, form a large racially and ethnically diverse sample for addressing questions related to race, racism, and social determinants of health as modifiers of associations between pandemic-related restrictions and child health outcomes. Further, the longitudinal design of each of the three preterm cohorts provides data on cohort members' health and developmental outcomes before, during, and after the pandemic.

How can ECHO preterm cohorts inform research on resiliency factors that may moderate the long-term effects of early life adversity?

Despite the many pre-, peri-, and post-natal adversities encountered by fetuses delivered extremely preterm, as many as one-third of children born before 28 weeks' gestational age who are discharged alive from the NICU have a positive health outcome, defined as the absence of intellectual deficit, cerebral palsy, epilepsy, autism spectrum disorder, severe hearing or visual impairment, obesity, asthma, attention deficit hyperactivity disorder, anxiety, and depression at 10 years of age.⁶⁰ A goal of the ECHO Program is to identify factors associated with positive health outcomes,¹⁰⁰ defined as "a set of resources that are used to adapt to environmental challenges, satisfy needs, and reach a person's goals ... assets that strengthen an individual's health."¹⁰⁰

Related to positive health is resilience, defined as "a multi-systemic dynamic process of successful adaptation or recovery in the context of risk or a threat."¹⁰¹ Factors that confer resilience are those that promote well-being or protect against adverse outcomes in children and adolescents who are at increased risk. For example, in a large Norwegian cohort of adolescents 16–19 years of age, a higher number of negative life events experienced by study participants was correlated with increased depressive symptoms, whereas fewer symptoms were reported by adolescents with potential protective factors, such as goal orientation, self-confidence, social competence, social support, and family cohesion. These findings suggest that even among children who experience negative life events, interventions to enhance resilience factors, such as social support and family cohesion, could reduce the frequency of depression.¹⁰²

Among children born with extremely low birth weight, resilience was associated with higher SES and favorable proximal home factors, such as higher stimulation for learning, higher parent-child relationship quality, and lower parent burden and distress.¹⁰³ In the ELGAN cohort, a positive health outcome was associated with higher SES and the absence of pre-pregnancy chronic maternal medical disorders, such as pre-pregnancy obesity or asthma.¹⁰⁴

Identifying factors that promote positive health provides targets for interventions to improve outcomes after very preterm birth. Proximal factors associated with higher SES, such as social support for parents, and enhanced educational stimulation, can be provided by supportive programs for families to improve health outcomes after very preterm birth. Direct assessment of parents' social support and educational resources, with instruments such as the Home Observation for Measurement of the Environment Inventory,¹⁰⁵ could identify families with greater need of supportive interventions.

In addition to identifying targets for intervention, ECHO researchers are focusing on identifying the mechanisms by which early life factors confer resiliency. Findings from the NOVI and ELGAN cohorts support the developmental origins of disease hypothesis and suggest that epigenetic markers in the placenta^{54,55} and neonatal tissue¹² are sensitive to early life exposures and are predictive of child health outcomes.^{50,63} Taken together, these findings suggest that epigenetic modifications could be a mechanism linking early-life exposures to health outcomes in childhood and beyond. Studies from the ELGAN cohort indicate that neonatal systemic inflammation is associated

with prenatal factors, such as SES,¹⁰⁶ placenta microorganisms,¹⁰⁷ and maternal obesity,¹⁰⁸ and is also associated with child outcomes 10 years later.^{31,34,36,109} Thus, neonatal inflammation is another potential mechanism for the developmental origins of health and disease.

SUMMARY

The ECHO-wide cohort study is a resource for researchers interested in child health outcomes among individuals born very preterm. Data from very preterm children currently participating in the ECHO-wide cohort, together with about 30,000 children born at term will soon be available publicly, and will include information about a broad range of environmental exposures and outcomes related to chronic illness among U.S. children. This resource provides child health researchers with many opportunities to improve understanding of modifiable risk factors and mechanisms leading to chronic illness in children, pointing the way to interventions to optimize the well-being of children in the U.S.

DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

DATA AVAILABILITY

The datasets for this manuscript are not publicly available, because per the NIH-approved ECHO Data Sharing Policy, ECHO-wide data have not yet been made available to the public for review/analysis. Requests to access the datasets should be directed to the ECHO Data Analysis Center, ECHO-DAC@rti.org.

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AUTHOR CONTRIBUTIONS

T.M.O. conceptualized and designed the study, obtained funding for the study, drafted the initial manuscript, and reviewed and revised the manuscript. M.M. conceptualized and designed the study, obtained funding for the study, analyzed data, and reviewed and revised the manuscript. J.L.A., B.L., and R.C.F. conceptualized and designed the study, obtained funding for the study, and reviewed and revised the manuscript. H.P.S., C.M., A.S., C.E., M.H., E.M., and S.P. conceptualized and designed the study and reviewed and revised the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Patient consent was not required.

ADDITIONAL INFORMATION

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ON BEHALF OF PROGRAM COLLABORATORS FOR ENVIRONMENTAL INFLUENCES ON CHILD HEALTH OUTCOMES

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