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Cohort profile: the Neonatal Intensive Care Unit Hospital Exposures and Long-Term Health (NICU-HEALTH) cohort, a prospective preterm birth cohort in New York City

Annemarie Stroustrup ,[1,2] Jennifer B Bragg,[1] Emily A Spear,[1] Andrea Aguiar,[3] Emily Zimmerman,[4] Joseph R Isler,[5] Stefanie A Busgang,[2] Paul C Curtin,[2] Chris Gennings,[2] Syam S Andra,[2] Manish Arora[2]

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For numbered affiliations see end of article.

Correspondence to
Dr Annemarie Stroustrup; annemarie.stroustrup@mssm.edu

ABSTRACT

Purpose The Neonatal Intensive Care Unit Hospital Exposures and Long-Term Health (NICU-HEALTH) longitudinal preterm birth cohort studies the impact of the NICU exposome on early-life development. NICU-HEALTH collects multiple biospecimens, complex observational and survey data and comprehensive multisystem outcome assessments to allow measurement of the impact of modifiable environmental exposures during the preterm period on neurodevelopmental, pulmonary and growth outcomes.

Participants Moderately preterm infants without genetic or congenital anomalies and their mothers are recruited from an urban academic medical centre level IV NICU in New York City, New York, USA. Recruitment began in 2011 and continues through multiple enrolment phases to the present with goal enrolment of 400 infants. Follow-up includes daily data collection throughout the NICU stay and six follow-up visits in the first 2 years. Study retention is 77% to date, with the oldest patients turning age 8 in 2019.

Findings to date NICU-HEALTH has already contributed significantly to our understanding of phthalate exposure in the NICU. Phase I produced the first evidence of the clinical impact of phthalate exposure in the NICU population. Further study identified specific sources of exposure to clinically relevant phthalate mixtures in the NICU.

Future plans Follow-up from age 3 to 12 is co-ordinated through integration with the Environmental Influences on Child Health Outcomes (ECHO) programme. The NICU-HEALTH cohort will generate a wealth of biomarker, clinical and outcome data from which future studies of the impact of early-life chemical and non-chemical environmental exposures can benefit. Findings from study of this cohort and other collaborating environmental health cohorts will likely translate into improvements in the hospital environment for infant development.

Trial registration numbers This observational cohort is registered with ClinicalTrials.gov (NCT01420029 and NCT01963065).

Strengths and limitations of this study

- The Neonatal Intensive Care Unit Hospital Exposures and Long-Term Health (NICU-HEALTH) cohort is the first comprehensive longitudinal preterm birth cohort with a primary focus on NICU-based environmental exposures.
- The NICU-HEALTH study comprises a large cohort of moderately preterm children with biological samples linked to detailed demographic and clinical data regarding the intensive care course and longitudinal follow-up to age 3 years using standardised assessment measures and survey tools.
- Mothers of preterm infants are also enrolled, and they provide both their own biospecimens and significant information about stressful life events, depressive symptoms and dietary history during pregnancy, during the NICU stay and after NICU discharge.
- NICU-HEALTH takes an exposomics approach throughout the highly controlled and continuously observed NICU hospitalisation, collecting data about the physical, chemical and social environment, in addition to biobanking specimens for multi-omic analyses.
- Although rates of medical morbidity related to prematurity among moderately preterm infants are low, confounding by indication can be challenging in some NICU-HEALTH analyses, requiring complex statistical techniques.

INTRODUCTION

While preterm infants now have high rates of survival,[1] they continue to experience significant neurodevelopmental impairments linked to preterm birth. Even 'mature' preterm infants born at 28–36 weeks' gestation have significantly higher rates of behavioural, cognitive and psychiatric deficits compared with term-born peers.[2–7] Beyond

neurodevelopmental abnormalities, children born preterm demonstrate elevated rates of lung disease[8 9] and maladaptive growth.[10 11] 'Prematurity', however, is not uniformly predictive or well-understood in the causal pathway of morbidity. The heightened risk of lifelong multisystem dysfunction associated with prematurity is only partially explained by severity of illness in infancy.[9–15] In fact, traditional perinatal risk factors—gestational age (GA), for example—have little prognostic value.[16] Although children born at the limits of viability or who suffer severe neonatal illness often have predictably poor outcome, the aetiology of significant deficits seen in the large population of moderately preterm infants with benign medical history remains poorly understood. Alterations in *developmental trajectory*, rather than focal end organ injury following preterm birth, are implicated.[6 17]

Early-life environmental exposures can alter developmental trajectories in critical and often unexpected ways to produce clinically important outcomes years later. Numerous prospective birth cohorts, often drawn from communities with high pollutant burden, have used maternal biomarkers as estimates of fetal exposure to explore the influence of the third trimester environment on long-term child health outcomes. Third trimester fetal life, a critical period for brain and lung development as well as for metabolic programming, is now known to be particularly sensitive to environmental perturbations.

Whether the normal developmental trajectory is impacted by environmental toxicants in the neonatal intensive care unit (NICU) has not been rigorously studied. In addition to providing life-sustaining treatments, the NICU confers significant exposure to chemical plasticisers, heavy metals, potentially toxic stress, social isolation and other environmental factors shown to be detrimental to brain development in studies of term-born fetuses and infants.[18–21] We believe that opportunities exist to improve outcomes of preterm infants by optimising the NICU from an environmental health perspective.

COHORT DESCRIPTION

The NICU Hospital Exposures and Long-Term Health (NICU-HEALTH) longitudinal preterm birth cohort is based in the premise that modifiable environmental exposures in the NICU contribute to developmental deficits in children born preterm. The NICU-HEALTH infrastructure facilitates detailed study of the NICU exposome and comprehensive assessment of early developmental progress, allowing us to measure the impact of modifiable environmental exposures during the preterm period on multisystem outcomes.

Study aims

NICU-HEALTH is a prospective environmental health cohort focused on the large population of moderately preterm infants.[22] Moderately preterm infants require extended hospitalisation in the NICU following birth, but have low rates of physiological derangement, sepsis, intraventricular haemorrhage or other medical predictors of poor outcome. Nonetheless, they have elevated rates of adverse neurobehavioural, pulmonary and growth outcomes. The goal of NICU-HEALTH is to determine the role of potentially modifiable NICU environmental factors that contribute to long-term neurodevelopmental, pulmonary and growth deficits of NICU graduates. To do this, we collect data throughout the NICU stay, with daily record of equipment and medication exposure, procedural experience and potentially stressful events. We collect a variety of biospecimens and evaluate multisystem outcomes longitudinally to provide a comprehensive cognitive, motor, behavioural, pulmonary and anthropomorphic phenotype through early childhood. Extensive maternal survey data and maternal biomarkers allow for estimation of the in utero environment. Longitudinal study visits through childhood allow for long-term follow-up (figure 1). NICU-HEALTH data analyses focus on identifying sources of NICU-based toxicants that can be mitigated.

Study population

Participant recruitment and informed consent

Mothers of eligible infants are approached for enrolment soon after NICU admission at the Mount Sinai Hospital. Initial verbal consent permits non-invasive collection of valuable biospecimens in the immediate period after birth; full informed consent during the infant's first week of life facilitates linkage of these specimens with comprehensive clinical data available prospectively and from maternal and infant medical records. Detailed survey work and objective assessments are conducted while the infant is hospitalised, such that loss to follow-up for early data is low. Our research team has pioneered collection techniques for preterm infants; the collected volume of biospecimens such as urine and saliva exceeds those of published studies.[23 24]

The NICU-HEALTH cohort displays racial, ethnic and socioeconomic diversity (table 1). Almost half of NICU-HEALTH participants report racial and/or ethnic minority status. This is more racial and ethnic diversity than the birth population at our hospital, which is 22% non-white. The per cent of participants of low socioeconomic status in our cohort is similar to that of our hospital population. Longitudinal follow-up of the NICU-HEALTH cohort is conducted through participation in the Environmental Influences on Child Health Outcomes (ECHO) programme.[25]

Phase I of NICU-HEALTH enrolled neonates with birth weight less than 1500 g born September 2011 through July 2013. Phase I focused on organic chemical exposure with biospecimen collection limited to urine, a single neurodevelopmental outcome assessment before NICU discharge and enrolment of infants but not mothers. Phase II enrolment commenced in March 2015 and continues through early 2019. Phase II switched to GA-based enrolment criteria (28–33 weeks) to decrease the incidence of major

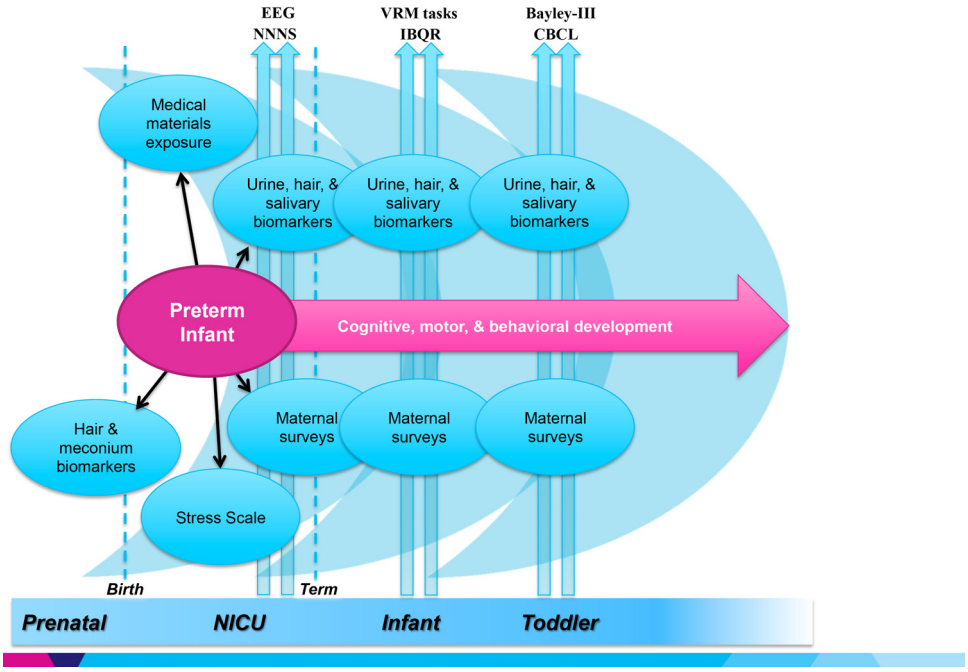

Figure 1 Participants are followed with serial biomarker and survey data as well as serial subjective and objective measures of development. EEG, electroencephalogram; CBCL, Child Behavior Checklist; IBQR, Infant Behavior Questionnaire-Revised; NICU, Neonatal Intensive Care Unit; NNS, non-nutritive suck; VRM, visual recognition memory.

morbidities of extreme prematurity in the cohort. Phase II expanded focus, with enrolment of both infants and mothers, banking of infant urine, stool, saliva, hair and blood, as well as maternal blood, hair and breast milk. Mothers complete comprehensive surveys including evaluation of maternal stress, mental health and IQ. Multiple infant outcome assessments are completed including dense-array electroencephalogram (EEG) and co-ordinated follow-up via multiple contacts during the first 2 years of life (table 2). Phase III will be launched in 2020 and will add a dedicated study visit at 7–8 months corrected age to complete objective assessments of memory, attention, social cognition and non-nutritive suck (NNS). Phase III will also include ECHO study visits for NICU-HEALTH participants aged 3–10.

Table 1 NICU-HEALTH enrolment, 2011 to date

Number of infants enrolled	275
Mean birth weight (g) of survivors to NICU discharge	1348
Mean gestational age (weeks) of survivors to NICU discharge	30.2
Multiple births (% of cohort)	49
Child's sex (% female)	50
Per cent of cohort reporting racial/ethnic minority status	49
Per cent of cohort with income ≤200% US federal poverty line	31

NICU, neonatal intensive care unit; NICU-HEALTH, Neonatal Intensive Care Unit Hospital Exposures and Long-Term Health.

Since all infants born prior to 35 weeks gestation require NICU hospitalisation and since healthy term-born children are at a different stage of development in the ex utero environment than preterm infants, there is no non-NICU 'control' arm for NICU-HEALTH. We rely on exposure variability within our cohort (figure 2) to meet our aims. Data collection through all phases includes direct observation of medical equipment exposures; phases II and III add prospective record of stressful events and observations of infants' social interactions. Longitudinal follow-up is achieved at clinically indicated visits to the NICU-Follow Up Program (FUP) and through the ECHO programme. The FUP is a clinical programme that conducts developmental and nutritional screening and offers family support and early intervention to all NICU graduates born before 33 weeks, and thus serves the entire NICU-HEALTH study population. The FUP sees children at 2–6 month intervals from NICU discharge to age 3 with retention greater than 85%. Biospecimens collected after NICU discharge will be analysed for community-based phthalate and stress exposure—important confounders of our primary assessment of the impact of NICU-based exposures on outcomes.

NICU-HEALTH enrolled 81 infants in phase I; phase II has enrolled 194 participants to date with planned enrolment of 225. We plan to continue enrolment to achieve a combined target over three phases of 400 infants.

Biospecimens

Infant urine

Urine collection is performed weekly in the NICU as previously described.[26] We place pre-screened cotton

Table 2 Selected NICU-HEALTH study procedures

Data/specimen/assessment		NICU	2–4 months	7–8 months	12 months	2 years	3 years	4 years	5 years	6 years	7 years
	Eligibility screen/informed consent	First week									
Biospecimens	Urine	Qweek	X	X*		X	X*	X*	X*	X*	X*
	Meconium/stool	Qweek									
	Hair—mother	X									
	Hair—child	X		X*	X	X		X*		X*	
	Infant blood	X									
	Breast milk	Qweek	X	X*							
	Child saliva	Qweek		X*		X					
	Primary teeth							X*	X*	X*	X*
Clinical data	Weight	Qday	X	X*	X	X	X*	X*	X*	X*	X*
	Length/height	Qweek	X	X*	X	X	X*	X*	X*	X*	X*
	Head circumference	Qweek	X	X*	X	X	X*	X*	X*	X*	X*
	Cranial ultrasound	2–3x									
	Pubertal development/tanner staging									X*	X*
Surveys	Medical history	Qday	X	X*	X	X	X*	X*	X*	X*	X*
	Medical equipment exposure	Qday									
	Visitor interactions	Qday									
	Neonatal Infant Stressor Scale[114]	Qday									
	Maternal depression (EPDS)[115]	X			X	X					
	Perceived Stress Scale[116]	X			X	X					
	Life events (CRYSIS-R)[117]	X			X	X					
	Maternal IQ (Raven)[118]	X									
	Maternal diet[119]	X	X	X*	X	X					
	Infant diet		X	X*	X	X					
	Maternal PTSD (PCL-C)[120]			X*		X					
	ELEAT Pregnancy Questionnaires[121]	X*									
	ELEAT Parent Questionnaires[121]	X*			X*					X*	

Continued

Table 2 Continued

Data/specimen/assessment		NICU	2–4 months	7–8 months	12 months	2 years	3 years	4 years	5 years	6 years	7 years
Outcomes	Dense-array EEG	X									
	NICU Network Neurobehavioral Scale	X									
	Infant Behavior Questionnaire—Revised[122]		X								
	Childhood Behavior Questionnaire[123]				X						
	Video-based attention tasks			X*							
	Non-nutritive suck assessment	X*		X*							
	Child Behavior Checklist[123]					X					
	NIH Toolbox Cognition Battery[124]						X*		X*		X*
	NIH Toolbox Motor Battery[124]										
	Bayley-III[125]					X					
	Brief Respiratory Questionnaire/spirometry[126]							X*		X*	
	Strengths and Difficulties Questionnaire[127]						X*		X*		X*
	Adaptive Behavior Assessment System[128]						X*		X*		X*
	PROMIS Physical Function—Mobility[129]										X*

Age at assessment is corrected age from due date.
*For implementation in NICU-HEALTH phase III.
EEG, electroencephalogram; EPDS, Edinburgh Postnatal Depression Scale; NICU, neonatal intensive care unit; NICU-HEALTH, Neonatal Intensive Care Unit Hospital Exposures and Long-Term Health; PCL-C, Post-traumatic stress disorder CheckList - Civilian version; PTSD, Post-traumatic stress disorder; Q, every.

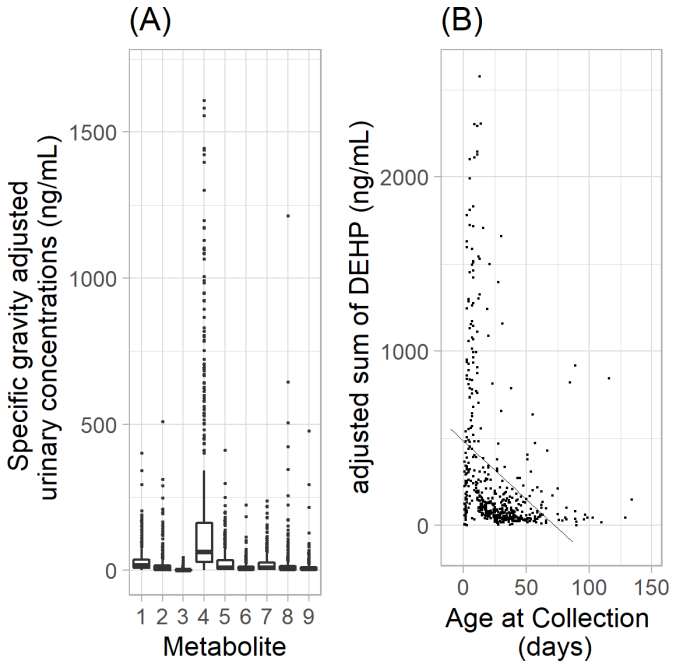

Figure 2 Distribution of representative phthalate biomarkers in NICU-HEALTH analysed to date. (A) Boxes mark 25th percentile, median and 75th percentile; bars mark 5th and 95th percentile. Interquartile ranges vary from 3-fold to 16-fold. (B) Phthalate exposure (represented by the sum of DEHP metabolites) decreases with chronological age. As preterm infants mature, they require less phthalate-exposing medical support. DEHP, di(2-ethylhexyl)phthalate; NICU-HEALTH, Neonatal Intensive Care Unit Hospital Exposures and Long-Term Health.

balls in the diaper; those not contaminated with stool are retained for urine extraction. Urine is squeezed from the cotton, refrigerated immediately and frozen at −80°C. Urine is similarly collected at follow-up visits. Urine can be used to identify organic chemicals and metals.

Child and maternal hair

A small segment of hair is cut from the nape of the neck of participant infants and mothers during the NICU hospitalisation. Maternal hair is collected to capture prenatal exposures based on known hair growth rates and the duration of gestation. Infant hair is sampled immediately before NICU discharge to capture exposures during the hospitalisation. Hair is again collected from the child at the 2-year-old follow-up visit. Hair is stored dry in paper envelopes at room temperature. Hair provides a measure of temporally accumulated exposure and can be used to identify distinct periods of cortisol elevation[27] or chemical exposure.[28] Hair collected during follow-up visits will allow estimation of post-NICU exposures to include as model covariates.[29]

Saliva: stress biomarkers in preterm infants

Biologically active free cortisol can be measured in all fluids; salivary cortisol reflects levels of free cortisol in blood.[30] Infants do not develop diurnal cortisol cycling until 44–48 weeks' postmenstrual age.[31 32] A saliva collection swab (Salmetrics, Carlsbad, California) is placed in the infant's mouth before feeding, then centrifuged. Saliva is stored frozen at −80°C pending batched cortisol immunoassay.[30]

Meconium

Meconium/stool is collected weekly from the diaper of NICU-HEALTH participant infants during the NICU hospitalisation. Specimens are transferred from the diaper to pre-screened polypropylene collection cups and immediately frozen at −80°C. Stool specimens are appropriate for organic or inorganic biomarker analysis and certain microbiome assessments.

Blood

Blood spots are collected on Whatman cards from infant heel-stick specimens at the time of clinically indicated phlebotomy in the week before NICU discharge. Cards are stored at room temperature and are appropriate for a wide variety of analyses. In phase III, cards will be stored frozen to allow future metabolomics studies.

Additional specimen collection in NICU-HEALTH phase III will include saliva for nucleic acids, toenails for chemical exposure and teeth for re-creation of the prenatal and early-life exposome.

Clinical data

Outcome assessments

Serial neurodevelopmental assessments through NICU-HEALTH (table 2) allow development of a neurophenotype through childhood including behavioural, cognitive and motor domains affected by environmental exposures.[19 33–41] We also collect longitudinal data on respiratory support during hospitalisation, respiratory diagnoses and growth parameters. Non-standard phenotyping methods are detailed below.

NICU Network Neurobehavioral Scale

The NICU Network Neurobehavioral Scale (NNNS), a standardised exam of infant behaviour, motor function and stress response[42 43] reported as 13 summary scores, is associated with motor, cognitive and behavioural function in childhood.[44] It is an established method for early detection of attention and motor deficits in preterm and toxin-exposed populations.[45–47]

Dense-array EEG

EEG is an objective measure of infant neurological function. Comfortable, commercially available dense-array mesh caps (Electrical Geodesics, Eugene, Oregon) can be placed on an infant in 3 min.[48] Dense-array EEG can detect varying electrocortical power that increases with development. This test quantifies crucial milestones for early neurodevelopment[49] including the development of functional connectivity,[48 50] visual attention, recognition memory[51] and processing pathways for visual[50] and language information.[52]

(Phase III) Memory, attention and social cognition tasks

NICU-HEALTH will soon include objective assessments of visual attention, information processing speed and working memory at 7–8 months' corrected age.[53–55] These novel assessments adapt existing psychological tasks using a standardised video-based approach with infrared eye-tracking technology to record and objectively quantify infant looking behaviour.

The attention and visual recognition memory tasks use a paired-comparison paradigm[53–57] with pairs of faces and of coloured geometric shapes.[54] Eye fixations are tracked using an infrared eye tracker (SR Research, Canada) to determine total looking time at novel stimuli, number and average duration of fixations and fixation shift rate between stimuli.[54]

The third task tests Theory of Mind (ToM), the ability to infer other people's intentions and beliefs and use them to predict behaviour. It is one aspect of cognition impaired in autism.[58 59] Infants possess ToM abilities that traditional 'false-belief' tasks are not sensitive enough to capture.[60 61] Our innovative task is based on the one developed by Kovács *et al*.[62]

(Phase III) Non-nutritive suck

NNS is one of the earliest motor skills in human development.[63] Sucking and feeding require co-ordination and neural integration across more than 26 muscle pairs and more than 5 cranial nerves.[64 65] As such, abnormalities in sucking and swallowing are considered markers of neonatal brain injury,[66 67] and delayed sucking and feeding occurs in approximately 35%–48% of infants with neonatal brain injuries.[68] Therefore, sucking and feeding behaviours can reflect development of central nervous system and potential neonatal brain injury, serving as a potential prognostic tool for detecting future developmental delays.[69 70] During a 5 min assessment with a dedicated pacifier-pressure transducer, we will measure NNS cycles per burst, cycles per minute, amplitude, burst per minute, frequency and burst duration.

Patient and public involvement

Although there was no formal involvement of NICU parents or the general public in the development of the research question and outcome measures chosen for NICU-HEALTH, clinicians within the research team identified the research question and outcomes as being important for NICU families from informal discussions with parents of NICU patients. Phase III of NICU-HEALTH will be informed by the ECHO programme and it has both a formal Stakeholder Engagement committee and a Burden Task Force to gather data about participant feedback on the experience of executing the study protocol. Data from outreach efforts by these groups will help shape future additions of the NICU-HEALTH protocol.

Planned statistical analyses

NICU-HEALTH was designed with two explicit goals: to quantify the impact of NICU-based phthalate exposures on neurodevelopment and to facilitate and investigate the role of NICU-based environmental exposures in the development of preterm infants across multiple organ systems. To address our complex data structure, we employ two statistical approaches commonly in NICU-HEALTH analyses: weighted quantile sum (WQS) regression, which allows for objective consideration of multiple concurrent exposures, and latent class analysis (LCA), which allows for grouping of participants by similar performance across multiple scales of complex neurodevelopmental assessment tools.

WQS regression creates an empirically weighted index that identifies 'bad actors' based on non-negligible weights and yields an estimated mixture effect of the association between the exposure index and an outcome.[71 72] Two steps are used to estimate a weighted index of standardised concentrations (eg, scored into quartiles) in a nonlinear model with a link function $g(\mu)$ to accommodate continuous, binary or count data: (A) $g(\mu) = \beta_0 + \beta_1 \sum_{j=1}^{c} w_j q_j + z'\varphi$ across 100 bootstrap samples and (B) $WQS = \sum_{j=1}^{c} \overline{w}_j q_j$ testing for the significance of the constructed WQS in a generalised linear model of the outcome. A test for the significance of $\beta 1$ is a test for a mixture effect, which may be subthreshold for individual components, in the direction associated with the parameter estimate; detection of a signal in the opposite direction is possible by estimating the weighted index with a constraint on $\beta 1$ to be <0 or >0. These constraints reduce ill-conditioning due to the complex correlations among the components. The strategy is robust to the correlation patterns in terms of sensitivity and specificity for identifying bad actors. The construction of weighted exposure indices can additionally be stratified by sex to test the effects of sex-specific mixtures in an integrated model, while also allowing for adjustment by additional relevant covariates.[73]

LCA is a probabilistic, model-based variant of traditional non-hierarchical cluster analysis[44 74] which we and other groups have used to classify participants into discrete data-driven groups based on the performance on multiple neurodevelopmental assessment tool subscales. The LCA can be used as a single neurodevelopmental outcome in multinomial logistic regression modelling to reveal associations between NICU-based exposures and the latent class. As in our prior work,[75] LCA can also facilitate probabilistic modelling of the association between a neurophenotype and concurrent NICU-based exposure to varying levels of multiple exposures.

Sample size

Sample size and power estimates are based on preliminary data from the NICU-HEALTH cohort. As one of the central goals of NICU-HEALTH is to facilitate study of the clinical impact of NICU-based environmental exposures, it is not powered on a single hypothesis. We propose to

Table 3 Sample size estimation for sexually dimorphic outcomes with NICU-HEALTH twin rate and estimated 20% loss to follow-up

Exposure	Representative NNNS Outcome Scales	Power 0.7	Power 0.8	Power 0.9
Phthalate mixture	NNNS Attention	190	229	293
	NNNS Handling	226	276	351
	NNNS Non-Optimal Reflexes	265	323	408
	NNNS Regulation	331	400	511
	NNNS Excitability	384	466	596

NICU-HEALTH, Neonatal Intensive Care Unit Hospital Exposures and Long-Term Health; NNNS, NICU Network Neurobehavioral Scale.

enrol 400 infants to achieve >80% power to detect differences in age-appropriate neurophenotypes. This number of participants was extrapolated from preliminary data on the relationship between NICU-based phthalate exposure on NNNS[76] performance (table 3) as described in Stroustrup *et al*,[26] and pilot data on the relationship between phthalate exposure and performance on the Bayley Scales of Infant and Toddler Development[77] or the Child Behavior Checklist.[78] Four hundred participants is an ample size to allow separate analyses of boys and girls for those exposures/outcomes known to be sexually dimorphic, for accommodation of the non-independence among twins in our population, and to account for an estimated 20% loss to follow-up. Published studies of environmental chemical or stress exposure in the NICU by other groups are based on cohorts of 6–63 participants.[23 24 79–88] Analogous studies of prenatal exposures on term-born infants are based on 150–400 participants.[89–91]

FINDINGS TO DATE

NICU-HEALTH has already contributed significantly to our understanding of phthalate exposure in the NICU. Phase I produced the first evidence of the clinical impact of phthalate exposure in the NICU population.[26] Further study identified specific sources of exposure to clinically relevant phthalate mixtures in the NICU.[92]

For these studies, we applied a mixture-based outcome-driven approach, WQS regression,[71] to assess the impact of concurrent exposure to multiple phthalates on performance on the NNNS. WQS generates a single index of exposure for the mixture allowing for an estimation of an overall mixture effect in a regression analysis. We used the geometric mean of the multiple concentration-adjusted measures of each monoester species to estimate NICU-based exposure for each infant. We then derived multiple WQS indices based on mixtures of monoester exposure, each weighted for a single NNNS summary scale adjusted for relevant covariates. Adjusted WQS regression indicated a significant association between NICU-based exposure to specific phthalate mixtures and *improved* performance on the NNNS Attention, Handling and Non-Optimal Reflexes summary scales.[26]

As NNNS performance improves with maturity, 'better' summary scale performance can be interpreted as attainment of neurodevelopmental milestones earlier than expected. Other studies have also reported a link between environmental exposures during the third trimester neurodevelopmental window and more rapid behavioural maturation. Specifically, Posner *et al*[93] found that term-born infants exposed to elevated maternal stress in late pregnancy demonstrated behavioural and neuroanatomical phenotypes expected for children of an older age. They hypothesised that the stressful in utero environment during the third trimester period of development provoked rapid maturation as a protective mechanism for an anticipated later-life stress. When followed into middle childhood, these children demonstrated phenotypes of inattention and hyperactivity, recapitulating the recognised association between prenatal exposure to

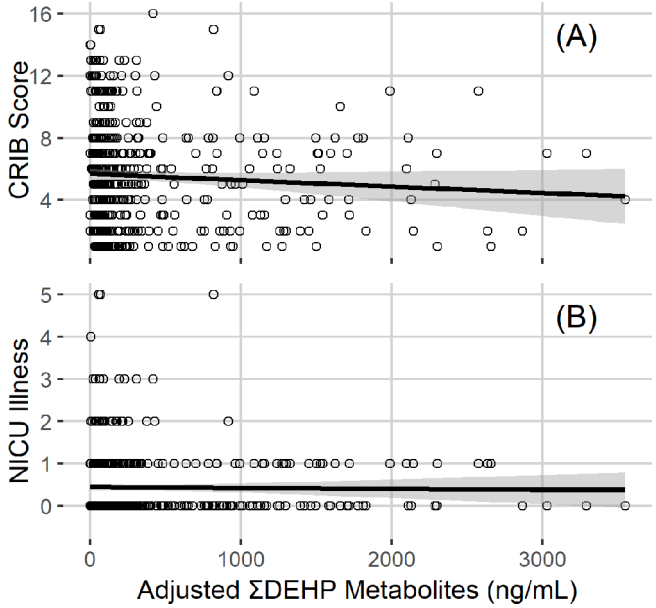

Figure 3 LOESS fit with SE bars showing the absence of significant relationship between NICU-based DEHP exposure and either (A) severity of illness at birth (CRIB score) or (B) NICU-based illness. DHEP, di(2-ethylhexyl)phthalate; LOESS, LOcally WEighted Scatter-plot Smoother; NICU, neonatal intensive care unit.

stress and poor behavioural outcome in middle childhood.[94–97] Early 'hyper-attention' became maladaptive with age.

As our goal of risk reduction in the NICU necessitates identifying specific sources of exposure, we sought to identify sources of the clinically relevant phthalate mixture exposure we previously identified.[26 92] In models accounting for concurrent equipment use, exposure to respiratory support was associated with DEHP biomarkers 50%–136% higher in exposed compared with unexposed infants (p=0.007–0.036). Phthalate mixtures clinically relevant to neurobehavioural development were significantly associated with non-invasive respiratory support.[92] This finding allows efforts to mitigate exposure to clinically relevant phthalate mixtures through improvements in medical material composition. Future study of the NICU-HEALTH cohort could inform relatively inexpensive NICU interventions (eg, use of medical materials that do not leach neurotoxic chemicals, guidance on infant stress reduction) with significant potential to reduce lifelong morbidities common among NICU graduates.

STRENGTHS AND LIMITATIONS

The scientific premise of our work, that NICU-based environmental exposures contribute to the abnormal development of preterm children, is supported by data linking exposures during the period of development that occurs while preterm infants are in the NICU with outcomes in term-born populations[94 98–108]; the heightened exposure to specific toxicants in the NICU[79 82 88 109–111] and our own group's early findings.[26 92] Traditional NICU neurodevelopmental research has focused on medical complications without accounting for the role of the NICU environment[6 7 16 112 113] and has failed to yield highly predictive outcome models. There are no prospective studies on the long-term neurodevelopmental impact of common, coincident NICU-based environmental exposures on the vulnerable and growing population of preterm infants. As NICU practice is constantly evolving, continued study of relevant materials and practice patterns are necessary to provide risk modification in the dynamic real-world setting.

Our cohort does have some limitations. Our patient population, preterm infants cared for in an academic level IV NICU, may not be representative of the entire NICU population. As data on 'typical' community-based exposure to phthalates in early infancy in non-NICU and non-preterm populations is not available—the youngest patients with phthalate biomarker measures in the National Health and Nutrition Examination Survey, for example, aged 6—comparison to a relevant non-NICU group is not possible. Confounding by indication presents an additional challenge in data analyses. Beyond phase I, we enrolled infants with low risk of serious morbidities of prematurity but predictably long NICU hospitalisation—those born after 28-0/7 to 32-6/7 weeks GA. This population requires care with a wide variety of medical equipment that is likely to convey exposure to chemical plasticisers. This equipment is needed to support immaturity in the absence of significant illness or physiological derangement. Analysis of data collected to date reveals no association between severity of illness at birth and biomarkers of exposure to phthalates, the family of organic chemicals most studied in our cohort to date (figure 3). Additionally, major morbidities of prematurity (sepsis, bronchopulmonary dysplasia, necrotising enterocolitis, intraventricular haemorrhage, retinopathy of prematurity) are not associated with phthalate biomarkers, nor is GA at birth. Nonetheless, we will continue to take an agnostic approach to all data interpretation, with comprehensive examination of indications that might explain any associations between the target exposures and outcomes.

COLLABORATION

Requests for collaboration, either sample analyses or data analyses using the NICU-HEALTH data repository, can be made in writing to the principal investigator once the primary analyses planned have been completed. The NICU-HEALTH study management group will evaluate the request and if written approval is provided, a prespecified analytical plan will be requested.

FUTURE DIRECTIONS

The NICU-HEALTH cohort will generate a wealth of biomarker, clinical and outcome data from which future studies of the impact of early-life chemical and non-chemical environmental exposures can benefit. We anticipate future analyses of the data and biospecimens collected, as well as future longitudinal follow-up of the NICU-HEALTH cohort beyond middle childhood. Findings from study of this cohort and other collaborating environmental health cohorts will likely translate into improvements in the hospital environment for infant development.

Author affiliations
[1]Pediatrics, Icahn School of Medicine at Mount Sinai, New York City, New York, USA
[2]Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York City, New York, USA
[3]Beckman Institute, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA
[4]Communication Sciences and Disorders, Northeastern University, Boston, Massachusetts, USA
[5]Pediatrics, Columbia University, New York City, New York, USA

Collaborators Requests for collaboration, either sample analyses or data analyses using the NICU-HEALTH data repository, can be made in writing to the principal investigator once the primary analyses planned have been completed. The NICU-HEALTH study management group will evaluate the request and if written approval is provided, a prespecified analytical plan will be requested.

Contributors AS and JBB designed the study, facilitated and co-ordinated the samples and data collection. AS, JBB and EAS obtained the clinical data. AS, JBB, AA, EZ and JRI designed and performed clinical phenotyping. SAB, PCC and CG designed and performed the statistical analysis plan. SSA and MA designed and conducted the environmental chemical analysis plan. AS drafted this manuscript, and all authors made significant contributions to this manuscript and have read and approved the final version of it.

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ORCID iD

Annemarie Stroustrup http://orcid.org/0000-0002-5667-6195

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