HHS Public Access

Author manuscript

Curr Epidemiol Rep. Author manuscript; available in PMC 2024 February 05.

Published in final edited form as:

Curr Epidemiol Rep. 2023 September ; 10(3): 148–157. doi:10.1007/s40471-023-00323-1.

Epidemiologic Advances Generated by the Human Health Exposure Analysis Resource Program

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Introduction

NIEHS established the Children's Health Exposure Analysis Resource (CHEAR) in 2015; a network of laboratories, a Data Center and Coordinating Center provides eligible investigators with laboratory and data analyses to add environmental exposures in children's health studies at no cost to the investigator [1*]. The Human Health Exposure Analysis Resource (HHEAR), is a continuation and expansion of CHEAR to include environmental sample analysis and health outcomes at all life stages. The remainder of this review we will refer to the network as HHEAR. HHEAR additionally provides laboratory analysis of environmental exposures in biospecimens from the Environmental influences on Child Health Outcomes (ECHO) program [2] The (ECHO) Program is designed to evaluate environmental factors affecting children's health by pooling 71 linked cohorts composed of >50,000 children the US. This review will summarize the published papers that have utilized HHEAR program resources across both programs. Together this will demonstrate how HHEAR supports environmental health research and we will identify the next steps needed to advance our knowledge in this field.

HHEAR Data Center and Repository:

The HHEAR Data Repository is maintained by the HHEAR Data Center (https://hheardatacenter.mssm.edu/) and consists of approved ancillary projects of existing NIH supported grants all of which had previously collected biospecimens and/or environmental samples appropriate for targeted and/or untargeted laboratory analyses along with available epidemiologic phenotype and health outcome data. The HHEAR Data Repository provides a secure venue for public access to biomarker and epidemiologic data from HHEAR projects with available de-identified datasets for download. HHEAR maintains an embargo period on all project data. The embargo ends after first publication that used data generated by the HHEAR resources or one year after all laboratory results are returned and, if requested, at least one data analysis report, whichever occurs first.

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Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Conflicts of interest: None declared.

Projects

Currently there are 50 projects accepted into the HHEAR program from a wide range of existing epidemiologic studies of various designs, the most common of which is longitudinal birth cohorts. Given that fetal development is generally a period of heightened vulnerability to environmental toxicants, birth cohorts allow for numerous opportunities to investigate factors critical to the health of pregnant women and development of their children. Other types of HHEAR projects involve clinical populations, including patients with liver disease, asthma or malaria. These studies examine associations of environmental factors with disease etiology or progression. At this time, there are 33 completed projects and of those, 28 are off embargo and have publicly available data. To date, there are 31 published papers from 17 unique HHEAR projects and 10 papers from ECHO projects.

Types of Exposures Measured

The HHEAR Lab network provides both targeted analyses of inorganic and organic toxicants, nutrients, and social-stress markers and untargeted analyses to assess the exposome and discovery of exposure-outcome relationships (see https://hhearprogram.org/).

The most common chemical classes analyzed in the published works that are the subject of this review are (number of papers in parentheses): trace elements (20); phthalates (11); phenols (7); tobacco biomarkers (4); and PFAS (5). These totals are not mutually exclusive as most projects have many chemical panels analyzed. HHEAR approved projects included an average of 4 targeted analyte panels (range 1-9).

This review includes 41 papers from HHEAR and ECHO projects that have all utilized HHEAR generated laboratory results from the most common chemical classes. The citations for these papers are provided at the beginning of each section below.

Findings by Exposure

Trace Elements [3**-21**]

Exposure to metals during pregnancy have health consequences for both the mother and fetus. Metal exposures can affect fetal growth, which can predict health later in life [22, 23]. HHEAR projects derive from studies that have analyzed single metal exposures [3**] and both single and metal mixtures [7**, 8**, 9**, 14**, 24, 25*, 26]. Metals are measured in blood [3**] or urine samples from one [3**, 7**, 8**, 9**, 25*] or more trimesters of pregnancy [4**, 7**, 14**, 26]

The pregnancy and birth-related outcomes include: preeclampsia [3**]; gestational glucose concentrations [5**]; fetal growth; birthweight [4**, 7**, 8**, 21**]; head circumference [8**, 9*]; femur length [8**, 9**]; and pre-term birth [4**, 20**].

There were 8 studies that examined fetal growth, including birth size and pre-term birth, several of which showed inverse associations with the more commonly studied metals, for ex. Hg and Pb. Others showed promising evidence for new associations previously not reported in the literature.

Fetal Growth and Birth Size—In both single metal and metal mixture analyses, arsenic (As), manganese (Mn), lead (Pb), and zinc (Zn) in first trimester blood were all associated with some birth measurement, varying by infant sex and exposure level of other metal mixture components [4**]. Specifically, higher As was associated with lower birthweight in males, Zn with larger head circumference in females, and Mn with longer birth length in sex-combined analysis. Interactions were found between Pb and Zn with head circumference, such that the negative association with Pb was attenuated at higher concentrations of Zn, and between As and Mn, As and birthweight negative association was stronger at higher concentrations of Mn. In two other studies examining similar metals, no associations with birthweight were found [8**, 9**]. However, As, barium (Ba), and Pb were negatively associated with femur length in one [9**] and urinary Zn and molybdenum (Mo), positively associated in the other study with repeated measures of fetal growth (femur length, head circumference and birthweight); positive associations were reported for urinary Zn and Mo, while selenium (Se) had an inverse association [8**].

In an urban Los Angeles cohort [7**] using a first trimester urinary metals mixtures analysis, consistent with previous research [27, 28], an inverse linear association for Hg and birthweight and a positive association for nickel (Ni) and birthweight was observed. A potential interaction between Hg and Ni was also identified. Ni is not essential, but has nutritional properties that may promote fetal growth [29]. In this same cohort, [10**] Mo was associated with a larger fetal size whereas Ba was associated with a smaller fetal size in mid-pregnancy. Two other HHEAR investigations found a positive association between urinary Mo and femur length [8**] as well as other fetal measures [9**], although the latter was not statistically significant, likely due to the small sample size (N = 56).

A pooled sample of 1,002 participants from the MADRES, NHBCS, and PROTECT cohorts found no cumulative effect of metal mixture on birthweight [21**]. However, mercury (Hg), antimony (Sb), and tin (Sn) were inversely associated with birthweight, while Ni had a positive association. Metal-growth associations varied by cohort, likely due to differences in metal distributions, unmeasured co-pollutants and confounders across their three distinct geographic locations.

Preterm Birth—As was associated with lower gestational age only in males with high concentrations of Mn and Pb in the same cohort that reported an association for As and low birthweight [4**]. In a Boston cohort, maternal urinary copper (Cu) in the third trimester was associated with increased risk of preterm birth in both single chemical analysis and in analyses for mixtures [20**].

A single exposure analysis makes biological sense when there is a specific hypothesis for a particular metal, as in the study where higher Mn concentration measured in blood during the first trimester was associated with lower risk of preeclampsia in a dose–response manner [3**]. Mn is an anti-oxidant and oxidative stress has been associated in the development of preeclampsia. Other studies have found this inverse association [30], however, to our knowledge this study is the first to establish temporality.

Epigenetics—Several projects examined potential mechanisms underlying the associations of metals with adverse birth outcomes and childhood health including: alterations in microRNA [13**]; DNA methylation [14**, 15**]; biomarkers of DNA copy number; and telomere length [6**]. The following HHEAR projects have identified unique associations with certain metals, as well as supporting previous findings with epigenetic changes associated with Pb.

Maternal exposure to Pb, Mn, and Se was associated with DNA copy number and telomere length in maternal second trimester and cord blood [6**]. In the same cohort, both positive and inverse associations with glucose concentrations measured at 26-28 weeks gestation were found for early pregnancy Ba and Hg, respectively [5**]. Alterations in miRNA were associated with Ba, Hg, and thallium(Tl) [13**], suggesting that Ba, Hg, and Tl may impact a common set of miRNA which target pathways critical for normal placental development and other key biological processes that are essential in early pregnancy. [13**].

Prenatal and early postnatal Pb exposure have been shown in rodent and human studies to be associated with epigenetic changes in the offspring [31, 32]. Several HHEAR projects investigated these associations. A study done in Mexico found first and third trimester and the cumulative measure of gestational Pb exposure were associated with several statistically significant changes in DNA methylation at birth [14**]. A subsample of 85 mother–child participants from this cohort expanded upon these findings and found DNA methylation at several genes mediates the association between lead exposure and neurodevelopmental scores at 24 months of age, although not statistically significant [16**]. Similarly, lead was associated with DNA methylation in cord blood in another cohort in the US [15**].

Nutrition—Adequate vitamin D is associated with improved absorption of not only calcium, but other essential metals [33]. One HHEAR project reported first trimester plasma vitamin D concentration was associated with lower levels of urinary Pb and Sn, and higher Mo levels [17**].

Neurologic and developmental outcomes—Previous research has shown the detrimental effects of certain metals on neurodevelopment outcomes. However, identifying periods of high susceptibility to metals remains challenging due to analysis of metals and outcomes in different developmental windows of exposures. The two HHEAR studies published in this area underline the importance of the complex interactions among metals.

Using a new statistical method developed through the work of HHEAR, the association between exposure to metal mixtures during second trimester of pregnancy and early life cognitive trajectories was investigated in a subset of a Mexican birth cohort [11**]. A positive association between Cu exposure and neurodevelopment at 24 months was dampened in the presence of high Pb, indicating an effect modification between joint Cu-Pb exposures.

A nested case-control analysis examined the effects of metals (and other chemicals) on neurodevelopment outcomes in children with developmental delays at 2-5 years of age

[12**]. No single metal was associated with the outcome, but the trace element mixture (As, TI, Cd, U, Mo), was significantly associated with increased odds of developmental delay.

Characteristics influencing metal exposures—Racial/ethnic disparities in urinary metals exposure was evaluated among a multi-ethnic sample of pregnant women living in the Northeastern U.S. [18**]. Black/Black-Hispanic women and White-Hispanic women had significantly increased urinary levels of cadmium (Cd), chromium (Cr), Pb and Sb than White, non-Hispanic women. The same four metals were higher among women in areas with higher crime, higher diversity, lower educational attainment, lower household income, and higher poverty.

One investigation identified known food sources of metals such as Hg with seafood and As with white rice, plus new potential sources of As and Hg exposure, including fresh fruits, green vegetables, and eggs [19**]. Another smaller study in Michigan [9**] observed associations between fast food consumption and Se, Sn, and Zn. These findings suggest that food can provide both nutrients and environmental contaminant exposures. Research that shows sources of exposure provides evidence to support recommendations, including informing pregnant women of the potential ingestion of detrimental and beneficial metals from both fast food and nutrient-rich food sources.

Phthalates, Phenols and Parabens [9, 12, 34**-45**]

Endocrine disrupting chemicals (EDCs) such as phthalates, phenols and parabens are environmentally ubiquitously. Thirteen studies from HHEAR and ECHO have investigated the broad health effects of exposure to these three EDC families.

DNA Methylation—One mechanism by which phthalate and phenol exposures may disrupt biological pathways is through alterations of the epigenome via DNA methylation [46*] triggering changes in the chromatin structure, and as a result, gene expression [47]. In mouse studies bisphenol and phthalate exposure led to differentially methylated regions in genes that regulate hepatic function [48, 49*], metabolism [50, 51*], neural and inflammatory pathways [52*, 53] as well as other epigenetic regulatory functions [54, 55].

Epidemiologic studies from HHEAR and ECHO have further supported the findings in mouse models. One study found that ∑DEPH (sum of measured monoester metabolites) exposure during pregnancy was associated with four CpG sites in male infants and hypomethylation of four other loci in female infants [34**]. Similarly, another study observed an association between increasing phthalate concentrations and hypomethylation in LINE-1, IGF2, and PPARA gene regions in infants, regardless of their sex [35**]. When gene pathway analyses were performed, both studies found disruptions in the PPAR pathway [34**, 35**], a major regulator of lipid metabolism and other PPAR subtypes in the liver [56], suggesting a link between phthalate exposure and metabolic health outcomes, a growing public health concern.

While evidence presented by these papers sound promising, the scope of studies investigating the relationship between phthalate metabolites and lipid metabolism continues to be limited. The majority use animal models or focus on targeted lipids, such as

triglyceride, LDL, and HDL [36**]. However, HHEAR seeks to provide researchers with the tools and data to narrow such existing gaps. For example, one study using multiple phthalate biomarkers found an association with lipid metabolites across all lipid hierarchy levels in blood samples collected from pregnant women [36**].

Another study found 38 differentially methylated sites in infant cord blood in response to maternal bisphenol exposure; enriched pathways were associated with the nervous system (GPCR), immune and neuroinflammation responses [43**]. Using the laboratory and data tools provided by HHEAR, investigators were also able to delve further and include bisphenol replacements in their analyses [43**]. In another study of pregnant women, investigators found that phenol replacement compounds are becoming ubiquitous in the population while trends in the prevalence of other phenols are decreasing [42**].

Growth and Development—Another period of rapid growth and development susceptible to toxicant exposure is during pregnancy for the developing fetus. Higher concentrations of the phthalate MCPP measured in the first trimester from a Michigan birth cohort was associated with an increase in birthweight whereas increased exposure to phenols had an inverse association with birthweight [9**]. Also this paper found higher concentrations of several phthalates and phenols among fast food consumers.

HHEAR not only facilitates the study of broad health effects during pregnancy, but also during other periods of rapid growth and development, such as puberty. A study in Chilean girls observed that EDC concentrations were significantly lower at late stage puberty and 1-year post-menarche compared to the pre-pubertal stage [37**]. Investigators also found significant positive associations between concentrations of DEHP metabolites [38**] and breast absolute fibroglandular and total breast volume [37**] at late stage puberty [37**].

Respiratory—While the endocrine disrupting properties of phthalates are well documented, few studies have described the relationship between phthalates and asthma-related symptoms, especially in the pediatric population [38**]. One HHEAR study found that in children 5-17 years of age with pre-existing asthma, high and low molecular weight phthalates have also been associated with increased symptoms and healthcare utilization [38**]. These associations remained significant in analyses utilizing biomarkers of phthalate replacements as well as symptoms and healthcare utilization in the past three months [38**].

Neurodevelopment—Exposure to EDCs and their effects on childhood neurodevelopment is another major area of research to which studies utilizing HHEAR have made sizeable contributions. Prenatal exposure to phthalates, phenols, and parabens as well as triclocarban (TCC) has been associated with poor birth outcomes [57, 58*], and is suspected to potentially have adverse neurodevelopmental effects [59*, 60, 61*].

One study found prenatal monoethyl phthalate (mEP) exposure was associated with Social Responsiveness Scale-2nd edition (SRS-2) t-scores in male children [39**]. Another study found high urinary concentrations of EDC mixtures increased the odds of having a diagnosis of autism spectrum disorder (ASD), developmental delay, or other early concerns compared to typically developing children [12**]. In the MARBLES cohort of mother-infant

pairs with a blood relative previously diagnosed with ASD, the placental metabolome of mothers of male infants was associated with neurodevelopmental outcomes even after adjusting for covariates [40**]. The same study also showed that an EDC mixture, which included phthalates, had a significant negative total and direct estimated effect on placental metabolites. Prenatal exposure of phenol and paraben mixtures was significantly associated with increased ASD risk in the MARBLES cohort [41**]. Single analyte analyses also suggested higher ethylparaben concentration was associated with an increased risk of non-typical developing children and ASD, respectively. This paper was the first to show evidence of significant effects of a wider range of phenols and parabens on neurodevelopmental outcomes in children [41**].

Oxidative Stress—Major findings in other studies that have used HHEAR provide strong support to utilize chemical mixture analyses in environmental health studies. For example, in a study investigating the association of oxidative stress biomarkers and EDCs, single chemical analyses showed negative associations, but in mixture analyses many positive associations became evident [45**]. In another study, investigators found EDC mixtures were associated with maternal and infant IL-6 but in isolated chemical analyses there was no association with IL-6 [44**]. Studies on EDC exposures and oxidative stress responses are sparse, but these studies demonstrate how accounting for synergistic/antagonistic effects of EDCs in mixtures is essential for environmental toxicant studies. As exposure naturally occurs as a mixture rather than in singularity [62*], it is vital that current and future epidemiologic studies include not just single chemical analyses but also mixture analyses.

Smoking [63**-66**]

Multiple Outcomes—Two HHEAR projects provide epidemiological evidence for the association between cotinine levels, a primary metabolite of nicotine/biomarker of smoking exposure [67, 68*], and adverse health outcomes. Additionally, their observations provide explanations for mechanisms that potentially underlie these relationships.

In African-American women, one study not only reported an association between cotinine levels and adverse birth outcomes, but also observed numerous perturbations in metabolic pathways during early and late pregnancy [63**]. Moreover, the identified metabolites were verified as closely linked and connected to several inflammation, oxidative stress, placental vascularization, and insulin action pathways. Using these findings investigators were able to build a biological network centered on the urea and TCA cycle connecting their observations of lipid, carbohydrate, and nucleotide metabolism disruption in response to cotinine levels [63**]. Another study in children with allergen sensitization, observed increased cotinine levels were associated with both increased days of asthma symptoms and increased hospitalizations over the previous year [65**] suggesting an interaction between allergenic exposures and chemical exposures on the impact of asthma control [65**]. Both studies contribute, in different ways, to our understanding of smoke-related disease and highlight the importance of making the HHEAR laboratory analyses available to researchers to enable this type of investigation.

Exposure Validation—The HHEAR lab has the ability to add cotinine biomarker measurements to projects, when they may otherwise have to rely solely on self-reported smoking. For example, a HHEAR intervention study used both self-reported smoking and saliva cotinine levels to measure smoking abstinence levels among parents of children who had presented to the pediatric emergency department because of asthma-related symptoms [64**]. Ultimately investigators were unable to find significant differences in tobacco abstinence, as well as cotinine levels, between the intervention and control conditions in this study. The authors attribute their null findings to multiple factors including consistency in administering the intervention, higher than anticipated quit rates in the control group, and "assessment reactivity" whereby participants in the control group are administered a "dose" of the intervention as a result of prompting from the assessment questionnaire [64**].

A study in pregnant mothers with low prevalence of smoking further elucidated the value of using both self-reported and biomarker measurements to ascertain smoking exposure during pregnancy [66**]. Investigators largely reported good concordance between the two types of measurements, but approximately 3% of smokers were still misclassified, their self-reported status not concordant with biomarker data, when solely relying on either source [66**]. Together these studies suggest that, if able, using both self-reported and biomarker measurements can minimize the likelihood of misclassification of exposure and improve the quality of analyses [64**, 66**]. For many investigators, the inclusion of both, especially costly biomarkers, is particularly challenging. However, HHEAR aims to reduce these barriers by providing laboratory analyses; not only to smoking biomarkers, but also panels of other chemicals imperative for understanding the exposome and the origin of disease.

Per- and Polyfluoroalkyl Substances (PFAS) [69**-73**]

PFAS exposure is ubiquitous in the U.S. Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are detectable in >90% of the population [74] with the main human exposure sources being water and food [75, 76]. There is growing interest in these compounds as PFAS-related adverse health outcomes have been observed in numerous studies.

A cohort of pregnant African American women in Atlanta, Georgia was used in 3 investigations to examine PFAS related outcomes. The first identified several predictors for serum PFAS concentrations, including parity, BMI, education, tobacco, and marijuana use, age of house, drinking water source, and cosmetic product use [69**]. Evidence from this cohort suggests exposure to certain PFAS may affect vitamin D biomarker concentrations. The effect of PFAS exposure on vitamin D during pregnancy is significant because perturbation of maternal hormone levels can result in profound health risks in both pregnant women and their fetuses [70**]. And lastly, higher serum concentrations of PFOA and PFNA in first trimester maternal samples were associated with reduced fetal growth [71**].

Investigating the mechanism underlying the adverse health effect of PFASs was studied in 102 overweight or obese young adults [72**]. Higher exposure to PFOA was significantly associated with higher glucose levels providing evidence that altered glucose metabolic pathways may increase cardiometabolic risk in young adults. In the same case-control

analysis, childhood PFOA, perfluoroheptanoic acid [73**], and a PFAS mixture was associated with increased odds of ASD [73**].

HHEAR Contributions to Environmental Health Research

HHEAR program resources enable investigations that contribute to understanding environmental health. These investigations expand the exposures studied, including analyses of chemical mixtures and less studied chemicals, broadening the definition of the environment. HHEAR has made it possible to answer environmental health questions beyond the parent study's initial objectives. For example, the VIVA cohort[77] originally designed to examine the effects of mother's peri/post pregnancy diet on child health outcomes, used the extant biosamples and was able to add metal exposure analyses to examine multiple outcomes [3**, 4**, 15**]. Another birth cohort of low income mothers from CA, was designed to investigate air pollution as an environmental contributor to childhood obesity [24].Using HHEAR, urinary metals analyses were added to investigate the association with childhood growth [7**, 10**]. These cohorts took advantage of the resources offered by HHEAR to expand their ability to examine environment-health associations because of the large, breadth of data and biosamples they have collected. Simultaneous exposures to multiple chemicals are more reflective of human exposures and therefore are important to study. Literature on the health effects of metal mixtures is sparse when compared to the established literature on the health effects of single metals. Many of the HHEAR papers have examined the impacts of individual chemicals as well as mixtures within one chemical group and sometimes more than one group. For example, the effect of lead on child neurodevelopment has been well researched, however, exposure to metal mixtures on child neurodevelopment has not.

Analyzing additional chemical panels at no cost to the investigator, HHEAR investigators have been able to move beyond the highly studied toxicants (e.g., As, Cd, BPA) in order to characterize trends in the ever-changing exposome [9**]. The effects of lead [78] and mercury [79] on neurological effects have been well established, whereas other trace elements have been less studied. Few studies have addressed elements such as cadmium or molybdenum and adverse neurological or neurodevelopmental outcomes [80, 81]. Several HHEAR supported investigations reported positive or negative associations for these less studied metals: Mo, Se, Mn, Ni and Ba with various birth outcomes. [4**, 7**-9**, 21**]. Mo and Ni may be important for promoting fetal growth. In contrast, Ba adversely impacted fetal growth at environmentally relevant concentrations. Additionally, individual element interactions, including Ni, Cu, Pb and Hg may also merit additional investigation. Results of these HHEAR supported investigations highlight the need for further research on the health consequences these metal exposures. HHEAR continues to expand its laboratory capabilities by including emerging EDCs. Recently, phenol and phthalate replacement chemicals have been identified in the population with increased frequency [42**]. Two HHEAR studies have observed negative health associations with use of alternative EDCs from decreased birthweight [34**] to increased asthma symptoms in children (BPF) [9**, 38**]. This suggests that alternative EDCs could have comparable effects to EDCs they are replacing meriting further investigation.

Next Steps

Recognition of the contribution of environmental chemical exposures to childhood disease has increased, yet there are still many gaps in our understanding due to limitations of available data sources [82*]. Individual longitudinal cohort studies overcome some of these data gaps, but often do not have adequate sample sizes to detect small effect sizes, study rare outcomes, or identify susceptible subgroups. The combination of studies with similar environmental exposure and health outcome data can overcome these limitations and the HHEAR Data Repository was specifically designed to accomplish this goal [83*]. This repository has developed a continuously growing ontology—a common vocabulary built on the data and laboratory results of all HHEAR projects [84]. The ontology terms enable the harmonization of all of the HHEAR project data with the goal of promoting the secondary analysis of pooled environmental health data. Next steps would be to combine studies using the harmonized data to examine exposure disease associations in large, diverse datasets and exposures across a broad range of developmental periods. This has great potential to advance environmental research by increasing the sample size and scope of scientific hypotheses examined in order to understand the complex determinants of disease. As more of the research community takes advantage of the resource, HHEAR will support the analysis of the exposome through the harmonization of studies enabled by a HHEAR-developed ontology for children's health, exposure and associated data, and metadata standards.

Financial support and sponsorship:

This work was supported by the Funding: National Institute of Environmental Health Sciences: U2CES026555.

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