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Maternal prenatal exposures to environmental chemicals and psychosocial stressors in the ECHO Program - implications for research on perinatal outcomes

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Abstract

Background: Exposures to environmental chemicals and psychosocial stressors during pregnancy have been individually associated with adverse perinatal outcomes related to birth weight and gestational age, but are not often considered in combination.

Methods: We characterized in the literature the prevalence and overlap of key stressors (environmental chemical exposure and psychosocial factors) that women experience during pregnancy. We discuss the National Institutes of Health's Environmental Influences on Child Health Outcomes (ECHO) program and its goal to understand the effects of a broad range of early environmental influences on child health and development by combining existing longitudinal cohorts that include more than 50,000 children across the U.S.

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Results: We reviewed types of psychosocial stressors and instruments used to assess them as well as classes of environmental chemical exposures that are known to adversely impact perinatal outcomes. We identified studies on the combined effect of maternal psychosocial stress and prenatal environmental chemical exposures that indicate they may interact to adversely affect perinatal outcomes, yet few studies have examined a broad range of psychosocial stressors and environmental chemicals. Of the 84 cohorts in ECHO, 38 collected data on environmental chemicals and psychosocial stressors and perinatal outcomes.

Conclusion: There is a need for integration of multiple exposures of environmental chemicals and psychosocial stressors in the investigation of adverse perinatal outcomes. The diverse geographies with varied participant demographics among the ECHO pregnancy cohorts will improve statistical power and generalizability of results and the capacity to compare regions with distinct place-based environmental and social stressors.

Keywords

Environment; Chemicals; Birth Outcomes; Stress

Introduction

Exposure to psychosocial stressors and environmental chemicals are ubiquitous during pregnancy and have been individually associated with adverse pregnancy outcomes, including low birthweight and preterm birth. Although the mechanisms by which these factors affect perinatal health are not fully known, hypotheses suggest that they may act upon similar biological systems. Due to structural racism and socioeconomic disadvantages, many of these chemical and stress exposures tend to cluster together, yet few studies have attempted to consider joint effects (*i.e.*, synergistic or additive).[1] Indeed, the combination, referred to as a “double jeopardy,” may have a greater impact than each individual factor, and result in amplified risk of adverse pregnancy outcomes.[2]

In this review, we define measures of environmental chemical and psychosocial exposures during pregnancy and examine the small literature on their combined effects on perinatal outcomes. We then describe the National Institutes of Health (NIH)’s Environmental Influences on Child Health Outcomes (ECHO) program as a unique opportunity to characterize complex combinations and interactions of multiple environmental and psychosocial stressors on perinatal outcomes. ECHO is comprised of 84 U.S. cohorts and will allow for integrated evaluation of multiple environmental and psychosocial stressors through collaborative research projects. Leveraging publicly available data from the ECHO cohorts, researchers will be able to develop a more comprehensive understanding of the complex effects of important prenatal exposures development, thereby informing interventions and prevention to reduce adverse perinatal outcomes.

Almost all ECHO cohorts will have information on key perinatal outcomes related to fetal growth (birth weight and weight for gestational age) and prematurity (gestational age at birth). Low birth weight (<2500 grams) occurs in 8% of births in the US.[3] The prevalence of preterm birth (<37 weeks gestation) is 10% in the U.S.[3] These outcomes are associated with increased risk of adverse health outcomes throughout childhood and into adulthood.[4]

Furthermore, adverse perinatal outcomes are heterogeneous within and between classifications, and although some share risk factors, they can have multiple etiologies. A large proportion of these outcomes cannot be explained by known risk factors and we have not fully characterized the potential contribution of chemical and stress exposures to adverse pregnancy outcomes. Thus, ECHO is well suited to address both the range of etiologies and these heterogeneous outcomes as the pregnancy cohorts included follow infants into childhood, thus allowing for future assessments of health in relation to outcomes in the perinatal period.

Environmental Chemical Exposures

Pregnant women are exposed to a myriad of environmental chemicals, many of which are known to have adverse health effects, including effects on perinatal outcomes such as low birthweight and preterm birth.[5, 6] Given that there are large number of environmental chemical exposures, existing chemical exposure assessment tends to rely mainly on targeted analytic chemistry methods, which focus on compounds selected *a priori* for analysis.[7] For example, only a few hundred chemical are routinely measured in humans through targeted methods,[6, 8] which are resource and time intensive to develop, whereas the potential number of chemical exposures that pregnant woman can face is likely much higher, given that there are about 8,000 industrial chemicals that are manufactured and used in high quantities in the U.S., and that chemical production is about 9 trillion pounds per year.[6] We focus on a subset of classes of environmental chemical exposures measured in the ECHO program, recognizing that there are others of interest for perinatal outcomes (such as environmental tobacco smoke and water disinfection byproducts) as well as new emerging contaminants that merit future research.

Persistent chemicals

Persistent environmental chemicals resist environmental degradation, bioaccumulate in food chains, and have long half-lives in humans. For some of these chemicals (*e.g.*, organochlorine pesticides (OCPs) and perfluoroalkyl substances (PFASs)), exposure is principally via diet (through exposures in drinking water, fish and meat)[9, 10] while for other chemical classes (*e.g.*, polybrominated diphenyl ethers (PBDEs)) human exposure is through consumer products like textiles, furniture, and electronics.[11] Alarmingly, many persistent chemicals (*e.g.*, polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT) and its metabolites, and perfluorooctanesulfonic acid (PFOS)) remain present in measurable levels in virtually all pregnant women despite being phased-out or banned in many parts of the world for decades.[5, 6] Prenatal exposure to these compounds, many of which are endocrine disrupting chemicals, have been shown to affect fetal growth and other developmental outcomes.[12, 13]

Non-persistent chemicals

In contrast to persistent environmental chemicals, non-persistent chemicals are rapidly metabolized and excreted by the body, often in a matter of days or even hours. Nevertheless, pregnant women show nearly ubiquitous exposure to several classes of non-persistent chemicals including phthalates, phenols, and parabens, thus making them pseudo-persistent.

[5, 14] These chemicals (*e.g.*, Bisphenol A (BPA) and diethylhexyl phthalate (DEHP)) are found in a wide array of consumer products, including plastics and canned and other food products, where they are introduced during processing and packaging.[15, 16] Certain phthalates, especially diethylphthalate, and parabens are also commonly found in personal care products.[17, 18] Phthalates, phenols, and parabens are all known endocrine disrupting chemicals, interfering with hormone production and/or activity of hormones, particularly during vulnerable periods in development, such as gestation.[19]

Heavy metals

Heavy metals enter the human body through primarily ingestion and inhalation.[20] Lead is the most studied metal and is teratogenic prenatally as well as toxic postnatally. Maternal exposure most often occurs through ingestion of dust from lead based paints or water contaminated by lead pipes.[20] Lead is readily transported across the placenta and can lead to epigenetic changes in the fetus.[21] Maternal and cord blood lead levels have been associated with lower birth weight, shorter birth length, and smaller head circumference.[22–25] Mercury, which enters the environment through sources such as coal-fired power plants, can enter the body through ingestion of food grown in contaminated soil, or fish that bioaccumulate mercury due to water pollution. Mercury and other heavy metals, such as cadmium and arsenic, have been related to reduced birth weight in a number of populations.[26–31]

Air pollution

Both indoor and outdoor air pollution, which include air toxics and criteria pollutants such as particulate matter less than 10 and 2.5 microns in aerodynamic diameter, nitrogen dioxide, carbon monoxide, sulfur dioxide and ozone, pose a risk to fetal and infant health. Air pollutants impact the fetus through maternal inhalation; the greatest harm may occur during developmental periods with high oxygen requirement.[32] Additionally, increased maternal alveolar ventilation rate during pregnancy can increase exposure to air pollutants. The pathologic effects of these pollutants are believed to be mediated by their effects on local and systemic inflammation. Higher exposure to particulate matter during pregnancy has been associated with respiratory-related and all cause infant mortality, low birthweight and preterm birth.[33–37]

Assessing environmental chemical exposures during pregnancy

Because directly measuring environmental chemical exposures reaching the fetus is typically not feasible, maternal exposures are used as a proxy. Several methods commonly used to assess maternal exposures are discussed below, and detailed information on exposure assessment during pregnancy is available elsewhere.[6, 38]

Biomonitoring of maternal matrices for environmental chemicals can provide important measures of internal doses integrated across exposure pathways,[39] and commonly used matrices include maternal blood, urine, and hair. Standardized collection, storage, processing and analytical protocols are critical for meaningful results[6, 40] and appropriate collection protocols vary widely by compound. For example, persistent chemicals may require only one measurement, while multiple measurements are recommended for non-persistent chemicals due to high within person variability over time.[38]

While biomonitoring may not offer insight into sources of exposure, maternal questionnaires are widely used to assess chemical exposures during pregnancy, including the presence, duration, frequency, and pattern of consumer product and pesticide use.[6, 38] Questionnaires may be used when biospecimen collection or other personal exposure monitoring methods (such as household air and dust monitoring), are not logistically or financially feasible, thus allowing a larger study sample size than possible with more direct measurement techniques. Limitations to questionnaires include recall bias and the challenge of capturing multiple exposures and sources.[38, 41] In contrast to the extensive set of validated instruments to assess psychosocial stressors during pregnancy (see below), there are few validated questionnaires to assess environmental chemical exposures on a personal level beyond analyzing biospecimens or monitoring personal environments directly.

Geographic Information Systems (GIS) can be used to integrate environmental monitoring data or other contextual spatial data sets into epidemiological analyses.[42, 43] A typical use of GIS for perinatal research is to estimate exposure to outdoor air pollution using monitoring data collected at or near study subjects' residences and workplaces.[44–46] The precision of GIS and environmental monitoring data as proxies for environmental chemical exposures depends on the availability of data on how individuals move through and interact with their environment.[40] Novel methods combining satellite data and modeling techniques will allow daily estimates of air pollution, temperature and greenspace with fine spatial and temporal resolution across the U.S.[47]

Psychosocial Stressors

Pregnant women are exposed to psychosocial stressors via many routes, including poverty and low socioeconomic status, major life events, pregnancy-related stressors, racial discrimination, and the presence of placed-based chronic stressors. These psychosocial stressors have been associated with adverse perinatal outcomes including low birth weight, small for gestational age and preterm birth.[48] We focus on those psychosocial risk factors most relevant to perinatal outcomes and the ECHO program goals of improving the child health.

Poverty and low socioeconomic status

The association between low socioeconomic status (SES) and increased risk for adverse perinatal outcomes is evident at both individual and neighborhood levels.[49, 50] Neighborhood socioeconomic factors may affect demographic groups differently; one study found stronger neighborhood SES effects for African Americans and Asian Americans in urban areas.[51] Mechanisms that may explain these socioeconomic-perinatal health links include reduced access to prenatal care,[50] variations in levels of bacterial vaginosis and cigarette smoking,[52] as well as increased rates of exposure to stressful life events.[53] Living in high poverty and highly segregated communities can further compound the effect of individual-level poverty on adverse birth outcomes through exposures to distressed physical environments (e.g. environmental hazards and dilapidated housing), fragmented social networks (lack of social support and political power) and limited health-related resources (health care, access to healthy food, recreational spaces, and transportation).[2]

Perceived and pregnancy-related stress

Self-report measures have been used to capture individual experience or perception of stress and worry, including both general stress and stress related to specific experiences. General levels of stress or distress in pregnancy are captured by self-reported measures such as the Perceived Stress Scale (PSS) or the State-Trait Anxiety Inventory (STAI). These measures are widely used across many studies with both healthy and clinical samples, allowing for a broader comparison between stress during pregnancy and in general. There are also measures of pregnancy-specific perceived stress, such as the Prenatal Distress Questionnaire (PDQ) and Pregnancy-Specific Anxiety Scale (PSAS), that focus on concerns about birth and the baby, over body weight or image, and emotional or relationship changes.[54] These questionnaires take into consideration how the individual feels about normative changes that occur during pregnancy, such as physical discomfort or shifts in social relationships, whereas a general self-report scale such as the PSS or STAI do not specify worries related to this specific life experience. The most significant limitation of measures such as the PDQ and PSAS is that they do not measure perceived stress about experiences unrelated to pregnancy.

Measures of pregnancy-specific stress, focusing on concerns about the baby's health and birth outcomes, are distinct, and clearly independent of the effects of more general stress.[54] Perinatal outcomes, such as preterm birth, are more reliably predicted by pregnancy-related stress than more general stress measures.[55, 56]

Stressful life events

Major life events, such as death of a family member, job loss, or divorce may contribute to stress, including during pregnancy. The study of stressful life events in pregnancy primarily focuses on self-reports of episodic life events in questionnaires or interviews, or alternatively, convenience samples of women who have collectively experienced a stressful life event during pregnancy.[57, 58] Perhaps the most commonly employed self-report measure of stressful life events in pregnancy is the Pregnancy Risk Assessment Monitoring System (PRAMS), which includes questions about financial, partner-related, emotional and traumatic life stressors. CDC surveillance studies that use PRAMS suggest that more than half of all US women report experiencing one or more stressful life events in the year before the birth of their child.[59]

Prospective pregnancy cohort studies have employed a variety of life event checklists, or they have collected data on exposure to stressful life events reported in a clinical interview for assessment of post-traumatic stress disorder.[60] Other event-based assessment tools include the Life Events Checklist (LEC) or the Traumatic Life Events Questionnaire (TLEQ).

An alternative method of studying and assessing psychosocial stress during pregnancy is the utilization of convenience samples of women who have collectively experienced a stressful life event during pregnancy. These events include natural disasters or other adverse events such as the 1998 Quebec Ice Storm,[58] the Dutch Famine,[61] or the 2001 World Trade Center attacks.[62] A recent meta-analysis examining stress during pregnancy noted small but

significant associations between adverse perinatal outcomes and both maternal reports of stressful life events and natural disasters during pregnancy. Of note, each of these effect sizes were smaller than that noted between pregnancy-specific stress and perinatal outcomes.[57] Recent discoveries related to transgenerational epigenetic processes have also focused attention on the potential impact of maternal childhood trauma on offspring development.[63] In addition to checklists assessing potentially stressful life events in proximity to the pregnancy, reports about early life stress, including childhood maltreatment and adversity, are often used as well. The Childhood Trauma Questionnaire (CTQ)[64] and Adverse Childhood Experience (ACE) questionnaire[65] are brief and easy to use measures that have been widely validated for assessment of these early experiences in pregnant populations.[66]

Discrimination

Measures such as the Krieger Experiences of Discrimination Scale (EOD)[67] have been employed to assess discrimination-related stressors. The EOD includes both a self-report of event-based experiences of discrimination and questions about worry related to discrimination. The EOD has been used in studies of racial discrimination during pregnancy,[68] but has not been formally validated for use in pregnant populations.

A recent study that directly compared stressors experienced by non-Hispanic White and Black women in pregnancy found that non-Hispanic Black women experienced higher levels of discrimination, and also had higher levels of biological indicators of stress (C-reactive protein and adrenocorticotropic hormones), relative to White women in the sample at the same socioeconomic status level.[69] These findings suggest that chronic stressors, specific to African American women, may impact their biological functioning during pregnancy, which may in turn be associated with their risk for adverse birth outcomes, a phenomenon known as “weathering”.[70]

Place-based sources of stress

Neighborhood environments can be important contributors to maternal chronic psychosocial stress that can function independently of individual-level stressors to impact health.[71, 72] A review of 28 studies found consistent relationships between poor neighborhood conditions and adverse perinatal outcomes after accounting for individual characteristics,[73] including neighborhood-level poverty,[74] and crime.[75] Evidence also suggests living in neighborhoods with higher rates of domestic violence increase the risk of giving birth to a small for gestational age infant compared to living in areas with low rates of domestic violence.[76] A systematic review and meta-analysis found racial residential segregation to be associated with higher risk of pre-term birth and low birth weight, particularly for African American women.[77] Built environment characteristics, such as urban green space, may promote maternal health and reduce stress and has been associated with increased birth weight,[78–80] while other residential environments, such as housing damage, have been associated with small for gestational age and lower birth weight.[81]

Biomarkers and potential mediators of exposures to psychosocial stressors

Recent studies exploring the mechanisms relating prenatal exposure to psychosocial stressors and perinatal outcomes have focused on biologic measures of the stress response,

including corticotrophin-releasing hormone (CRH) and telomere biology. CRH plays a critical role in the physiologic response to stress by regulating release of adrenocorticotropic hormone from the anterior pituitary lobe, which in turn stimulates cortisol secretion from the adrenal cortex.[82] Evidence suggests positive associations between psychosocial stress and increased levels of CRH in maternal plasma during pregnancy.[83, 84] CRH produced in the placenta has been implicated as one of the primary endocrine mediators in the physiology of pregnancy and of spontaneous labor and studies suggest that it may be associated with increased risk of fetal growth restriction.[85, 86, 87]

Telomeres are DNA-protein complexes that cap the end of chromosomes and protect the cell's genomic stability.[87] Telomere length is a biomarker of cellular aging since telomeres shorten with cell replication. Telomere length is regulated by both genetic and environmental factors including chronic stress exposure. For example, shorter telomere length has been associated with conditions of chronic adversity, such as longer working hours,[88] chronic caregiving,[89] and lower socioeconomic status.[90] The mechanisms linking stress to telomere shortening are uncertain, but immune and inflammatory pathways along with oxidative stress production are suspected.[87] Shorter maternal telomeres have been associated with intrauterine adversity or growth restriction in animal[91, 92] and human[93, 94] studies. Researchers also seek to better understand the extent to which biomarkers of stress response such as telomere length mediate observed relationships between maternal perceptual and place-based stress exposures and developmental outcomes in offspring.[95]

Human studies on combined effects of psychosocial and environmental stressors during the prenatal period

A systematic review of human studies investigated the combined effects of prenatal environmental chemical exposures and maternal psychosocial stressors on perinatal outcomes found a paucity of research that addressed this question.[1] The review identified only 17 papers published between 1971 and 2013. Twelve studies examined smoking and environmental tobacco smoke (ETS) (and two also included alcohol consumption); four studies evaluated air pollution, traffic density and/or highway proximity; and one occupational study assessed benzene as the chemical exposure of interest. Most studies measured maternal prenatal psychosocial stress in terms of socioeconomic status (SES) ascertained from maternal characteristics, such as educational attainment, social class, household income, as well as neighborhood poverty level, and/or food affordability. Maternal race/ethnicity was also evaluated to a lesser extent. One study examined low prenatal mood (question from PRAMS) as a measure of psychosocial stress.

In general, prenatal chemical exposures exerted stronger effects on perinatal outcomes than did maternal stress measures; however, the effects of environmental chemicals on birth weight were more pronounced for women who were also experiencing higher psychosocial stress exposures (*e.g.*, low SES) during pregnancy. For this current review, we focus on environmental chemicals and psychosocial stressors excluding smoking and ETS.

Prenatal air pollution and psychosocial stressors

In two studies on air pollution, modest inverse associations between air pollution and birth weight were reported, with stronger effects observed in black than white women.[34, 96] Studies examining birth outcomes in relation to traffic-related pollution and SES were less consistent. Two studies on traffic-related air pollution (TRAP) effects and perinatal outcomes found an increased risk of preterm birth[37] and low birth weight,[97] with stronger effects of TRAP among pregnant women with lower compared to higher SES. A third study reported that pregnant women with higher SES were more likely to experience preterm birth, small for gestational age and especially low birth weight associated with TRAP.[98] Discrepancies between studies may be attributable to differences in SES variable definitions (*e.g.*, individual versus neighborhood measures of household income, poverty, unemployment, income from public assistance and maternal educational attainment), population differences in geography, as well as sample size given the modeling of interaction terms.

Occupational stress and benzene

A few studies have assessed the combined effects of work-related stress and occupational exposures to chemicals among pregnant women. One study found that work stress combined with occupational exposure to benzene was associated reductions in birth weight while each stressor alone did not show an association in a cohort of 792 pregnant women working at a large petrochemical company.[99]

Since the systematic review was conducted in 2013, we have identified 9 additional human studies that assessed the combined effect of maternal stress and prenatal environmental chemicals excluding smoking and ETS exposure.[37, 100–107] Taken together, these newer studies indicate that environmental chemical exposures such as air pollution may interact with maternal psychosocial stressors during pregnancy to adversely affect perinatal outcomes and have combined effects in either mediation analyses or their statistical interactions, yet few studies have quantitatively examined these associations beyond studies of air pollution.

Moreover, there is a limited number of studies that have examined a full range of prenatal psychosocial stressors as we have outlined above—factors such as discrimination, adverse events, depression, and past trauma in combination with environmental chemical exposures. Further, the range of environmental chemicals analyzed has been limited and has not included compounds such as flame retardants, PFASs, BPA, and phthalates, for which the main sources of exposure are diet and consumer products.

Biological mechanisms for a combined effect

Figure 1 presents a schematic of proposed biological mechanisms shared and possibly potentiated by the combined exposures to psychosocial and environmental stressors affecting perinatal outcomes. Environmental chemicals can enter the maternal circulation and/or reproductive tract secretions through direct skin/mucosal contact, ingestion or inhalation. Through the maternal circulation the chemicals may come into direct contact with the placenta and cause either direct tissue damage or subtler but equally harmful inflammatory

perturbations, interference with the microbial colonization of the placenta, as well as downstream epigenetic changes that may be either directly caused by the chemicals or be microbiome-mediated.[108] Placental inflammation and disturbances in maternal microbiomes have been implicated in low birth weight and preterm birth[109–111] and placental measures have been documented as moderators of most known maternal factors/processes that affect birth weight (maternal age, parity, SES, race/ethnicity).[112] In addition to directly harming the placenta, prenatal environmental chemical exposures can negatively influence maternal health, including possible effects on the kidney, liver, cardiovascular, metabolic and immune function, that can lead to or exacerbate gestational disease or hypertension, which in turn may lead to adverse perinatal outcomes. Other chemicals may lead to disturbances in the maternal microbiome,[113] which in turn is implicated in poor perinatal outcomes including adverse fetal growth outcomes and preterm birth.[109, 114]

Endocrine-disrupting chemicals may affect the hypothalamic pituitary adrenal (HPA), hypothalamic-pituitary-gonadal axis (HPG), hypothalamic-pituitary-thyroid (HPT) and gluco-psychosocial axes,[115, 116] which could translate into downstream immuno-endocrine disturbances and inflammatory activation. The molecular and systemic mechanisms of chemical damage to mother and placenta may be shared with and potentiated by the psychosocial stressors. Evidence shows the link between psychosocial stress and inflammation through activation of the HPA axis and an imbalance of pro-inflammatory cytokines and growth factors which are under neuroendocrine control at both systemic and reproductive tract levels.[117] Increased levels of cytokines have been detected in the peripheral blood in association with psychosocial stress and depression.[118119–122] Cytokines produced in the central nervous system in response to psychosocial stress can change responsiveness within the HPA axis, thus making it more vulnerable to other stressors and potentially provoking cytokine cascades in the periphery that are known to modulate different aspects of the reproductive function.[123,124, 125] Among the cytokines induced by psychosocial stress is IL-6, which has been implicated in spontaneous preterm delivery.[126]

The Environmental Influences on Child Health Outcomes (ECHO) Program

Environmental Influences on Child Health Outcomes (ECHO) is a research program launched by the National Institutes of Health in 2016 to understand the effects of a broad range of early environmental factors on child health and development. ECHO includes 84 existing longitudinal cohorts that will include more than 50,000 children from diverse racial, geographic, and socioeconomic backgrounds across the U.S. Together, many of these cohorts follow participants from before they are born through childhood and adolescence.

The greatest strength of ECHO is in its ability to pool data from multiple cohorts to increase sample sizes to the thousands rather than the more typical hundreds. This increase in statistical power will allow for examination of multiple exposures and multiple outcomes. An additional strength is the diverse geographic representation with varied demographics that exists across the ECHO cohorts. This variability will improve generalizability as well as the ability to compare regions with distinct psychosocial and environmental stressors (Figure 2).

The ECHO Data Analysis Center (DAC) developed several surveys to ascertain the collection of common data elements, including psychosocial stressors and environmental chemical exposures, from the ECHO cohorts. The cohorts specified if data elements were ever collected for mothers, fathers, and children and the timing of the data collection (*e.g.*, prenatal life stage). The current paper uses survey data on recruitment site locations (Module 2 release date: 01/31/2018); perinatal outcomes and psychosocial stressors in the mother's prenatal lifestage (Module 3 release date: 03/23/2018); and, assays for stress biomarkers and chemical exposures (Module 4 release date: 05/01/2018). All assays have already been run or the cohorts noted that they will be run in the future on banked specimens. The response rate for these surveys was 100%. SAS (version 9.3) was used for data analyses and ESRI ArcGIS (version 10.5.1) was used to map recruitment sites to the zip code centroid.

ECHO will also have the ability to examine various psychosocial and/or environmental stressors in relation to key perinatal outcomes. Here we describe exposure data from 80 ECHO cohorts that have data on both gestational age at birth and birthweight (Table 1, Figure 3). Sixty cohorts had at least one psychosocial stress measure. Specifically, 39 cohorts measured perceived stress (*e.g.*, perceived stress scale, racial discrimination, economic stress, psychological stress, social networks, interpersonal violence, neighborhood violence, and stressful life events); 17 have data on stress biomarkers (*e.g.*, any stress assay, CRH, cortisol, adrenocorticotropic hormone, and/or telomere length) in mothers (prenatal, infant lifestage) and/or infants; and, 50 cohorts have place-based measures of stress (*e.g.*, address data that may be combined with other datasets and/or built environment measures [food-related, activity-related and proximity to alcohol and tobacco outlets]). In addition, thirty-eight cohorts have data on environmental chemical exposure during the mother's prenatal lifestage. Specifically, 17 cohorts have measured levels of at least one persistent chemical (*e.g.*, perfluorinated compounds, PBDEs, PCBs, organochlorine pesticides, and/or organophosphate insecticides); 22 cohorts have measured non-persistent chemicals (*e.g.* phenols, phthalates); 15 cohorts have measured metals or metalloids; and 49 cohorts have data on air pollution (*i.e.*, PAHs, measured/estimated or planned indoor/personal air pollution, and/or measured/estimated or planned outdoor air pollution). Of note, thirty-eight cohorts have existing data on prenatal exposure to psychosocial stressors and environmental chemicals as well as perinatal outcome data.

Analyses of these combinations of factors will depend on the research question of interest. Potential options include investigations of effect modification (*i.e.*, statistical interaction) where the effects of environmental chemicals on perinatal outcomes may differ at among women with different levels of psychosocial stress. Mediation analyses may also be of interest to quantify whether environmental chemical exposures mediate the relationship between psychosocial stressors and perinatal outcomes (*e.g.*, low socioeconomic status leading to higher environmental chemical exposures and subsequent adverse outcomes) or vice versa (*e.g.*, environmental chemical exposures affecting psychological stress and subsequent adverse outcomes).

ECHO will also include coordinated measurement of chemical exposures from banked biospecimens (such as breast milk, placenta, microbiome samples, maternal and child hair, children's teeth, as well as urine and blood) collected by participating cohorts and program-

wide collection of additional questionnaire data on psychosocial stressors is planned. Biospecimens may also be used to assess biomarkers of stress response in addition to environmental chemical exposures. These data will be made publicly available to a broader community of children's health researchers, and provide unprecedented opportunities for multidisciplinary teams to conduct novel explorations and robust analyses that advance scientific understand of both social and environmental determinants of perinatal outcomes and children's future health.

Conclusion

The combined effects of environmental chemicals and psychosocial stressors are emerging as potentially important, yet understudied factors that affect perinatal and children's future health. We focused on perinatal outcomes as critical predictors of infant morbidity and mortality and as well as chronic diseases in adulthood. The ECHO cohort has a unique opportunity to evaluate nearly 40 cohorts with prenatal data on both chemical and psychosocial stress exposure. Additionally, the ECHO cohort has deeper, holistic and more robust measures of psychosocial stress, allowing analyses of the potential interactions and mediating pathways that have yet to be fully evaluated in the US. Analysis of this important data will allow for new insights into potential risk factors of low birthweight and preterm birth that can inform and shape new interventions and prevention strategies to improve child health across the U.S.

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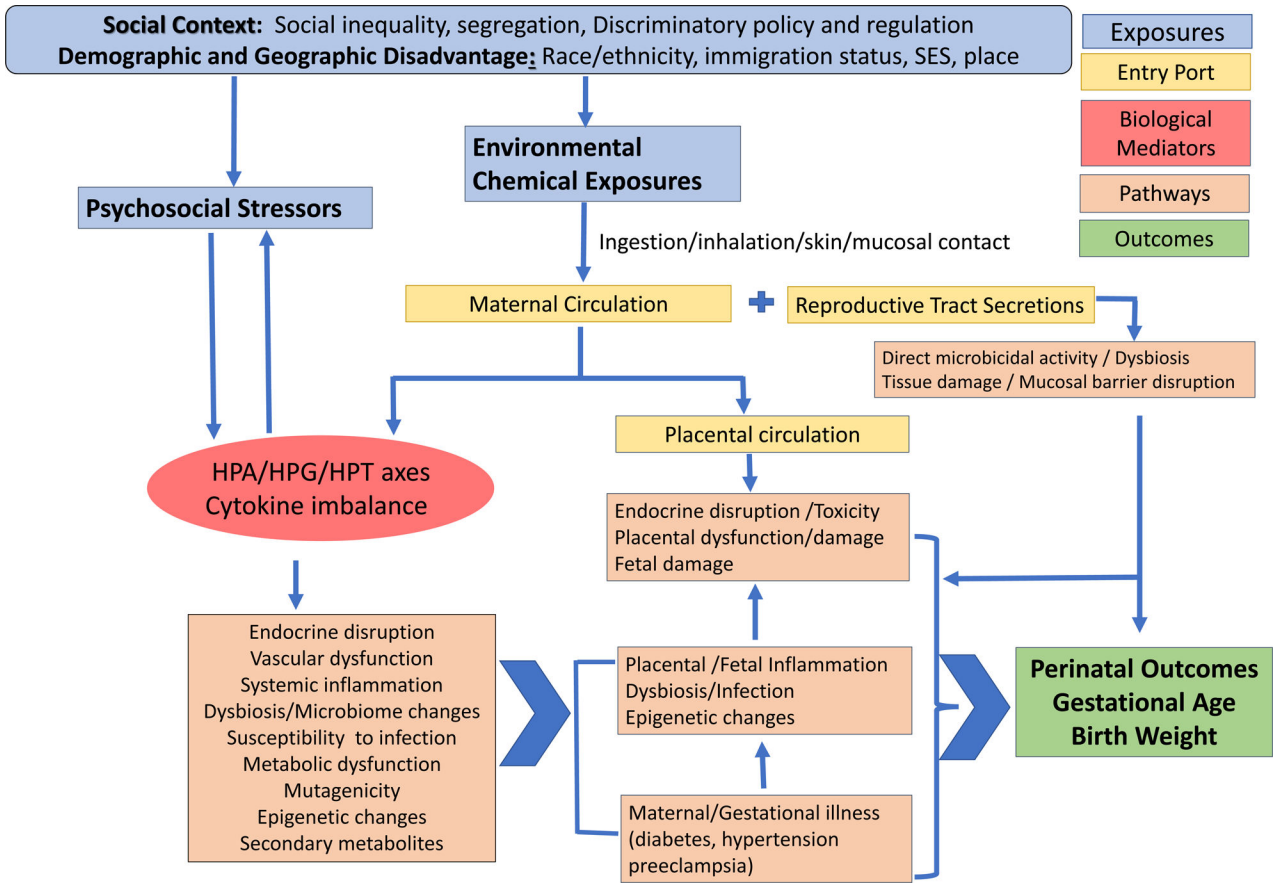

Figure 1:

Schematic of biological mechanisms shared and potentiated by combined exposures to psychosocial and environmental stressors that adversely affect perinatal outcomes

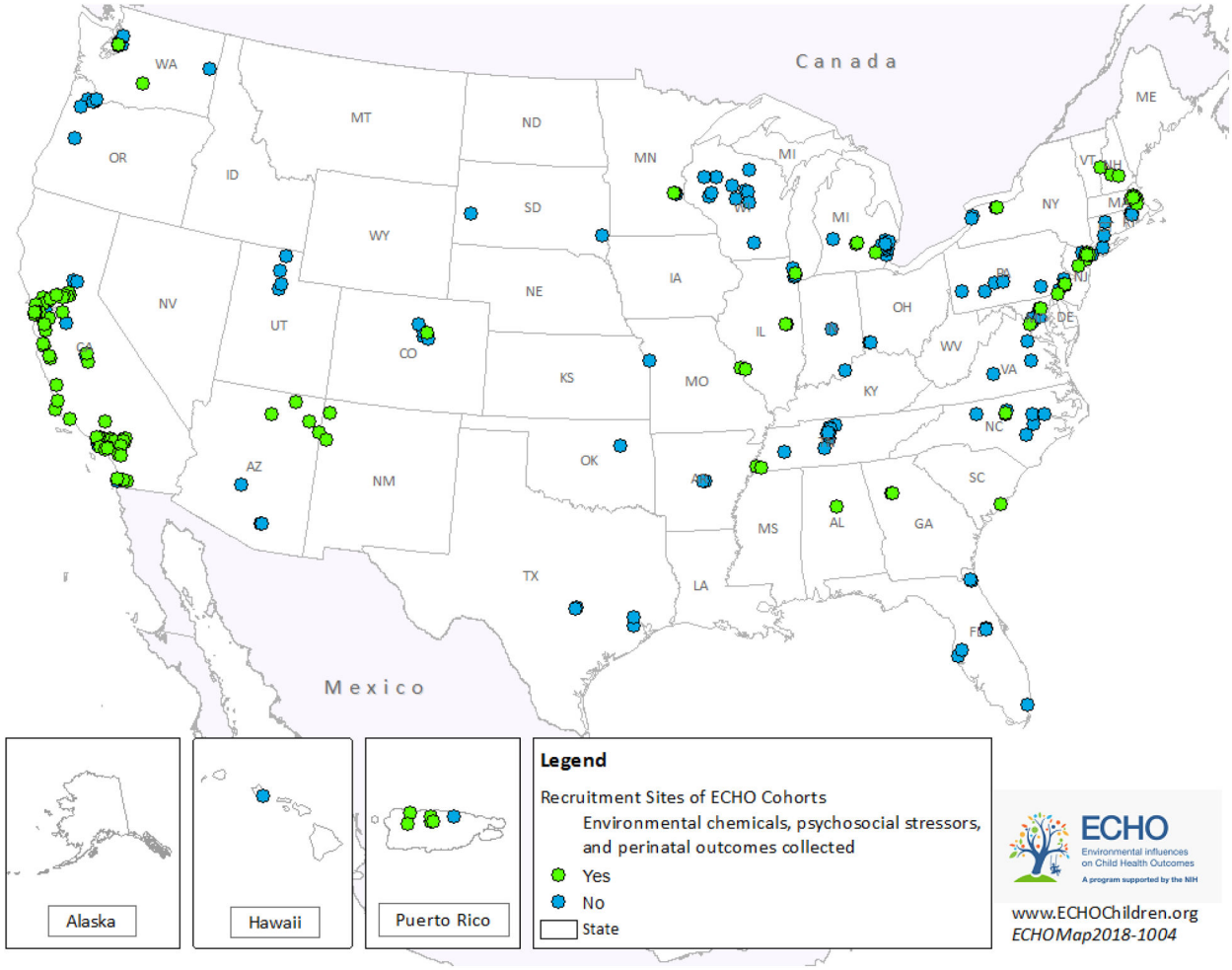

Figure 2:
Recruitment sites of ECHO cohorts

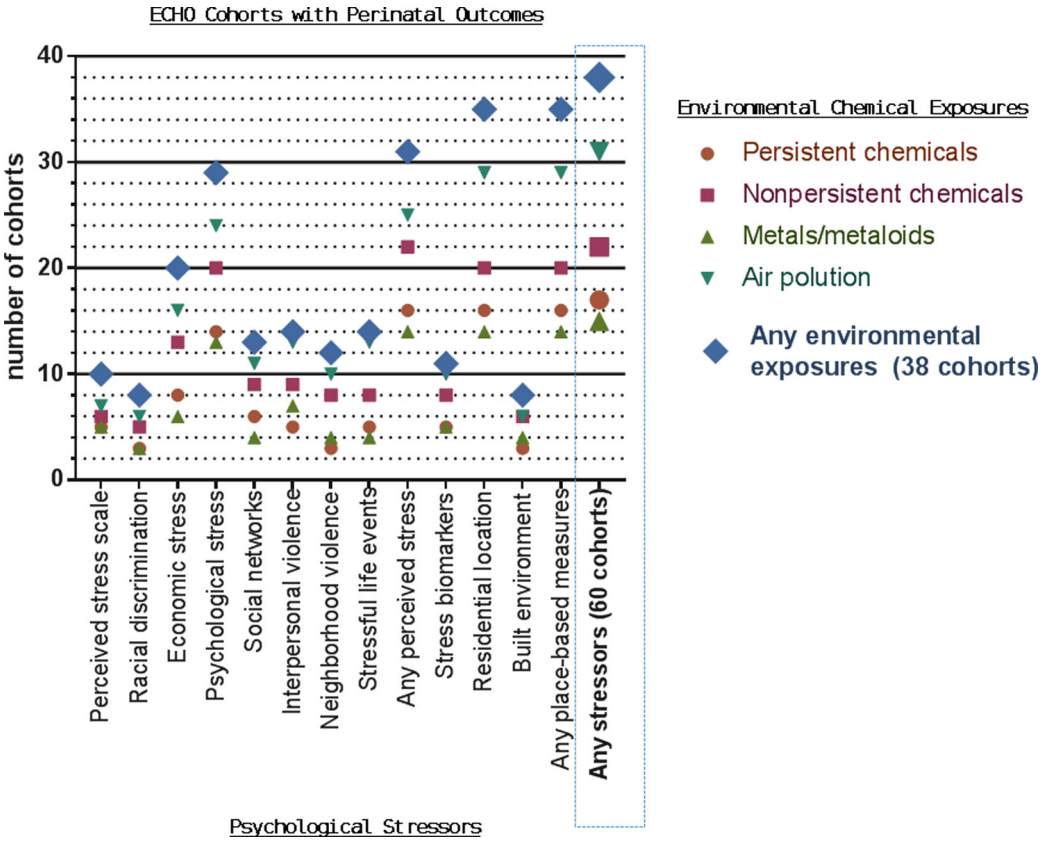

Figure 3:
ECHO cohorts with combined environmental and social stressor data

Table 1:

Breakdown of ECHO Pregnancy Cohorts by Environmental Chemical/Pollutant and Social Stressor Measures

			Persistent Chemicals					Non-persistent Chemicals		Metals		Air Pollution		
			Perfluorinated compounds *	Polybrominated diphenyl ethers *	Polychlorinated biphenyls *	Organochlorine pesticides *	Organophosphorus insecticides *	Phenols *	Phthalates *	Metals or metalloids *	PAHs *	Indoor/ personal air pollution **	Outdoor air pollution **	*Environmental exposures (any)*
	Total		9	13	10	8	6	19	16	15	15	16	29	38
Perceived Stressors	**Perceived stress scale**	12	4	5	3	2	2	5	3	5	2	4	6	10
	Racial discrimination	9	3	2	1	1	1	4	3	3	2	5	6	8
	Economic stress	26	5	5	3	2	5	11	8	6	8	10	15	20
	Psychological Stress	37	7	10	8	7	5	17	15	13	13	15	23	29
	Social networks	15	3	4	3	3	4	7	7	4	6	5	11	13
	Interpersonal violence	20	4	4	4	2	3	6	6	7	7	9	12	14
	Neighborhood violence	18	3	3	2	2	2	7	5	4	5	8	10	12
	Stressful life events	19	2	3	2	1	4	5	6	4	6	6	12	14
	Stress biomarkers †	17	4	3	2	2	3	6	6	5	6	7	10	11
Place-based Stressors	**Residential location** ‡	50	8	12	9	7	6	18	15	14	14	16	27	35
	Built environment §	9	2	3	2	1	2	5	4	4	3	4	5	8
	Stressors (any)	60	9	13	10	8	6	19	16	15	15	16	29	38

NOTE: Based on 80 cohorts with both gestational age and birth weight data; measures are for mother during prenatal life stage unless otherwise noted

*Assay already run + biospecimen banked (extant) to run assay in future

**Measured/ estimated or planned

†Any stress biomarker, Corticotropin-releasing hormone, Cortisol adrenocorticotropic hormone, Telomere length; Based on assays in mother's prenatal or infant lifestage AND child's infant lifestage

‡Address, geocoded address, zip code, census track, residential history

§Food-related environment, activity-related environment, proximity to alcohol/tobacco