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Associations between combined exposure to environmental hazards and social stressors at the neighborhood level and individual perinatal outcomes in the ECHO-wide cohort

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ABSTRACT

Limited studies examine how prenatal environmental and social exposures jointly impact perinatal health. Here we investigated relationships between a neighborhood-level combined exposure (CE) index assessed during pregnancy and perinatal outcomes, including birthweight, gestational age, and preterm birth. Across all participants, higher CE index scores were associated with small decreases in birthweight and gestational age. We also observed effect modification by race; infants born to Black pregnant people had a greater risk of preterm

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birth for higher CE values compared to White infants. Overall, our results suggest that neighborhood social and environmental exposures have a small but measurable joint effect on neonatal indicators of health.

1. Introduction

Perinatal outcomes such as low birthweight (LBW), small or large for gestational age (SGA or LGA), and preterm birth (PTB) can have lasting consequences for child and adult health. For example, infants born SGA may experience rapid weight gain during a period of "catch up" growth that is associated with a higher risk of obesity in childhood (Ong and Loos, 2006). SGA and LBW babies are also at higher risk of asthma, delayed neurodevelopment, and metabolic disorders later in adulthood (Jornayvaz et al., 2016; Longo et al., 2013; Nam and Lee, 2018; Ong and Loos, 2006; Savchev et al., 2013; van Wassenaer, 2005; Xu et al., 2014). Individual-level risk factors for adverse perinatal outcomes include younger and advanced age at delivery, low socioeconomic status, gestational diabetes or hypertension during pregnancy, malnutrition, stress or depression, and active and secondhand smoke exposures, among others (Goldenberg et al., 2008; Valero de Bernabé et al., 2004).

In addition to these important individual-level risk factors for adverse perinatal outcomes, epidemiologic studies have revealed that environmental and social stressors also increase risk at the neighborhood-level (Kane et al., 2017; Ncube et al., 2016). A recent meta-analysis of studies examining neighborhood deprivation scores and birth outcomes reported significant associations between higher scores and PTB and SGA (Vos et al., 2014). However, lower neighborhood SES has been linked to LGA in other studies (Boubred et al., 2020; Wentz et al., 2014). Similarly, a systematic review of built environment characteristics and birth outcomes found that decreased neighborhood built environment quality was associated with higher risk of adverse birth outcomes (Nowak and Giurgescu, 2017). Poor environmental conditions and higher prevalence of social stressors at the neighborhood level are reflective of the harmful legacy of policies such as redlining and residential segregation (Bailey et al., 2021; Groos et al., 2018; Gutschow et al., 2021). Thus, the existing literature supports the hypothesis that neighborhood environments, potentially a reflection of structural racism (Payne-Sturges et al., 2021), are risk factors for perinatal health outcomes, even when accounting for individual-level risk factors.

Few prior studies have examined neighborhood-level exposures to multiple environmental and social stressors in the same study population (Burris and Hacker, 2017). Examining these combined exposures is important for understanding how total neighborhood contexts can impact early life outcomes. Studies on the potential for neighborhood-level socioeconomic status to modify the relationship between air pollutants and birth outcomes suggest the interactions between neighborhood factors may be synergistic (Généreux et al., 2008; Mekonnen et al., 2021; Padula et al., 2014; Ponce et al., 2005; Yi et al., 2010). These studies investigated relationships between SES and single environmental exposures. For example, Généreux et al., 2008 included distance to roadways as the exposure of interest, Padula et al. (2014) included ambient carbon monoxide, nitrogen dioxide, and particulate matter, and Mekonnen et al. (2021) included particulate matter and ozone. A review of interactions between social determinants and environmental exposures on perinatal and childhood health outcomes found that 28 of the 39 (72%) review studies reported synergistic associations between social and environmental factors (Appleton et al., 2016). Of the perinatal outcome studies included in this review, all focused on a narrow set of environmental exposures (e.g., single pollutants or traffic-related air pollution). More recently, a systematic review and meta-analysis of interactions between prenatal exposure to exogenous chemicals and psychosocial stress on perinatal outcomes found that combined exposures to chemicals and stress were associated with more restricted fetal growth compared to either exposure alone among half the studies included (n = 10 studies in human populations), though there was limited evidence of interaction, potentially due to the variability observed among studies (Vesterinen et al., 2017).

Because no environmental hazard or social stressor is experienced singularly, it is important to investigate the effects of combined exposures that more accurately reflect real-world experiences on human health outcomes (National Institute of Environmental Health Sciences, 2018). In an earlier study leveraging data from a single cohort (Healthy Start, based in Colorado) that is a member of the Environmental influences on Child Health Outcomes (ECHO)-wide Cohort consortia, a relationship was observed between higher exposures to combined social stressors and environmental risks (assessed as a single exposure index value that assumed a multiplicative effect for environmental and social risk factors) and decreased birthweight (Martenies et al., 2019). However, questions remain regarding the effects of combined environmental and social stressors measured at the neighborhood level in other regions with potentially differing exposure levels. Birth outcomes such as PTB and LBW show regional trends in the United States, with risks being highest in the South and lower in the West, Midwest, and Northeast (Peterman et al., 2022). Differences in environmental hazards and social stressors at the neighborhood level may partially explain these trends.

Understanding the joint effect of neighborhood-level factors on perinatal outcomes is an important strategy for identifying public health interventions to reduce or prevent pediatric chronic diseases such as obesity or asthma, as these outcomes are associated with PTB, LBW, and SGA (Nam and Lee, 2018; Sonnenschein-van der Voort et al., 2014; Xu et al., 2014, p. 201; Zhang et al., 2018). In this expanded analysis, we leveraged data from the ECHO-wide Cohort to investigate the effects of combined environmental and social stressors on perinatal outcomes, including birthweight, PTB, SGA, and LGA. We replicated existing methods for assessing multiple exposures to develop a national-scale exposure index for cohort participants. This index includes indicators of environmental hazards and social vulnerability measured at the neighborhood level (operationalized as census tracts). Our hypothesis was that higher combined exposure index scores, which reflect worse neighborhood conditions, would be associated with lower birthweight and higher odds of PTB, SGA, and LGA.

2. Methods

2.1. Study population

ECHO combines 69 ongoing pediatric cohorts across the U.S. into one ECHO-wide Cohort. The goal of ECHO is to study environmental factors associated with child health (Gillman and Blaisdell, 2018). ECHO data include a combination of extant study-specific data with prospective data collection using a common protocol. The current analysis uses previously collected or extant data to evaluate the association between census tract-level social and environmental stressors and perinatal outcomes. Individual study cohorts were eligible for this analysis when more than 30 participants had both residential history during the period of interest (2010–2019) and perinatal outcome data. Cohorts that excluded or oversampled for adverse birth outcomes were included in this analysis and potential selection bias was evaluated through a series of sensitivity analyses. Participant addresses were geocoded in ArcGIS Pro Streetmap Premium Geocoder. Over 85% of addresses had a high-quality match (point or specific street address), which was required for inclusion in this analysis. We then assigned a census tract identifier to each participant address using the 2010 census tract boundaries.

All participants were consented into their original cohort studies using approved methods. All participants provided additional consent to share data with the ECHO consortium. The ECHO-wide Cohort Data

Collection Protocol was approved by either the ECHO single IRB or the ECHO cohort's local IRB.

2.2. Exposure assessment

Our primary predictor of outcomes in this study was a combined exposure (CE) index that characterized exposure to several environmental hazards and social stressors, at the level of the census tract. For the overall development of the index, we leveraged methods developed for CalEnviroScreen 3.0 (Cushing et al., 2015) with some modifications based on data availability. Details about these methods are included below.

2.2.1. Environmental exposure index (ENV)

The environmental exposure index was generated from continuous estimates derived from seven unique input datasets. The inputs were categorized under two broad themes: 1) air pollution and 2) the built environment. We developed an annual ENV score for the years 2010–2019. We briefly describe the data inputs here. Additional details about how we treated each variable in our index are provided in the supplemental materials.

Air pollutant data included annual average estimates of particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) and ozone from the Fused Air Quality Surface Downscaling (FAQSD) Files (US Environmental Protection Agency, 2021), toxic air emissions from EPA's Risk-Screening Environmental Indicators (RSEI) model (US Environmental Protection Agency, 2014), and traffic density at the census tract level from road segment spatial files from the U.S. Department of Transportation's Highway Performance Monitoring System (US Department of Transportation, 2020). Features of the built environment included tree canopy and impervious surfaces from the National Land Cover Database (Multi-Resolution Land Characteristics [MRLC] Consortium, n.d.) and proximity to Superfund sites (US Environmental Protection Agency, 2015).

Annual census tract values for raw inputs were converted to percentiles; percentile values were calculated by dividing the continuous distribution of a given variable into 100 equal intervals, assigning a new rank value for each estimate, and rescaling the distribution from 0 to 1. Rank values of input variables were then averaged to generate the air pollution score and the built environment score. If one or more inputs were available for each of the air pollution and the built environment scores, the environmental index for a given tract was calculated. Consistent with the formation of the CalEnviroScreen 3.0 index (Cushing et al., 2015), the final environmental index is the weighted average of an air pollution score and a built environment score: [(Air Pollution Score * 1) + (Built Environment Score*0.5) / 1.5]. Values for the ENV index could range from 0 to 1.

2.2.2. Social exposure index (SOC)

The social exposure index used in this analysis was borrowed from the Centers for Disease Control and Prevention's social vulnerability index (SVI) (Agency for Toxic Substances and Disease Registry, 2021). The SVI describes the relative vulnerability of every U.S. census tract based on 15 social factors and is intended to help public health officials and emergency response planners identify neighborhoods of greatest need before, during, and after a hazardous event. We elected to use these indicators because they represent the variety of social stressors and socioeconomic conditions that might influence birth outcomes via stress or access to care (Nkansah-Amankra et al., 2010). The SVI has recently been used in other studies to explore associations between social vulnerability and PTB (Givens et al., 2021) and pregnancy complications (Knupp et al., 2022). Additionally, because the SVI is an existing tool, national level data for all included indicators were available for the time periods included in our study.

The 15 social factors are grouped into four themes: 1) socioeconomic status, which includes the percentage of the population with income below the poverty level, the percentage of the population ages 25 and older without a high school diploma, the percentage of the population ages 16 and older who are unemployed and seeking work, and per capita income, 2) household composition and disability, which includes the percentage of the population ages 65 and older, the percentage of the population ages 17 and younger, the percentage of the population ages 5 and older with a disability, and the percentage of households with children that have a single parent, 3) minority status and language, which includes percentage of the population who identifies as other than non-Hispanic White and the percentage of the population ages five and older who speak English "less than well"; and, 4) housing type and transportation, which includes the percentage of housing units in buildings with ten or more units, the percentage of housing units that are mobile homes, the percentage of housing units with more than one person per room (crowding), the percentage of housing units with no vehicle, and the percentage of the population living in group quarters. The percentile ranking is first calculated for all raw input values and then an overall ranking is assigned to each tract which is the sum of the individual variable rankings with a higher value always indicating greater vulnerability. The overall ranking was used for the social exposure index in this analysis, with every census tract receiving a score between 0 and 1.

The SVI data were acquired from data products labeled as 2010, 2014, 2016, and 2018 but whose inputs are 5-year estimates from the American Community Survey (ACS) from 2006 to 2010, 2010–2014, 2012–2016, and 2014–2018, respectively. Considering the temporal span of the estimates, the SVI scores were applied to the social exposure index with more attention to estimate midpoint years. CDC data from 2010 were applied to 2010, 2014 to 2011–2012, 2016 to 2013–2015, and 2018 to 2016–2019.

2.2.3. Combined exposure index

The combined exposure (CE) index was calculated as the product of ENV and SOC indices (i.e., CE = ENV * SOC). We opted to use the multiplicative approach to calculate the combined exposure index for two reasons. First, the multiplicative approach is used in similar indices combining data on environmental and social exposures (August et al., 2021; Cushing et al., 2015; US Environmental Protection Agency, 2019). Second, there is evidence suggesting an interaction between neighborhood factors (e.g., neighborhood SES) and environmental exposures (e.g., air pollution) on individual-level health outcomes in adults and children (Appleton et al., 2016; Chi et al., 2016; Généreux et al., 2008; Hazlehurst et al., 2018; Padula et al., 2014; Ponce et al., 2005; Wing et al., 2017; Yi et al., 2010). Values for the final CE could theoretically range from 0 to 1. In practice, because the minimum values for ENV and SOC are >0, the range for the CE does not include 0.

Participants were assigned an annual average CE value based on the census tract of the reported residential address during pregnancy. When a pregnancy was contained in one calendar year, we used the annual value assigned to that census tract. When the pregnancy fell between two calendar years, we used a time-weighted average based on the number of months of pregnancy in each year. For participants who moved during the pregnancy, we similarly used a time-weighted average based on the number of months spent at each residence.

We also modeled CE as a categorical measure (as tertiles) to assess the dose-response relationship. When deriving tertiles, we compared the CE level of the census tract a participant resided in during their pregnancy to that of other census tracts where at least one other analytic cohort participant resided in the same year. For pregnant people who moved and for pregnancies that spanned two calendar years, we used CE values from the year or census tract when she experienced the longest gestation period.

2.3. Outcomes

The primary outcomes were birthweight (continuous, in grams), gestational age at birth (continuous, in weeks), and infant birthweight-for-gestational age z-score (continuous, no unit). We also included the following binary outcomes as secondary outcomes: low birthweight (LBW) (defined as birthweight <2500 g), preterm birth (PTB) (defined as gestational age at birth <37 weeks), small-for-gestational age (SGA) (defined as birthweight-for-gestational age <10th percentile), and large-for-gestational-age (LGA) (defined as birthweight-for-gestational age >90th percentile).

Data on outcomes of interest were collected by each participating cohort based on their established protocols. ECHO perinatal data come from several sources including parental medical records, child medical records from birth, and pregnant person/caregiver self-report. If available, outcomes were based on data from medical record abstraction. If medical records data were not available, outcomes were based on biological pregnant parent or other caregiver report.

For birthweight, the first weight measured after birth (ideally within hours of delivery) was used. Gestational age was based on a data quality hierarchy; estimates from ultrasounds (first or second trimester) were prioritized over gestational age estimates based on last menstrual period, followed by estimates at delivery and parental self-report. We calculated birthweight-for-gestational age z-score, SGA, and LGA using the Intergrowth-21st standard (Villar et al., 2014), which had been previously derived for all ECHO participants from whom data were available. We excluded non-singleton births, any participant missing data on singleton status or infant sex, or infants with a gestational age at birth <168 or >300 days according to the Intergrowth-21st guidelines.

2.4. Potential confounders/covariates

We defined confounders as covariates associated with the exposure (CE) and the outcome (infant birth outcomes) but not on the causal pathway. Confounders selected *a priori*, all assessed at the individual level, included pregnant person age at delivery (continuous), race (categories: White, Black, and other, which included Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and multiple race or other race), ethnicity (categories: non-Hispanic, Hispanic), educational level (categories: less than high school; high school degree, GED or equivalent; some college, no degree and above), tobacco use during pregnancy (categories: never/ever), and second-hand cigarette smoke exposure during pregnancy (categories: never/ever). The selection of these variables was based on the previous literature (Kane et al., 2017; Morello-Frosch et al., 2010; Ncube et al., 2016; Nowak and Giurgescu, 2017; Shmool et al., 2015; Vos et al., 2014) and informed by a directed acyclic graph (Fig. S3).

For pregnant person education level, we first used data reported during pregnancy and then imputed using education level from later life stages. For a small proportion of missing covariate data (3.7% for pregnant person race, 2.2% for pregnant person ethnicity, 3.7% for pregnant person education level, 17.2% for tobacco use during pregnancy, 31.5% for second-hand cigarette smoke exposure during pregnancy; Table 1), we assumed the data were missing at random and used the multiple imputation by chained equations method (10 imputations and each with 10 iterations) to impute these data (Donders et al., 2006; Stuart et al., 2009). We imputed data for the five pre-term/NICU cohorts and the 36 other cohorts separately. We calculated the regression estimates using the average of the 10 estimates derived from the imputed datasets, and we calculated the standard errors of the regression parameters using Rubin's rules.

2.5. Statistical analyses

2.5.1. Associations between the combined exposure (CE) index and perinatal outcomes

To examine the associations of CE with infant birth outcomes, we used linear regression (for continuous outcomes: birthweight, gestational age, and birthweight-for-gestational-age z-score) and Poisson

Table 1
Characteristics of mother-infant pairs (N = 13,046).

Pregnant person characteristics	
Age at delivery, years, mean (SD)	30.7 (5.5)
Missing	84
Race[a], n (%)	
White	8472 (67%)
Black	1670 (13%)
Asian	739 (6%)
Native Hawaiian or other Pacific Islander	67 (1%)
American Indian or Alaska Native	222 (2%)
Multiple race or other race	1390 (11%)
Missing	486
Ethnicity[a], n (%)	
Non-Hispanic	10196 (80%)
Hispanic	2565 (20%)
Missing	285
Marital status[a], n (%)	
Married or living with a partner	7377 (81%)
Widowed, separated, or divorced	345 (4%)
Single, never married, or partnered but not living together	1404 (15%)
Missing	3920
Educational level[a], n (%)	
Less than high school	916 (7%)
High school degree, GED or equivalent	1862 (15%)
Some college and above	9788 (78%)
Missing	480
Tobacco use during pregnancy[a], n (%)	
Never	10006 (93%)
Ever	790 (7%)
Missing	2250
Second-hand cigarette smoke exposure during pregnancy[a], n (%)	
Never	7394 (83%)
Ever	1542 (17%)
Missing	4110
County type (metro vs. non-metro) based on Rural-Urban Continuum Codes (RUCC), n (%)	
Metro counties (RUCC ≤3)	11091 (85%)
Non-metro counties (RUCC >3)	1955 (15%)
Infant characteristics	
Infant sex[a], n (%)	
Male	6798 (52%)
Female	6244 (48%)
Missing	<5
Singleton birth[a], n (%)	
Yes	11637 (96%)
No	499 (4%)
Missing	910
Birthweight, grams, mean (SD)	3171.2 (788.2)
Gestational age at birth, weeks, mean (SD)	38.0 (3.5)
Birthweight-for-gestational age z-score, mean (SD)	0.3 (1.0)
Missing[b]	1444
Preterm birth, n (%)	
Yes	1921 (15%)
No	11125 (85%)
Low birthweight, n (%)	
Yes	1654 (13%)
No	11392 (87%)
Large-for-gestational age[a,b], n (%)	
Yes	1882 (16%)
No	9720 (84%)
Missing[b]	1444
Small-for-gestational age[a,b], n (%)	
Yes	717 (6%)
No	10885 (94%)
Missing[b]	1444
Infant birth year, n (%)	
2010	289 (2%)
2011	1421 (11%)
2012	1461 (11%)
2013	1312 (10%)
2014	1444 (11%)
2015	1397 (11%)
2016	1139 (9%)
2017	1301 (10%)
2018	1560 (12%)
2019	1722 (13%)

Abbreviations: SD = standard deviation, GED = General Educational Development, NICU = newborn intensive care unit.

[a] For categorical covariates with missing observations, missing observations were not included in the denominator when deriving percentages for the categories with known values.

[b] For birthweight-for-gestational age z-score, large-for-gestational age, and small-for-gestational-age, there were 1444 missing due to non-singleton birth, missing singleton status or infant sex, or gestational age at birth <168 or >300 days.

regression with robust variance estimates (for binary outcomes: PTB, LBW, LGA, and SGA) models. We used generalized estimating equations (exchangeable correlation structure and robust variance estimates) to account for within-cohort clustering. We started with crude (unadjusted) models and adjusted for pregnant person age at delivery, race, ethnicity, education level, cigarette smoking during pregnancy, and second-hand cigarette exposure during pregnancy. We also estimated the Intraclass Correlation Coefficient to examine potential clustering of participants by study cohort (*i.e.*, the original study that recruited the participant) and census tract.

2.5.2. Effect modification analyses

We considered several potential effect modifiers. First, previous studies have suggested that pregnant person race or ethnicity or socioeconomic status may be important effect modifiers in the relationship between neighborhood factors and birth outcomes (Banay et al., 2017; Culhane and Goldenberg, 2011; Heo et al., 2019; Kothari et al., 2016; Masi et al., 2007). Therefore, we examined whether the associations of CE with infant birth outcomes differed by pregnant person race (White vs. Black), ethnicity (non-Hispanic vs. Hispanic), and education level (less than high school vs. high school degree, GED or equivalent vs. some college and above). We did not conduct subgroup analyses in infants born to pregnant people whose race was not White or Black due to the small sample size of these groups (6% for Asian, 1% for Native Hawaiian or other Pacific Islander, 2% for American Indian or Alaska Native, and 11% for "multiple race or other race"). Second, the relationships between environmental hazards or social stressors and perinatal outcomes may differ by infant sex (Ae-Ngibise et al., 2019; Deguen et al., 2021; Flom et al., 2018; Lakshmanan et al., 2015). Therefore, we included an analysis investigating effect modification by sex (male vs. female). Lastly, there may be differences in the effects of neighborhood-level contextual factors depending on urbanicity (Bertin et al., 2015; Kent et al., 2013; Li et al., 2020). In this third effect modification analysis, we stratified participants based on the 2013 Rural-Urban Continuum Code (RUCC) for the county in which they lived the longest during pregnancy (US Department of Agriculture, 2020). Due to limited numbers of participants with high (less urban) RUCC scores, we dichotomized RUCC scores as ≤ 3 (metro) vs > 4 (non-metro).

To examine potential effect modification, we examined the stratum-specific associations for each subgroup and included a product term of the potential effect modifier and the CE levels in the multivariable-adjusted linear models to derive interaction p-values. We considered a two-sided $p < 0.10$ as evidence for effect modification based on the p-value of the interaction terms.

2.5.3. Sensitivity analyses

We conducted several sensitivity analyses to assess the robustness of the findings. First, to examine the potential impact of selection bias, we excluded five cohorts in which all children were recruited from newborn intensive care units (NICU, n = 782) and one cohort in which no children were born preterm (n = 180). Second, we conducted a "leave one out" analysis to examine the influence of any one cohort on the study results. Third, to assess how much moving during pregnancy influences the results, we excluded participants who moved to different census tracts during pregnancy (n = 744). Fourth, to assess the impact that multiples had on the results for birthweight gestational age, LBW and PTB, we excluded participants who did not have singleton pregnancies (n = 499). (SGA, LGA, and birthweight-for-gestational age z-score were already restricted to singleton births.) Lastly, to serve as a comparison to our main models of the associations between CE and the perinatal outcomes, we modeled the ENV, SOC, and their interaction term in multipollutant models.

We conducted analyses using Stata (version 16.0; StataCorp). Except for the tests for interaction, we considered a two-tailed $p < 0.05$ as statistically significant.

3. Results

Of the 60,182 ECHO-wide Cohort participants who provided residential history data (n = 28,600), we included data from 13,046 infants recruited into 41 individual cohorts with both geocoded prenatal addresses and perinatal outcomes in our study period, 2010–2019 (Fig. S1). Participants lived in urban, suburban, and rural parts of the country (Fig. S2), though most (85%) lived in metropolitan counties. Infants included in our cohort were born between 2010 (2%) and 2019 (13%). Most infants, 52% of whom were male, were born to pregnant people who identified as White (67%) and non-Hispanic (80%), with at least some college education (78%). Most (96%) of the infants were singleton births. The mean (standard deviation) GA at birth was 38.0 (3.5) weeks with 15% of births considered preterm. On average, babies weighed 3171 (788) grams at birth, with 6% and 16% categorized as SGA and LGA, respectively. (Table 1).

Exposure to environmental hazards and social stressors varied among study participants. In general, there was more variability in the SOC component of the CE index than the ENV component (Table 2). The interquartile ranges for the SOC and ENV were 0.56 and 0.21, respectively. The raw exposure values used to calculate the ENV, SOC, and CE at the census tract level are summarized in Table S2. On average, combined environmental exposures were highest in the western United States and the Midwest (Illinois, Indiana, and Ohio). Social exposure index scores were highest in southern and western United States. Overall, the highest CE index scores were observed in the western United States, New York, and the Midwest (Fig. 1).

In our main analyses investigating associations between our CE index and perinatal outcomes, higher combined exposures were associated with lower birthweight, shorter gestational periods, and lower risk of LGA (Table 3). After accounting for individual-level covariates, a standard deviation (SD) increase in the CE (0.186) was associated with a 14.90 g (95% CI: -28.62, -1.18g) decrease in birthweight and a 0.08 week (95% CI: -0.12, -0.03 week) decrease in gestational age at delivery. An SD increase in CE was also associated with lower risk of LGA (RR = 0.94, 95% CI: 0.89, 1.00). When categorizing the CE into tertiles, we observed monotonic relationships, where associations between higher CE and shorter gestational age strongest in the third tertile (relative to the first tertile). We did not observe associations between the CE and the other perinatal outcomes.

In our stratified analysis, we observed effect modification by pregnant person race on associations between CE and LBW, PTB, and LGA

Table 2
Summary of ENV, SOC, and CE index values assigned to each participant based on the residential history. Values are time-weighted based on the number of months spent in a census tract. (N = 13,046).

Index	SD	Min	25th Percentile	50th Percentile	75th Percentile	Max
ENV	0.166	0.02	0.35	0.47	0.56	0.92
SOC	0.305	0.001	0.20	0.45	0.76	1.00
CEI	0.191	0.00005	0.06	0.18	0.39	0.83

Abbreviations: ENV: environmental exposure component of the CE index; SD: Standard deviation; SOC: social exposure component of the CE index; CEI: combined exposure index.

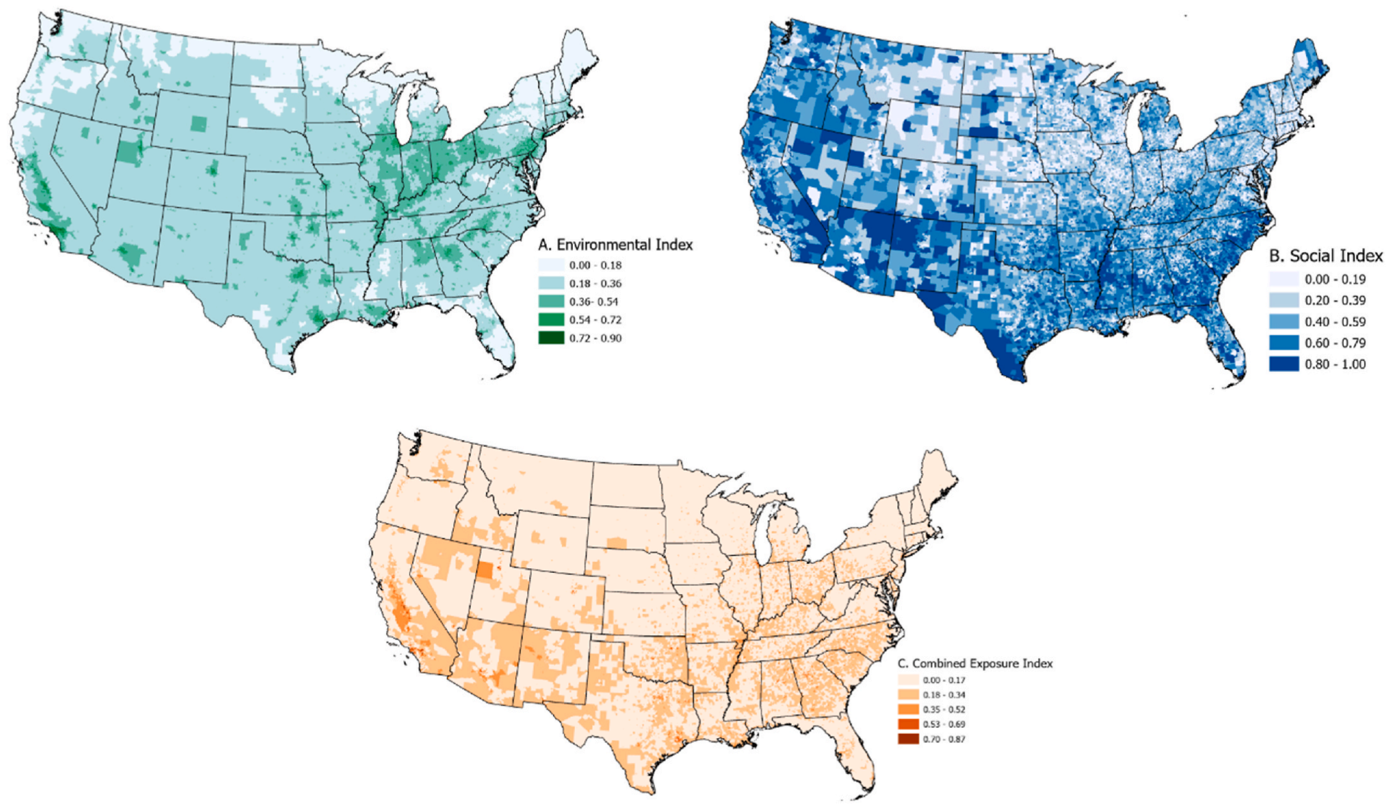

Fig. 1. Maps showing the average index scores by census tract across all years of the study.

Table 3
Associations (estimates and 95% confidence intervals) of combined exposure indices with infant birth outcomes (N = 13,046[a]). Adjusted associations significant at α = 0.05 have been bolded.

Outcome	Estimates	Levels of combined exposure			
		Tertile 1	Tertile 2	Tertile 3	Per SD increment (SD = 0.191)
		n = 4854	n = 4050	n = 4142	
Birthweight (grams)	Crude	Reference (0)	-48.19 (-85.31, -11.07)	-94.55 (-143.80, -45.30)	-50.23 (-72.75, -27.72)
	Adjusted[b]	Reference (0)	-24.47 (-53.77, 4.83)	-21.12 (-52.36, 10.12)	**-14.90 (-28.62, -1.18)**
Gestational age at birth (weeks)	Crude	Reference (0)	-0.12 (-0.22, -0.03)	-0.27 (-0.39, -0.15)	-0.15 (-0.20, -0.09)
	Adjusted[b]	Reference (0)	**-0.08 (-0.16, -0.003)**	**-0.12 (-0.23, -0.02)**	**-0.08 (-0.12, -0.03)**
Birthweight-for-gestational age z-score (n = 11,602)	Crude	Reference (0)	-0.05 (-0.11, 0.01)	-0.15 (-0.23, -0.06)	-0.08 (-0.11, -0.04)
	Adjusted[b]	Reference (0)	-0.01 (-0.06, 0.05)	-0.01 (-0.07, 0.06)	-0.01 (-0.04, 0.02)
Low birthweight	Crude	Reference (1)	1.07 (0.97, 1.17)	1.14 (1.02, 1.29)	1.07 (1.01, 1.14)
	Adjusted[b]	Reference (1)	1.05 (0.96, 1.14)	1.05 (0.97, 1.14)	1.03 (0.99, 1.07)
Preterm birth	Crude	Reference (1)	1.07 (0.99, 1.15)	1.13 (1.02, 1.26)	1.06 (1.01, 1.11)
	Adjusted[b]	Reference (1)	1.06 (0.99, 1.13)	1.07 (0.97, 1.17)	1.03 (0.99, 1.08)
Large-for-gestational-age (*n* = 11,602)	Crude	Reference (1)	0.94 (0.87, 1.03)	0.74 (0.64, 0.85)	0.86 (0.81, 0.91)
	Adjusted[b]	Reference (1)	1.01 (0.93, 1.10)	0.90 (0.79, 1.03)	**0.94 (0.89, 1.00)**
Small-for-gestational-age (*n* = 11,602)	Crude	Reference (1)	1.17 (0.96, 1.43)	1.37 (1.12, 1.67)	1.13 (1.02, 1.24)
	Adjusted[b]	Reference (1)	1.08 (0.90, 1.30)	1.07 (0.88, 1.30)	1.01 (0.93, 1.09)

Abbreviations: SD = standard deviation.
[a] Unless otherwise indicated.
[b] Adjusted for age at delivery, race, ethnicity, education level, tobacco use during pregnancy, and second-hand smoke exposure during pregnancy.

(Table 4, Table S3). Among Black pregnant people, the RR for LBW was 1.11 (95%CI: 1.01, 1.21) per SD increment in the CE, whereas among White pregnant people the RR was 0.99 (95% CI: 0.95, 1.03) (p value for the interaction: 0.02). Risks for preterm birth due to an SD increase in the CE among Black participants (RR = 1.08, 95% CI: 1.00, 1.16) were higher compared to White participants (RR = 0.99, 95% CI: 0.95, 1.03) as well (p value for the interaction: 0.06). Black pregnant people had a lower risk of LGA (RR = 0.81, 95% CI: 0.66, 1.00) compared to White pregnant people (RR = 0.96, 95% CI: 0.89, 1.02) for the same increase in CE (p value for the interaction: 0.03). Black pregnant people also experienced greater decreases in gestational age (β = -0.15 weeks, 95% CI: -0.25, -0.06 weeks) due to an SD increase in CE compared to White pregnant people (β = -0.01 weeks, 95% CI: -0.08, 0.06 weeks), although the p-value for the interaction term was not significant (0.11).

Pregnant person educational attainment, a proxy for socioeconomic status, modified the association between CE and gestational age (p-value for the interaction: 0.06). Among pregnant people with higher educational attainment (some college and above), an SD increase in CE was associated with a 0.07 week decrease (95% CI: -0.11, -0.03 weeks) in gestational age; among those with less than a high school education, CE

Table 4
Associations (estimates and 95% confidence intervals) of combined exposure indices with infant birthweight, gestational age at birth, low birthweight, and preterm birth: stratified analyses by race/ethnicity and education level. Estimates show the multivariable adjusted associations of per standard deviation (SD) increment in combined exposure indices with infant birth outcomes.

Groups	N	Birthweight (grams)	Gestational age at birth (weeks)	Low birthweight	Preterm birth
Overall (Adjusted[a] estimates from Table 3)	13,046	-14.90 (-28.62, -1.18)	-0.08 (-0.12, -0.03)	1.03 (0.99, 1.07)	1.03 (0.99, 1.08)
Pregnant person race					
White	8472	-1.58 (-20.83, 17.68)	-0.01 (-0.08, 0.06)	0.99 (0.95, 1.03)	0.99 (0.95, 1.03)
Black	1670	-39.48 (-82.98, 4.02)	-0.15 (-0.25, -0.06)	1.11 (1.01, 1.21)	1.08 (1.00, 1.16)
P-interaction	N/A	0.150	0.105	0.021	0.060
Pregnant person ethnicity					
Non-Hispanic	10,196	-9.20 (-25.54, 7.14)	-0.05 (-0.10, 0.01)	1.02 (0.98, 1.06)	1.03 (0.99, 1.08)
Hispanic	2565	-23.55 (-53.95, 6.85)	-0.14 (-0.25, −0.03)	1.07 (1.00, 1.16)	1.06 (0.97, 1.14)
P-interaction	N/A	0.602	0.563	0.727	0.874
Pregnant person education					
1: Less than high school	916	-24.07 (-69.07, 20.93)	-0.09 (-0.31, 0.13)	1.00 (0.89, 1.13)	1.05 (0.89, 1.24)
2: High school degree, GED or equivalent	1862	-35.84 (-65.79, -5.89)	-0.10 (-0.23, 0.03)	1.07 (0.98, 1.17)	0.98 (0.89, 1.07)
3: Some college and above	9788	-11.72 (-28.64, 5.20)	-0.07 (-0.11, -0.03)	1.04 (1.00, 1.08)	1.05 (1.00, 1.09)
P-interaction	N/A	0.192 (2 vs. 1)	0.261 (2 vs. 1)	0.174 (2 vs. 1)	0.686 (2 vs. 1)
		0.334 (3 vs. 1)	0.063 (3 vs. 1)	0.235 (3 vs. 1)	0.198 (3 vs. 1)
Infant sex					
Male	6798	-3.06 (-22.70, 16.59)	-0.05 (-0.11, 0.01)	1.01 (0.96, 1.06)	1.03 (0.99, 1.08)
Female	6244	-27.18 (-44.93, -9.43)	-0.11 (-0.17, -0.05)	1.06 (1.00, 1.12)	1.04 (0.98, 1.10)
P-interaction	N/A	0.968	0.483	0.576	0.336
Metro vs. non-metro counties					
Metro	11,091	-13.02 (-26.36, 0.31)	-0.08 (-0.12, -0.04)	1.03 (0.99, 1.07)	1.04 (1.00, 1.08)
Non-metro	1955	-108.39 (-201.16, -15.63)	-0.46 (-0.83, -0.10)	1.07 (0.93, 1.23)	1.11 (0.95, 1.30)
P-interaction	N/A	0.012	0.001	0.248	0.207

Abbreviations: GED = General Educational Development, N/A = not available.
[a] All models presented in this table were adjusted for age at delivery, race (if not stratified by race), ethnicity (if not stratified by ethnicity), education level (if not stratified by education level), tobacco use during pregnancy, and second-hand smoke exposure during pregnancy.

was not associated with a change in gestational age (β = -0.09, 95% CI: -0.31, 0.13). We also observed differences in the risk of PTB by education attainment, although p values for the interaction term between CE and education were not significant. The risk of preterm birth associated with an SD increase in the CE among pregnant people with some college education and above was 1.05 (95% CI: 1.00, 1.09); we did not observe associations between CE and PTB for those with less than a high school education or a high school degree or equivalent.

Urbanicity (metro counties vs. non-metro counties) modified the associations between CE and birthweight (p for the interaction = 0.01) and gestational age (p for the interaction = 0.001) (Table 4). Participants in non-urban counties experienced larger decreases in birthweight and gestational age relative to those living in urban counties. Among participants living in non-urban counties, an SD increase in the CE was associated with a 108.39 g decrease (95% CI: -201.16 g, -15.63 g) in birthweight and a 0.46 week (95% CI: -0.83, -0.10) decrease in gestational age. Comparatively, pregnant people living in urban counties had a 13.02 g decrease (95% CI: -26.36 g, 0.31 g) in birthweight and a 0.08 week (95% CI: -0.12, -0.04) decrease in gestational age per SD increase in CE.

We did not observe effect modification by either pregnant person ethnicity (Hispanic vs. non-Hispanic) or infant sex (Table 4, Table S3).

Our results were robust and generally not sensitive to the inclusion of cohorts recruiting exclusively from neonatal intensive care units, the inclusion of participants who moved during their pregnancies, the inclusion of multiple births, or the inclusion of cohorts that recruited only term infants (Table S4). In our main analysis, an SD increase in CE was not associated with the risk of LBW. After excluding NICU cohorts, an SD increase in the CE was associated with RR of 1.08 (95% CI: 1.01, 1.16) for LBW and after excluding participants who moved during pregnancy, an SD increase in the CE was associated with a RR of 1.04 (95% CI: 1.00, 1.08) for LBW. When excluding multiple births, the RR for LBW was 1.04 (95% CI: 1.00, 1.08). Similarly, an SD increase in CE was not associated with the risk of PTB in the main analysis. After excluding NICU cohorts, an SD increase in the CE was associated with RR of 1.08 (95% CI: 1.01, 1.16) for PTB and after excluding participants who moved during pregnancy, an SD increase in the CE was associated with a RR of 1.04 (95% CI: 1.00, 1.08) for PTB. When excluding multiple births, the RR for LBW was 1.04 (95% CI: 1.00, 1.08). Point estimates for other perinatal outcomes were similar across our sensitivity analyses (Table S4 and Table S5). In leave-one-cohort-out models, we found that most estimates were similar to the overall estimates (Figs. S4 and S5).

When modeling the ENV and SOC components of the CE as separate predictors, we observed similar trends in the associations between ENV and birthweight and LGA and SOC and gestational age (Table S6). In two-pollutant models (ENV + SOC) that were adjusted for all individual covariates, an SD increase in ENV was associated with a 20.44 g decrease (95%CI: -39.82 g, -1.05 g) in birthweight and a RR of 0.89 (95%CI: 0.82, 0.96) for LGA. An SD increase in SOC was associated with 0.07 week decrease (95% CI: -0.11, -0.03) in gestational age.

4. Discussion

Although data on environmental and social stressors are widely available, few studies have examined their combined effects on birth outcomes. Existing studies have been limited to single metropolitan areas or states, where the range of exposures may be reduced relative to the nation as a whole. To address this knowledge gap, we leveraged the large ECHO-wide cohort data set to examine how the neighborhood environmental and social context influences perinatal health. In a study of 41 cohorts from across the United States, we used an index summarizing combined exposures to multiple stressors and examined associations with perinatal outcomes. The use of a combined index that considered environmental hazards and social stressors allowed us to capture several components of the neighborhood context in a single construct and use a categorical analysis to examine potential dose-response relationships. Consistent with our original hypothesis, we found that higher combined exposures were associated with poorer outcomes, including lower birthweight and shorter gestational age. However, we observed no associations with other outcomes of interest, including birthweight for gestational age z-score, preterm birth, low birthweight, and small-for-gestational age in our primary analysis of the full cohort. In stratified analyses, we found some evidence of effect modification by race, pregnant person education, and urbanicity for some outcomes included in our analysis. When examining effects for the two component scores as separate predictors, ENV scores were associated with gestational age and LGA and SOC scores were associated with PTB, suggesting different components of the index may be driving some of the observed associations for the particular set of neighborhood-level exposures we are considering.

Overall, our findings are generally consistent with previous studies relying on similar index-based methods to capture multiple stressors. In the Colorado-based Healthy Start cohort study that motivated this expanded analysis, combined exposures (assessed as an index) were associated with lower birthweights (Martenies et al., 2019). Similar results were observed in California, where components of the CalEnviroScreen tool (pollution burden, particulate matter exposures, and drinking water contamination scores) were associated with higher odds of preterm birth (Huang et al., 2018). In Fresno, CA, higher pollution scores were associated with increased odds of preterm birth; notably, the effects of environmental exposures were stronger in areas of low socioeconomic status (Padula et al., 2018). In a recent paper using the Childhood Opportunity Index, which measures favorable social, educational, and environmental conditions within a neighborhood, higher scores were associated with higher birthweight and lower risk of intrauterine growth restriction among infants in upstate New York (Appleton et al., 2021). Our analysis, which includes data from several regions of the country, adds to the growing body of evidence suggesting a combined effect of neighborhood-level environmental and social factors on perinatal outcomes.

Although the effect estimates we observed in this study were small, they are indicative of potentially large risks when applied to the full population of infants born in the United States. In our cohort, an SD increase in the CE was associated with a 15 g decrease in birthweight. Between 1990 and 2012 the mean birthweight among first-born singleton infants decreased by 67 g on average (Tilstra and Masters, 2020). Small decreases in mean birthweight at the population level shift the overall birthweight distribution, resulting in more infants born with LBW. In recent years, rates of singleton LBW births have increased in the United States, driven primarily by the increase in the rate of moderately LBW births (1500–2499 g) (Womack et al., 2018). The risks in adulthood to infants born preterm or LWB are well documented and include cardiovascular and respiratory diseases (Luu et al., 2016; Visentin et al., 2014). Although further evidence is needed to draw conclusions, our results suggest neighborhood-level exposures may be contributing to these overall trends and indicate there may be important policy approaches available to improve both perinatal health and health later in life.

Questions regarding the joint effects of social stressors and environmental exposures, particularly during the prenatal period, on health outcomes are of growing interest (Koman et al., 2018; Padula et al., 2020). Neighborhood conditions are known to be associated with stress (Boardman, 2004), which is a risk factor for adverse birth outcomes (Dole et al., 2003; Hobel et al., 2008; Nkansah-Amankra et al., 2010). However, the specific mechanisms underlying these effects are still not fully understood. Oxidative stress and inflammation have been identified as shared pathways for both environmental factors and social stressors to jointly impact perinatal outcomes (Erickson and Arbour, 2014; Rakers et al., 2020). Both pregnant person cortisol, which is an indicator of psychosocial stress, and isoprostanes, which are biomarkers of oxidative stress, are associated with perinatal outcomes including preterm birth and birthweight (Eick et al., 2020; Guardino et al., 2016; Rosen et al., 2019). An alternative hypothesis is that social stressors mediate or modify associations between environmental exposures and perinatal outcomes (Brunst et al., 2018; Deguen et al., 2021; Erickson et al., 2016). Our findings and those of other similar studies suggest there may be a combined effect of these types of exposures on prenatal and infant health and that future studies should aim to elucidate the mechanisms driving these associations.

Importantly, our study provides additional evidence that environmental hazards and social stressors assessed at the neighborhood level may be contributing to health disparities in infant outcomes by race. Our current analysis does not allow us to fully examine disparities using the framework presented by Ward et al. (2019), but our results are consistent with other studies of disparities by race. Pregnant people who identified as Black in our study had higher relative risks of PTB and LBW compared to White pregnant people; they also experienced greater decreases in gestational age associated with higher CE levels compared to White participants. Disparities in LBW and PTB across racial groups in the United States are well documented (Blumenshine et al., 2010; Grobman et al., 2018; Lu and Halfon, 2003). The etiology of these disparities is still not fully understood (Grobman et al., 2018), but factors such as psychosocial stress or structural racism may contribute to adverse perinatal outcomes (Almeida et al., 2018). For example, a recent meta-analysis reported that higher levels of segregation were associated with greater odds of PTB and low birthweight among Black pregnant people but generally not among White pregnant people (Mehra et al., 2017). Given the complicated relationships between race, psychosocial stress, and neighborhood quality, further elucidation of the pathways between neighborhood context and birth outcomes is needed to better inform public health strategies to address these disparities.

For both birthweight and gestational age, we found evidence that urbanicity was an effect modifier. Lower birthweights and shorter gestational periods associated with combined exposures for participants living in rural areas might reflect differences in access to health care and other resources. Access to obstetric care in rural counties in the United States has decreased over the last decades (Hung et al., 2017), mirroring trends in overall health care access (Douthit et al., 2015). Losing access to obstetric care has been associated with more preterm births in the United States (Kozhimannil et al., 2018) and will be an important consideration in future work examining the rural neighborhood context for perinatal outcomes.

We also observed effect modification by pregnant person educational attainment in the unexpected direction. In our study, associations between CE scores and decreases in gestational age were observed among pregnant people with higher educational attainment. These results may be driven by the large number of participants we have living in metropolitan areas where the relationship between environmental exposures and socioeconomic status (SES) is sometimes counterintuitive. For example, higher environmental exposures have been documented in higher SES areas in New York City and in Denver, Colorado (Martenies et al., 2019; Savitz et al., 2014; Shmool et al., 2015). Additional clarification of these findings is warranted to assess how SES and urbanicity might jointly modify these associations.

There are important limitations to note when interpreting the results of our study. First, key exposure data were not available for all years, so we relied on imputation or other methods to fill temporal gaps. Second, limitations in the available exposure data prevented us from using a finer temporal resolution than annual averages. For many of the exposures included in our analysis, there may be important impacts based on the timing of exposure during pregnancy that are not captured by our exposure assessment methods. Third, we did not include every available environmental data set when developing our index. For example, to capture risks associated with air toxics, we opted to use the RSEI, which is updated each year based on the Toxic Release Inventory. An alternative data source, which includes additional pollutants but is updated less frequently, is the National Air Toxics Assessment (NATA) data set which includes additional sources of air toxics. Exclusion of this data set may have influenced census tract rankings. Fourth, due to differences across states in how environmental data are collected and made available, we were not able to include all potentially relevant environmental exposures, e.g., our index did not include pesticides or water contaminants that may influence perinatal health outcomes (Huang et al., 2018). Fifth, due to limitations in sample size, we were not able to examine effect modification for all race and ethnicity groups. Previous work has demonstrated that exposures to environmental hazards and incidence of adverse birth outcomes are higher among Asian, Native Hawaiian, and Pacific Islander populations (Dongarwar et al., 2021; Grineski et al., 2019; Payne-Sturges et al., 2022) and American Indian or Alaska Native populations (Dashner-Titus et al., 2018; Lewis et al., 2015). Sixth, we used census tracts as our unit of analysis. Census tracts may not be the most meaningful unit of analysis for investigating the role systemic racism plays in health outcomes; boundaries that reflect the scope of public policy (e.g., school districts or municipal boundaries) may be more appropriate for some exposures (Riley, 2018). Lastly, the use of an index is helpful for reducing the dimensionality of our data set but does not allow us to identify the specific exposures driving these associations.

Despite these limitations, our study had several strengths. First, we were able to leverage the large ECHO-wide cohort to include data from more than 10,000 participants living throughout the United States. Second, we were able to evaluate exposures from several geographic regions of the country. The geographic diversity in our study population is an improvement over previous studies that have focused on single metropolitan areas or states. Third, we were able to leverage a comprehensive data set on participant residential history that accounts for moving during pregnancy. This allowed us to time-weight our exposures during pregnancy and assess the influence of moving on our study results. Lastly, we were able to use medical record data to assess our outcomes of interest and limit the challenges associated with self-reported data.

Moving forward, these data will have value for exploring how environmental and social factors may jointly impact childhood health. However, several recommendations follow from our work to improve future studies. First, we need better national-level environmental and social stressor datasets that capture the variety of hazards to which we are exposed. For example, national-level datasets on water pollutants and pesticides are needed to expand the environmental exposure index (ENV) to cover multiple pathways of exposure. Additionally, data sets on crime and other issues that relate to perceived safety are needed to reflect additional pathways by which social determinants influence perinatal health. Second, whenever possible, national data sets should reflect the temporal variability in exposures. Data averaged to the annual level cannot be linked to sensitive windows during gestation. However, given how environmental and social data are collected, this may be challenging for several indicators included in this index. Lastly, more work is needed to assess how these exposures may interact. Future studies should leverage recently developed statistical methods, e.g., Bayesian Kernel Machine Regression or quantile-based g-computation, to address prenatal exposure mixtures to better identify the effects of components within the mixture on perinatal outcomes (Bobb et al., 2015; Harley et al., 2017; Keil et al., 2020; Valeri et al., 2017).

5. Conclusions

Our study adds to the growing body of evidence suggesting there are important effects of multiple exposures on perinatal health outcomes. Our exposure assessment methods captured several of the key environmental and social stressors associated with perinatal health. By leveraging the ECHO Cohort, which includes participants enrolled in studies across the country, we were able to demonstrate that the associations observed in previous studies were relevant on a national scale. Although the effect sizes observed here were generally small, they represent potentially large impacts when applied to the entire United States population. While our use of an exposure index does not allow us to determine the nature of the interactions between these exposures, our results support the need for additional datasets that better capture the range of hazards that exist at the neighborhood scale and more research to assess the potentially complex ways in which these exposures influence perinatal outcomes and infant health.

Declaration of competing interest

The authors have no interests to declare.

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Appendix A. Supplementary data

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