RESEARCH

Using non-parametric Bayes shrinkage to assess relationships between multiple environmental and social stressors and neonatal size and body composition in the Healthy Start cohort

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Abstract

Background: Both environmental and social factors have been linked to birth weight and adiposity at birth, but few studies consider the effects of exposure mixtures. Our objective was to identify which components of a mixture of neighborhood-level environmental and social exposures were driving associations with birth weight and adiposity at birth in the Healthy Start cohort.

Methods: Exposures were assessed at the census tract level and included air pollution, built environment characteristics, and socioeconomic status. Prenatal exposures were assigned based on address at enrollment. Birth weight was measured at delivery and adiposity was measured using air displacement plethysmography within three days. We used non-parametric Bayes shrinkage (NPB) to identify exposures that were associated with our outcomes of interest. NPB models were compared to single-predictor linear regression. We also included generalized additive models (GAM) to assess nonlinear relationships. All regression models were adjusted for individual-level covariates, including maternal age, pre-pregnancy BMI, and smoking.

Results: Results from NPB models showed most exposures were negatively associated with birth weight, though credible intervals were wide and generally contained zero. However, the NPB model identified an interaction between ozone and temperature on birth weight, and the GAM suggested potential non-linear relationships. For associations between ozone or temperature with birth weight, we observed effect modification by maternal race/ethnicity, where effects were stronger for mothers who identified as a race or ethnicity other than non-Hispanic White. No associations with adiposity at birth were observed.

Conclusions: NPB identified prenatal exposures to ozone and temperature as predictors of birth weight, and mothers who identify as a race or ethnicity other than non-Hispanic White might be disproportionately impacted. However, NPB models may have limited applicability when non-linear effects are present. Future work should consider

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a two-stage approach where NPB is used to reduce dimensionality and alternative approaches examine non-linear effects.

Keyword: Birth weight, Adiposity, Environmental mixtures, Social stressors, Air displacement plethysmography, Non-parametric Bayes shrinkage

Background

Birth weight and adiposity at birth are important neonatal indicators of infant, childhood, and long-term health. At the population level, seemingly small shifts in mean birth weight over the past few decades have been associated with population-level increases in the proportion of neonates born low birth weight (LBW; < 2500 g) or small for gestational age (SGA; below the 10th percentile for each completed week of gestation) [1–3]. SGA and LBW babies are at higher risk of childhood obesity, asthma, delayed neurodevelopment, and metabolic disorders later in adulthood [4–10]. Similarly, adiposity at birth, which is a measure of the proportion of body mass that is fat mass, is a potentially important predictor of obesity and metabolic disease risk later in life [11, 12].

The existing literature demonstrates the ability of both individual-level and neighborhood-level exposures to influence birth weight and adiposity in the neonatal period. Individual-level factors include maternal characteristics such as age and race/ethnicity, maternal behaviors such as active smoking and physical activity, and metabolic factors such as obesity or gestational diabetes [13–15]. At the neighborhood level, both environmental and social factors have been linked to these neonatal outcomes. These factors include higher neighborhood deprivation index scores [16], low neighborhood affluence [17], poor quality built environments (e.g., higher rates of vacant buildings or proximity to major roadways) [18, 19], and higher ambient air pollutant exposures [20–24].

Although there is evidence to suggest that both social and environmental factors are associated with birth weight and adiposity, few studies have examined the combined effects of exposures to hazards in multiple domains (*i.e.,* physical, social, and chemical exposures). There is growing interest in understanding the joint effects of both environmental hazards and social stressors to understanding how total neighborhood contexts can impact early life outcomes [25, 26]. Although the underlying mechanisms have not been fully elucidated, there are several hypothesized pathways by which prenatal exposure to environmental hazards and social stressors might impact neonatal growth and development. For example, oxidative stress and inflammation are pathways common to both environmental hazards and social stressors [27, 28]. Alternatively, social stressors experienced during the prenatal period may modify the effects

of environmental hazards [29–31]. Evidence from previous studies suggests there may be important interactions between neighborhood factors environmental and social hazards, and that the effect of these combined stressors on birth outcomes may be synergistic [32–35]. Additionally, neighborhood environmental and social conditions reflect the legacy of structural racism in the United States perpetuated by redlining and racial segregation [36–39]. Thus, investigating the combined effects of neighborhood level factors that influence health represents an important opportunity to address longstanding health disparities.

We previously tested associations between neonatal outcomes combined prenatal factors at the neighborhood level in the Healthy Start cohort using an index-based exposure assessment method [40]. We reported lower birth weights and lower adiposity for infants born to mothers with higher combined exposure index scores after controlling for key individual-level risk factors. Our index-based approach provided information on where public health interventions might be most effective for improving neonatal outcomes. However, the use of an index did not allow us to identify which exposures or combination of exposures were driving these associations and thus identify the underlying etiologic agent. Alternative approaches that accommodate large numbers of exposure variables and potential interactions between these exposures are needed to better characterize these associations and identify targets for future public health interventions [41].

Using data from the Healthy Start cohort, we expanded upon our previous study by employing a non-parametric Bayes shrinkage (NPB) approach to examine linear associations between our neighborhood-level determinants and neonatal outcomes. For this data set, we needed to identify a statistical method that would be capable of handling variable selection among potentially highly correlated exposures within the context of interactions between exposures and between exposures and covariates. NPB is designed to facilitate selection among a large number of correlated predictors in a single model, thus having an advantage over traditional multipollutant models [42, 43]. We compared the results of our NPB model to single-exposure models (linear regression models). Because NPB is a linear modeling framework, we also utilized generalized

additive models to explore potential non-linear exposure–response relationships. Based on the results of our previous study [40], we hypothesized that specific social exposures (*e.g.,* neighborhood level socioeconomic status) within the prenatal exposure mixture measured were driving associations with lower birth weight and adiposity.

Methods

Study population and study area

We used data from the ongoing Healthy Start pre-birth cohort study for this analysis. Details on the Healthy Start cohort are available elsewhere [44]. Briefly, pregnant women aged 16 or older expecting singleton births were recruited from the University of Colorado Hospital outpatient obstetrics clinics between 2009 and 2014. Two prenatal study visits that included a physical exam and questionnaires were conducted at median 17- and 27-weeks of gestation; additional data were abstracted from medical records. Our analysis did not exclude infants based on their term birth status (*i.e.,* we included pre-, full- and post-term births). All mother–child dyads who had an address at enrollment within the study area were eligible for this analysis. The Healthy Start study protocol was approved by the Colorado Multiple Institutional Review Board.

Although the Healthy Start study originally recruited participants from the nine county Denver metropolitan area, the study area for this analysis consisted of most census tracts within a smaller three county area (Adams, Arapahoe, and Denver counties). These counties were included due to the availability of exposure data (described next). We excluded the two eastern most census tracts within these counties because they were rural and not considered part of the metropolitan area. Census tracts were chosen to represent neighborhoods as they were the smallest spatial unit for which reliable exposure data were available.

Exposure assessment

We selected our environmental and social exposures based on the indicators used by the CalEnviroScreen tool [45, 46] with some additional area-specific variables to reflect sources relevant to Denver, CO. Because our research question focused on the neighborhood context, all exposure variables were assessed at the census tract level and assigned to participants based on their address at the time of enrollment into the Healthy Start study. We briefly describe our exposure variables below. Additional details on our exposure variables are available elsewhere [40].

Ambient air pollution and temperature

We included two measures of ambient air pollution, fine particulate matter ($PM_{2.5}$) and ozone (O_3) and a variable for temperature. Monitoring data collected between 2009 and 2014 were obtained from the US Environmental Protection Agency [47]. Daily measurements at each monitor were averaged to biweekly concentrations. For $PM_{2.5}$ and temperature we used the mean of all 24-h measurements and for O_3 we used the mean of all daily 8-h maximum concentrations recorded during the two-week period. We used ordinary kriging to estimate biweekly measurements at each census tract centroid. Biweekly air pollutant and temperature exposures were then assigned to each participant based on the address at enrollment and the timing of conception and delivery and averaged over the duration of the pregnancy.

Built environment characteristics

We included nine exposure variables related to the built environment. The temporal resolution for these data was usually one year; we assumed minimal change in these variables between the start and end of our study period (2009–2014) These included: the mean percent tree cover and mean percent impervious surface within the census tract from the 2011 National Land Cover Database [48]; the mean annual average daily traffic (AADT) of road segments within the census tract from the Highway Performance Monitoring System [49]; and the minimum distance (in km) from the census tract centroid to hazardous land use sites, including Toxic Release Inventory sites, National Priority List sites, waste management sites, major emitters of criteria pollutants, confined animal feeding operations, and oil and gas wells [50–52].

Social stressors

Social stressor variables were intended to capture socioeconomic status (SES), demographic trends, and susceptibility at the neighborhood level. We included five variables from the 2010–2014 American Community Survey: the percentage of the population with less than a high school diploma, that was unemployed, and that identified as a race/ethnicity other than non-Hispanic white and the percentage of household speaking limited English or in poverty [53]. Crime incidence data were available from the Inter-university Consortium for Political and Social Research and the Denver Open Data Catalog [54, 55]. We used these incidence data to calculate 5-year rates of violent crimes and property crimes for each census tract. Data to calculate census-tract level hospitalization rates for respiratory and cardiovascular diseases came from the Colorado Hospital Association.

Outcomes

Our two outcomes of interest were birth weight and adiposity at birth. Birth weight was measured at the time of delivery or was abstracted from medical records. Fat mass and fat-free (lean) body mass were measured within three days of birth using air displacement plethysmography (PEA POD, COSMED, Rome, Italy). Additional details on the PEA POD measurements for the Healthy Start cohort are available elsewhere [44]. We calculated adiposity (% fat mass) as fat mass divided by total body mass [56].

Covariates

We selected our model covariates a priori by considering those included in our previous study [40] and other studies investigating the effect of neighborhood-level exposures on neonatal outcomes [16–18, 57–59]. Final covariate selection was informed by a directed acyclic graph. We included: maternal race/ethnicity, pre-pregnancy body mass index (BMI), and active smoking and secondhand smoke exposure. We excluded alcohol consumption because previous work in this cohort found levels were generally low among cohort participants and not associated with infant body composition measures [60, 61]. Consistent with our prior work and that of others [40, 62], maternal educational attainment was included as a proxy for family-level socioeconomic status (SES) because it is a consistent and reliable predictor of health outcomes for women and children [63, 64] and tends to be a more stable proxy for SES over time compared to income [65, 66]. We also included two measures of stress and depressive symptoms, Cohen's Perceived Stress Scale (CPSS) and the Edinburgh Postnatal Depression Scale (EPDS), which were administered to mothers during their prenatal visits. Infant covariates included year of conception and sex. To address the potential for residual spatial autocorrelation, we included the longitude, latitude, and an interaction term (longitude × latitude) for the participant residential location. To account for temporal trends, we included the season of conception. For the adiposity models, we also included the number of days between delivery and PEA POD measurements. We did not adjust for gestational age in our models because our directed acyclic graph indicated gestational age was on the causal pathway.

Because individual-level race or ethnicity may modify the relationships between exposures and neonatal outcomes [67], we conducted sensitivity analyses where we stratified our results by maternal race/ethnicity (non-Hispanic White (NHW) vs. all other race and ethnic categories).

Statistical analysis

All analyses were performed in R version 4.0.3 [68]. Prior to model fitting, exposures, outcomes, and covariates were summarized as means and standard deviations (SD) or frequencies as appropriate. To examine the potential for selection bias we assessed differences between included and excluded participants using chi square tests for categorical variables and t-tests for continuous variables. Categorical covariates were converted to indicator variables. To account for differences in units across the exposure variables and covariates, continuous variables were scaled prior to fitting the regression models.

Non-parametric Bayes shrinkage model

Our goal for this paper was to select from a complex mixture of neighborhood-level factors exposures that were associated with birth weight and adiposity. Therefore, our primary analysis used NPB, which is a Bayesian statistical method that fits a linear model with main effects of all exposures and all pairwise interactions while implementing both variable selection and regularization [42]. Specifically, NPB applies a Dirichlet zero-spiked process prior to the regression coefficients for each exposure. The Dirichlet process prior has a point mass at 0, which allows the model to select out exposures that have little influence on the outcome. Exposures with similar effects on the outcome can be clustered and assigned the same regression coefficient in the model. This reduces the variance in the presence of high correlation between the exposures. A similar approach is applied to the interaction effects. Here we included two-way interaction terms between each of the exposure variables and between each exposure and covariate. All interaction terms were selected with an additional zero-spiked Dirichlet process.

Our NPB model has the following form:

$$y_I | \beta, \gamma, \zeta, \delta, \sigma^2 \sim N(y_o + x_i^T \beta + z_i^T \zeta + w_i^T \gamma, \sigma^2) \tag{1}$$

where x_i is a vector of exposures, z_i is a vector of pairwise multiplicative interactions between the exposures or the exposures and the covariates, w_i is a vector of covariates, and σ^2 is the error variance. We implemented our NPB model using the "mmpack" package in R [69]. Posterior means and 95% credible intervals for the regression coefficients are reported for a standard deviation increase in each exposure metric. Consistent with other studies, we used 0.5 as the threshold for which posterior inclusion probabilities (PIPs) were considered to be indicative of an important effect of the exposure on the health outcome [70, 71]. Additional details on fitting the NPB model, including a description of the priors, is included in the Supplemental Materials.

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Because variable selection by the NPB model may depend on the specification of hyperparameters, we conducted a sensitivity analysis in which the α and β values of the Gamma distributions for hyperparameters α_1 and α_2(see Text S1 in the Supplemental Materials) were set to 0.5, 1, 2, and 4.

Single exposure linear regression models
To serve as a comparison to the NPB method, we fit separate linear regression models for each exposure-outcome pair. These linear models were adjusted for all relevant covariates listed in Covariates. Results from these linear regression models were reported for a standard deviation increase in each exposure.

Generalized additive model
In a supplemental analysis meant to assess potential non-linear effects of our NPB-selected exposures of interest on birth weight or adiposity, we fit separate generalized additive models (GAMs) for any variables selected with NPB based on a PIP > 0.5. We used a smoothed term with penalized splines for the continuous exposures identified in the NPB model. Models were adjusted for all covariates listed in Covariates. We also repeated our sensitivity analysis and stratified GAMs by maternal race and ethnicity as described in Covariates. GAMs were fit in R using the "mgcv" package [72] and visualized using the "mgcViz" package [73].

Results
Study population
Our analytic cohort consisted of 897 mother–child dyads enrolled in the Healthy Start study, representing 64% of the original study population (Table 1). Of the excluded participants, $n = 51$ were excluded because they were missing data on birth weight, $n = 259$ were excluded because they lived outside the three-county study area, $n = 172$ were excluded because they were missing data on smoking exposures, and $n = 37$ were excluded because they were missing data on infant sex. There were few differences between included and excluded study participants (Table 1). Although birth weights were similar on average, we observed slightly higher adiposity for excluded participants. Included participants were also less likely to be non-Hispanic white and had higher mean CPSS compared to excluded participants. We did not observe any other differences between included and excluded participants for any of the other covariates of interest in this study.

Exposure assessment
Exposures to environmental and social factors varied across participants (Table 2). Coefficients of variation

were generally high (> 25%) for most (74%) of the exposures. Variability was lowest for the air pollutant exposures (mean $PM_{2.5}$ and mean O_3) and mean temperature across pregnancy. Correlations between environmental exposures and between environmental and social exposures were generally moderate (Pearson's coefficients ranged from -0.5 to 0.7). Correlations tended to be stronger between the social determinants of health (Pearson's coefficients ranged from -0.1 to 0.9; Figure S1).

Regression results
Nonparametric Bayes shrinkage
The NPB model, which included all exposures of interest in the same model, suggested that few of our exposures were strongly associated with birth weight (Table 3) based on our criterion of PIP = 0.5. Credible intervals for the posterior means were generally wide and contained zero. Only one variable had a PIP above 0.5 and a credible interval that did not contain zero: the interaction between mean ambient ozone concentration and temperature across pregnancy. A 3.1 ppb increase in mean O_3 assessed across the pregnancy was associated with a 6.4 g decrease in birth weight (95% credible interval: -65.1 g to 6.9 g) and a 4.8 °F increase in mean temperature across pregnancy was associated with a 13.1 g increase (95% credible interval: -18.6 g to 189.3 g). For every 1 SD increase in temperature, the decrease in birth weight for a 1 SD increase in ozone was 162.0 g (95% CI: -242.3 g to -117.8 g) greater than expected if effects of the two exposures were additive. A plot showing the relationship between predicted and observed birth weight is included in the Supplemental Materials (Figure S2).

None of the exposures considered in the NPB model for adiposity had credible interval that did not contain zero nor a PIP greater than the 0.5 threshold (Table 3). In general, we did not observe relationships between our exposures of interest and adiposity at birth. A plot showing the relationship between predicted and observed adiposity is included in the Supplemental Materials (Figure S3).

Neither the birth weight nor the adiposity model was sensitive to changes in the gamma distribution parameters for the mass concentration hyperparameter (Tables S2 and S3). For the four sensitivity analyses conducted, no differences in variables selected by the NPB model were observed.

We observed evidence of effect modification by maternal race/ethnicity in our NPB models for birth weight (Table 4). When stratifying by maternal race/ethnicity, we only observed an effect of temperature and ozone for participants who identified as a race or ethnicity other

Table 1 Summary of outcomes and covariates for the study population

Variable		Full Cohort (n = 1410)	Included (n = 897)	Excluded (n = 513)	P-value[a]
Birth weight (g)	mean ± SD	3205 ± 538	3208 ± 527	3199 ± 559	0.776
Adiposity (% fat mass)[b]	mean ± SD	9.2 ± 4.0	9.0 ± 4.0	9.5 ± 3.9	0.028
Maternal Race/Ethnicity					0.003
Hispanic/Latina	n (%)	351 (25)	238 (27)	113 (22)	
White non-Hispanic	n (%)	751 (52)	445 (50)	306 (60)	
African American	n (%)	219 (16)	154 (17)	65 (13)	
Other	n (%)	89 (6)	60 (7)	29 (6)	
Maternal age (years)	mean ± SD	27.8 ± 6.2	27.6 ± 6.2	28 ± 6.2	0.254
Mean CPSS Score	mean ± SD	18.8 ± 3.1	18.6 ± 3.1	19.2 ± 3.1	0.002
Mean EPDS Score	mean ± SD	4.4 ± 3.4	4.3 ± 3.3	4.6 ± 3.7	0.125
Pre-pregnancy body mass index (kg/m^2)			0.583		
Underweight (< 18.5)	n (%)	44 (3)	30 (3)	14 (3)	
Normal (18.5—25)	n (%)	727 (52)	453 (51)	274 (54)	
Overweight (25—30)	n (%)	355 (25)	235 (26)	120 (24)	
Obese (> 30)	n (%)	280 (20)	179 (20)	101 (20)	
Maternal education level					0.816
Less than high school	n (%)	204 (14)	137 (15)	67 (13)	
High school or GED	n (%)	259 (18)	166 (19)	93 (18)	
Some college/Associate's	n (%)	334 (24)	208 (23)	126 (25)	
Bachelor's Degree	n (%)	309 (22)	196 (22)	113 (22)	
Graduate Degree	n (%)	304 (22)	190 (21)	114 (22)	
Any smoking during pregnancy?					0.940
No	n (%)	1286 (91)	819 (91)	467 (91)	
Yes	n (%)	124 (9)	78 (9)	46 (9)	
Any SHS exposure during pregnancy?					0.662
No	n (%)	924 (75)	666 (74)	258 (76)	
Yes	n (%)	314 (25)	231 (26)	83 (24)	
Infant sex					0.508
Female	n (%)	646 (48)	438 (49)	208 (47)	
Male	n (%)	696 (52)	459 (51)	237 (53)	
Gestational age (weeks)	mean ± SD	39.2 ± 1.9	39.3 ± 1.8	39.1 ± 2.2	0.052
Term status					0.147
Pre-term (< 37 weeks)	n (%)	90 (7)	60 (7)	30 (6)	
Early Term (37 to < 39 weeks)	n (%)	331 (24)	200 (22)	131 (28)	
Full Term (39 to < 41 weeks)	n (%)	802 (59)	538 (60)	264 (57)	
Late Term (41 to < 42 weeks)	n (%)	126 (9)	87 (10)	39 (8)	
Post-term (>= 42 weeks)	n (%)	15 (1)	12 (1)	3 (1)	
Low birth weight (< 2500 g)	n (%)	104 (8)	67 (7)	37 (8)	0.805
Days from delivery to PEA POD (days)	mean ± SD	1.6 ± 2.4	1.6 ± 2.5	1.8 ± 2.3	0.235

Abbreviations: CPSS Cohen Perceived Stress Scale, EPSD Edinburgh Postnatal Depression Scale, SHS Secondhand smoke

[a] Chi square test for categorical variables; Student's t test for continuous variables

[b] Defined as (fat mass/total body mass) × 100%. Sample sizes for the adiposity variable are n = 1141 for the full cohort, n = 786 for the included cohort and n = 357 for the excluded cohort

than NHW. For mothers who did not identify as NHW, for every 1 SD increase in temperature, the decrease in birth weight for a 1 SD increase in ozone was 206.2 g (95% CI: -258.3 g to -156.1 g) greater than expected if effects of the two exposures were additive.

Linear models

Following traditional epidemiological approaches, we also examined linear relationships between each individual exposure variable and our outcomes of interest. Of the 21 exposure variables included in our study, most

Table 2 Summary statistics for all environmental and social exposures considered in the nonparametric Bayesian shrinkage model (*n* = 897)

Variable	Units	Mean ± SD	Min	Median	Max	CV
Environmental exposures						
Mean $PM_{2.5}$	µg/m^3	7.5 ± 0.6	5.8	7.5	9.1	8%
Mean O_3	ppb	48.0 ± 3.1	40.8	47.8	58.3	8%
Mean temperature	°F	52.2 ± 4.8	37.3	52.4	66.4	9%
Tree cover	%	6.3 ± 3.1	0.2	6.1	18.7	50%
Impervious surfaces	%	40.5 ± 13.3	0.3	42.5	82.4	33%
AADT	Vehicles/d-km^2	10,344 ± 8203	21	9074	54,618	79%
Distance to TRI sites	km	3.9 ± 2.6	0.1	3.3	21.9	66%
Distance to NPL sites	km	5.5 ± 3.3	0.0	5.5	23.6	60%
Distance to waste management sites	km	5.2 ± 2.3	0.5	5.0	11.7	44%
Distance to major emitters	km	8.3 ± 3.2	0.3	8.7	21.0	38%
Distance to CAFOs	km	36.8 ± 6.8	7.1	37.4	55.1	18%
Distance to mines or wells	km	3.4 ± 2.1	0.1	3.1	10.5	62%
Social exposures						
CVD hospitalizations	n/10,000	244.0 ± 45.2	127.9	243.8	471.8	19%
Respiratory hospitalizations	n/10,000	165.2 ± 33.0	95.2	164.1	319.8	20%
Violent crimes	n/1,000	12.8 ± 6.3	0.6	15.3	81.8	49%
Property crimes	n/1,000	55.4 ± 36.0	10.6	55.9	472.7	65%
Less than HS diploma	%	16.5 ± 12.7	0.0	12.8	56.9	77%
Unemployment	%	9.7 ± 5	1.8	8.7	27.5	51%
Households in poverty	%	15.3 ± 10.9	0.0	13.9	79.0	71%
Households speaking limited English	%	8.3 ± 8.3	0.0	5.8	39.1	100%
Percent persons of color	%	54.3 ± 22.9	2.7	54.6	93.7	42%

Abbreviations: AADT Annual average daily traffic, *CAFO* Confined animal feeding operation, *CV* Coefficient of variation, *CVD* Cardiovascular disease, *HS* High school, *NPL* National priorities list (Superfund sites), O_3 Ozone, $PM_{2.5}$ fine particulate matter, *TRI* Toxic release inventory

(*n* = 14; 67%) were associated with lower birth weight, though most confidence intervals for the coefficients were wide and contained zero (Table S1). The strongest associations were seen for the percentage of adults in the census tract who were unemployed (β = -40.9 g, 95% CI: -76.8 g to -4.9 g) and the distance (km) to the nearest waste site (β = 39.7 g, 95% CI: 4.1 g to 75.4 g).

For adiposity (% fat mass), the linear regression models showed similar lack of association with most of the exposures of interest (Table S1). The strongest effect on % fat mass was observed for the rate of property crimes at the census tract level (β = -0.31 percentage points, 95% CI: -0.59 g to -0.04 percentage points) and the distance to waste sites (β = 0.36 percentage points, 95% CI: 0.07 to 0.66 percentage points). For most exposures, the confidence intervals were wide and contained 0.

Generalized additive models

We examined potential non-linear effects for ozone and temperature using a GAM, adjusting for the same covariates included in the main NPB model (Fig. 1). To avoid overinterpreting effects at the margins, we restricted the axes to show the middle 95% of O_3 and temperature observations. Plots showing the full range of data are available in the SDC (Figure S4). The exposure–response curve for the smoothed O_3 and temperature term suggested a non-linear association between these exposures and birth weight (Fig. 1A). The accumulated local effect (ALE) plot for temperature showed an inverted-U shaped exposure–response relationship (Fig. 1B); the non-linear effect for ozone was less evident, with the ALE plot suggesting a more linear effect (Fig. 1C). The plots shown in Fig. 1 also suggest that the effect of temperature on birth weight is stronger than the effect of O_3. We conducted a sensitivity analysis fitting the GAM with a dataset restricted to the middle 95% of O_3 and temperature observations (Figure S5). These plots showed similar trends as those in Fig. 1.

Results from GAMs stratified by maternal race/ethnicity showed similar effect modification as observed for the NPB models (Fig. 2, Figure S6). For stratified models where extreme values were excluded (Fig. 2), we observed non-linear associations between temperature and ozone for mothers who identified as a race/ethnicity other than non-Hispanic White (Fig. 2D-F) but not for non-White mothers (Fig. 2A-C).

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Table 3 Posterior means, 95% credible intervals, and posterior inclusion probabilities (PIPs) for each census tract level exposure regression coefficient in the NPB model, adjusted for all individual-level covariates. Results are presented for a 1 SD increase in each exposure

Variable	SD[c]	Birth Weight (g)		Adiposity (% Fat Mass)	
		Posterior Mean[a] (95% CI)	PIP	Posterior Mean[a,b] (95% CI)	PIP
Environmental Exposures					
Mean $PM_{2.5}$ ($\mu g/m^3$)	0.6	-2.4 (-29.3, 8.5)	0.31	-0.01 (-0.16, 0.11)	0.32
Mean O_3 (ppb)	3.1	-6.4 (-65.1, 6.9)	0.37	-0.02 (-0.24, 0.09)	0.36
Mean temperature (°F)	4.8	13.1 (-18.6, 189.3)	0.38	-0.01 (-0.20, 0.12)	0.32
Mean O_3 × Mean temperature		-162.0 (-242.3, -117.8)	1.00	-0.01 (-0.09, 0.00)	0.04
Tree cover (%)	3.1	-0.4 (-12.1, 11.6)	0.25	0.00 (-0.15, 0.11)	0.28
Impervious surfaces (%)	13.3	-0.7 (-14.4, 7.4)	0.25	-0.01 (-0.15, 0.09)	0.29
AADT (vehicles per day-km^2)	8203	0.7 (-9, 18.2)	0.24	0.01 (-0.08, 0.21)	0.28
Distance to TRI sites (km)	2.6	-1.1 (-18.9, 8.9)	0.27	-0.01 (-0.17, 0.11)	0.32
Distance to NPL sites (km)	3.3	0.0 (-11.7, 14.6)	0.26	0.00 (-0.13, 0.14)	0.30
Distance to waste sites (km)	2.3	3.0 (-7.4, 39.2)	0.31	0.03 (-0.07, 0.34)	0.33
Distance to major emitters (km)	3.2	0.0 (-10.7, 13.1)	0.24	0.01 (-0.09, 0.19)	0.29
Distance to CAFOs (km)	6.8	-2.1 (-31, 14.2)	0.34	-0.02 (-0.24, 0.14)	0.35
Distance to mines or wells (km)	2.1	-1.7 (-22.6, 8.9)	0.31	-0.03 (-0.27, 0.07)	0.38
Social Exposures					
CVD hospitalizations (n per 10,000)	45.2	-1.4 (-18.4, 5.9)	0.28	-0.02 (-0.22, 0.08)	0.35
Resp. hospitalizations (n per 10,000)	33.0	-2.5 (-26.8, 5.0)	0.30	-0.02 (-0.21, 0.05)	0.35
Violent crimes (n per 1,000)	6.3	-0.3 (-12.2, 9.2)	0.25	-0.01 (-0.16, 0.09)	0.32
Property crimes (n per 1,000)	36.0	-1.5 (-18.3, 5.2)	0.28	-0.06 (-0.35, 0.03)	0.49
Less than HS diploma (%)	12.7	-1.1 (-17.9, 10.6)	0.29	-0.01 (-0.20, 0.09)	0.32
Unemployment (%)	5.0	-6.6 (-51.3, 2.5)	0.40	-0.03 (-0.30, 0.05)	0.37
Households speaking limited English (%)	10.9	-1 (-16.2, 6.9)	0.25	0.00 (-0.12, 0.19)	0.31
Households in poverty (%)	8.3	-1.1 (-15, 6.6)	0.26	-0.02 (-0.22, 0.06)	0.33
Persons of color (%)	22.9	-0.5 (-13.1, 12.6)	0.26	0.00 (-0.13, 0.15)	0.29

[a] Models are adjusted for: maternal race/ethnicity, maternal educational attainment, maternal pre-pregnancy BMI, maternal age at delivery, maternal smoking during pregnancy, second-hand smoke exposure during pregnancy, mean perceived stress scale score across pregnancy, mean postnatal depression score across pregnancy, season of conception, year of conception, longitude, latitude, and the interaction between longitude and latitude

[b] Models of adiposity are also adjusted for the number of days between delivery and PEA POD measurements

[c] Effect estimates are reported for a 1 standard deviation increase in each exposure variable

Discussion

Here we leveraged a non-parametric Bayesian shrinkage approach to identify which components of a mixture of exposures were driving previously reported associations between an exposure index and lower birth weight among infants born in the Denver metropolitan area. Using our mixtures approach (NPB), we identified the interaction between mean O_3 concentrations and mean temperatures across the entire pregnancy as an important predictor of birth weight. Additional analyses using a GAM indicated that the relationship between O_3, temperature, and birth weight may be non-linear. Our NPB results differed from those of the linear regression models, which identified only distance to waste sites, property crime rates, and unemployment as associated with our

outcomes of interest and were likely biased by confounding from other correlated exposures.

Our results differ in some ways from other studies reported in the literature. For example, we did not identify an association between $PM_{2.5}$ and birth weight in our cohort, which contradicts several other studies (as reviewed by Sun et al.) [74]. Our inability to detect this association may be in part due to the exposure metric used or due to low $PM_{2.5}$ exposures in the study area. Average and maximum $PM_{2.5}$ exposures across pregnancy in our cohort (7.5 and 9.1 $\mu g/m^3$, respectively) were below the National Ambient Air Quality Standard for $PM_{2.5}$ (annual average of 12 $\mu g/m^3$). A similar Healthy Start study relying on trimester-specific averages derived from monitoring data also reported no association

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Table 4 NPB models for birth weight stratified by maternal race/ethnicity (non-Hispanic White vs. all other race/ethnicity groups). Posterior means, 95% credible intervals, and posterior inclusion probabilities (PIPs) for each census tract level exposure regression coefficient in the NPB model. The model is adjusted for all individual-level covariates except race/ethnicity.[a] Results are presented for a 1 SD increase in each exposure

Variable	Non-Hispanic White ($n = 445$)		All other Race/Ethnicity ($n = 452$)	
	Posterior Mean[b] (95% CI)	PIP	Posterior Mean[b] (95% CI)	PIP
Environmental Exposures				
Mean $PM_{2.5}$ (µg/m³)	1.3 (-14.1, 27.8)	0.32	-15 (-94.3, 13.1)	0.45
Mean O_3 (ppb)	-1.3 (-23.4, 17.6)	0.35	-15.5 (-103.5, 11.8)	0.43
Mean temperature (°F)	-1.1 (-22, 14.5)	0.33	0.9 (-36.2, 43.8)	0.32
Mean O_3 × Mean temperature	-3.6 (-71.4, 0.0)	0.06	-206.2 (-258.3, -156.1)	1.00
Tree cover (%)	-0.1 (-15.3, 17.5)	0.31	1.2 (-19.9, 31.3)	0.27
Impervious surfaces (%)	-1.3 (-20.4, 10.9)	0.31	-1 (-29.4, 19.6)	0.25
AADT (vehicles per day-km²)	-0.9 (-18.7, 11.9)	0.30	3.3 (-10.5, 38.2)	0.28
Distance to TRI sites (km)	-2.3 (-26, 9.7)	0.35	3.5 (-15.3, 43.9)	0.30
Distance to NPL sites (km)	0.0 (-14.8, 20.7)	0.29	0.9 (-28.8, 32)	0.29
Distance to waste sites (km)	1.6 (-12.1, 31.9)	0.33	8.4 (-9.9, 65.4)	0.38
Distance to major emitters (km)	-1.0 (-17.8, 10.2)	0.31	7.8 (-8.7, 63.2)	0.35
Distance to CAFOs (km)	-0.3 (-22, 24.8)	0.35	-5.4 (-83.8, 36)	0.36
Distance to mines or wells (km)	-1.8 (-24.1, 12.2)	0.35	-0.4 (-33.9, 28.7)	0.29
Social Exposures				
CVD hospitalizations (n per 10,000)	-1 (-19.1, 13.4)	0.32	-2.5 (-47.8, 27.3)	0.32
Resp. hospitalizations (n per 10,000)	-0.8 (-17.8, 12.1)	0.30	-16.4 (-93.6, 6.3)	0.45
Violent crimes (n per 1,000)	-1.1 (-18.7, 11.5)	0.31	4.5 (-10.4, 48.6)	0.30
Property crimes (n per 1,000)	-1.9 (-22.2, 9.7)	0.32	1.9 (-15.1, 31.4)	0.26
Less than HS diploma (%)	-2.8 (-30.6, 6.9)	0.33	1.5 (-22.2, 36.4)	0.28
Unemployment (%)	-2.9 (-29.3, 6.7)	0.34	-12.3 (-80.2, 7.3)	0.41
Households speaking limited English (%)	-0.7 (-16.3, 12.4)	0.30	-2.2 (-39.8, 19.4)	0.27
Households in poverty (%)	-2.4 (-27.4, 8.0)	0.33	1.3 (-21.5, 34.5)	0.26
Persons of color (%)	-0.6 (-16.5, 12.3)	0.29	1.6 (-19.4, 35.5)	0.28

[a] Models are adjusted for: maternal educational attainment, maternal pre-pregnancy BMI, maternal age at delivery, maternal smoking during pregnancy, second-hand smoke exposure during pregnancy, mean perceived stress scale score across pregnancy, mean postnatal depression score across pregnancy, season of conception, and year of conception
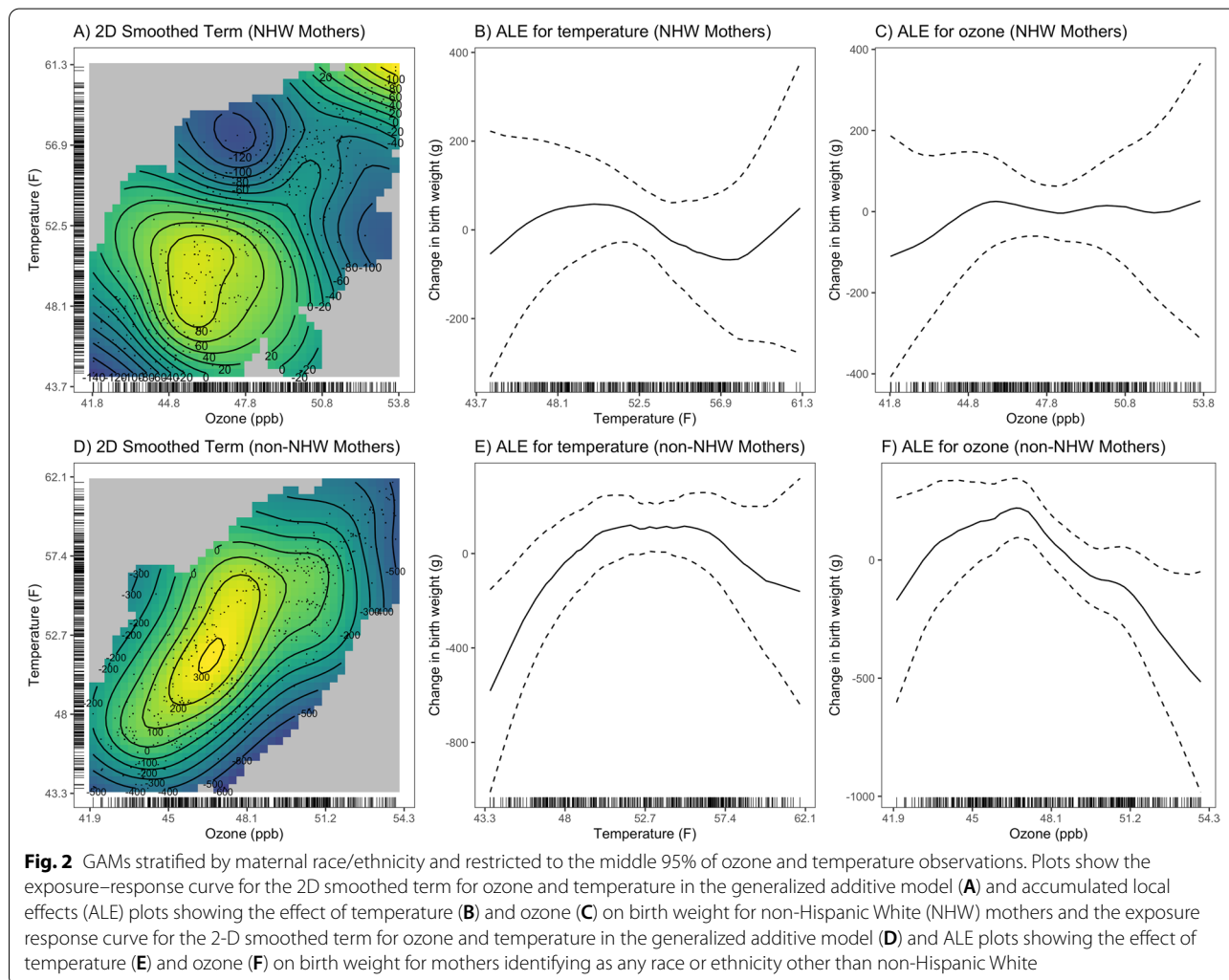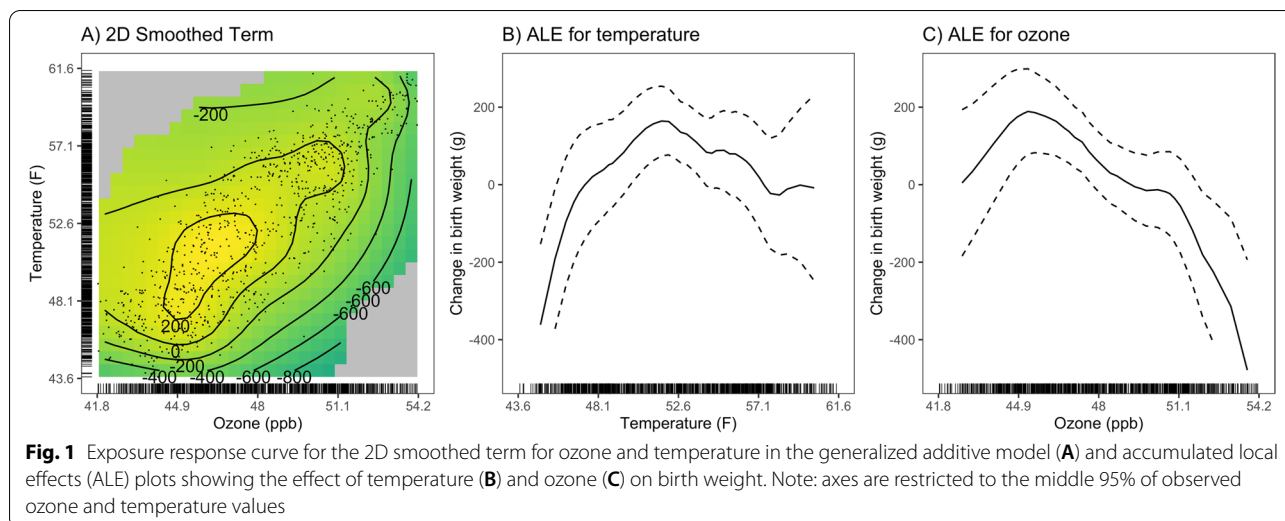
[b] Effect estimates are reported for a 1 standard deviation increase in each exposure variable

between $PM_{2.5}$ and birth weight or adiposity [75]. In general, intraurban gradients of $PM_{2.5}$ tend to be relatively flat and regulatory monitors poorly reflect variability from local sources [76]. Other pollutants such as black carbon that better reflect local sources in the region and characterize intraurban gradients in concentration may be more useful in future studies [77].

Our results indicating an interaction between temperature and O_3 on birth weight are more consistent with previous studies [78]. Although this association has been reported less frequently in the literature, O_3 exposures have been associated with lower birth weight (measured continuously) or increased odds of low birth weight (< 2,500 g) [78, 79]. Associations between both higher and lower temperatures and lower birth weight

have also been reported [80–83]. Both ozone and ambient temperature exposures have been linked to systemic inflammation in adults [84–88]. Thus, we hypothesize that our results showing a relationship between temperature and O_3 on birth weight may be due to maternal systemic inflammation, which is known to influence fetal growth [89].

Importantly, our study provides additional evidence of effect modification by maternal race and ethnicity on associations between environmental hazards and child health outcomes. Associations between our exposures of interest and birth weight were stronger for mothers from historically minoritized race or ethnicity groups compared to non-Hispanic White mothers. Several studies in the past two decades have reported racial disparities

Fig. 1 Exposure response curve for the 2D smoothed term for ozone and temperature in the generalized additive model (**A**) and accumulated local effects (ALE) plots showing the effect of temperature (**B**) and ozone (**C**) on birth weight. Note: axes are restricted to the middle 95% of observed ozone and temperature values

Fig. 2 GAMs stratified by maternal race/ethnicity and restricted to the middle 95% of ozone and temperature observations. Plots show the exposure–response curve for the 2D smoothed term for ozone and temperature in the generalized additive model (**A**) and accumulated local effects (ALE) plots showing the effect of temperature (**B**) and ozone (**C**) on birth weight for non-Hispanic White (NHW) mothers and the exposure response curve for the 2-D smoothed term for ozone and temperature in the generalized additive model (**D**) and ALE plots showing the effect of temperature (**E**) and ozone (**F**) on birth weight for mothers identifying as any race or ethnicity other than non-Hispanic White

in low birth weight, which is more likely as population mean birthweights shift downward, over the last few decades [90–92]. Relationships between race or ethnicity, neighborhood quality, and neonatal outcomes are complicated, but stress is a likely mediating factor [93].

There were important differences between the results of the single-exposure linear regression analysis and the results from the NPB model. In the linear regression models, higher exposures to social stressors tended to be associated with lower birth weights and adiposity in the linear regression models, though the confidence intervals for the regression coefficients tended to be wide and contain zero. These results are consistent with our previous index-based analysis which found that associations between a combined exposure index and birth weight were likely driven by the social stressor component of the score [40]. However, the NPB model identified the interaction between ozone and temperature as being an important predictor of birth weight. Neither temperature nor ozone were associated with birth weight in the linear regression models. Differences between results derived from the NPB model and the linear regression models may be due to residual confounding by co-exposures in the single-exposure linear regression models. These models also do not include the interaction term that was important in the NPB model. The exposures included in our data set are moderately to highly correlated, and a single-exposure model is likely not sufficient to address this correlation. Using NPB as a modeling approach allowed us to consider each of these exposures at once in a framework that allows correlated exposures to be assigned similar coefficients when effects cannot be separated [43].

Additionally, differences between our NPB model and our original index-based approach also suggest that our combined exposure index may have characterized factors in the neighborhood that are not fully explained by any one variable. Notably, temperature was not included in our original index. Our exposures were originally chosen to reflect the combination of factors often included in screening tools for environmental justice concerns, *e.g.,* CalEnviroScreen [45] or EJScreen [94]; thus, we may have captured trends in neighborhood quality rather than specific etiologic factors for lower birth weight and adiposity. Future mixtures-based approaches for birth weight should consider moving beyond the typical indicators of health and neighborhood quality and focus more on those exposures that are suspected of being causally linked to neonatal outcomes.

There are some important limitations to our approach that should be considered when interpreting these results. First, the census tract estimates of exposure generally have limited temporal resolution. Due to the limitations of publicly available data at the spatial resolution used here, we relied on annual or five-year average estimates for most of our exposures. Second, there is no universal definition for neighborhood, and census tracts may not be the most meaningful unit of analysis; boundaries that reflect policy or other jurisdictional boundaries (e.g., school districts or municipal boundaries) may be more appropriate for some exposures [95]. Third, as discussed above, we chose our exposures based on existing screening tools rather than specific exposures known to be associated with birth weight and adiposity. Future work should consider how and for what purpose existing public health indices are developed and may develop separate indices for different types of health outcomes. Lastly, we focused on a single metropolitan area where the range of exposures is limited. Replication of these methods in multi-city studies should broaden the range of exposures and better elucidate the relationships between multiple environmental and social hazards and neonatal health.

Despite these limitations, our approach demonstrated the strengths of using NPB in a mixtures context. Our use of NPB allowed us to include a large number of correlated exposures, which would otherwise be a challenge in a multipollutant model due to the potential for multicollinearity and variance inflation [42]. In this context, NPB has advantages over the least absolute shrinkage and selection operator (LASSO) which is widely used for variable selection. In particular, LASSO tends to perform poorly when variables are highly correlated [96, 97]. Additionally, LASSO does not account for uncertainty in variable selection [42]. In contrast, NPB can cluster and assign equal regression coefficients to exposures, which reduces the effect of correlation among exposures and is a strength when it is difficult to separate the effects of the two exposures [43]. In future cases where more than two exposures are identified, methods like Bayesian Kernel Machine Regression (BKMR) may be useful. BKMR is a flexible approach for modeling the effects of exposure mixtures that is capable of identifying nonlinear main effects and interactions among mixture components [98], though it may not be well suited for selecting among a large number of predictors [43], Thus, a two-stage approach where NPB models reduce the number of candidate predictors and methods like BKMR explore the complex interactions between exposures of interest might be most appropriate.

Overall, our NPB model, which was designed to select among a large number of correlated exposures, identified a joint effect of O_3 and temperature as important predictor of birth weight, and the GAM indicated these association may be non-linear. Our results suggest there is a potential role for neighborhood-level

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environmental and social stressors in the prenatal period to influence fetal growth, but that additional studies are needed to identify important drivers in this exposure mixture. Future work may consider imputing missing values for key covariates to increase the sample size available for more complex statistical approaches such as BKMR. Further, it will be crucial to examine non-linear dose response relationships when assessing the effects of joint exposures assessed at the neighborhood level. When non-linear relationships are anticipated, additional variable selection approaches could be considered [99].

Abbreviations

AATD: Annual average daily traffic; ALE: Accumulated local effect; BKMR: Bayesian Kernel Machine Regression; BMI: Body mass index; CPSS: Cohen's Perceived Stress Scale; EPDS: Edinburgh Postnatal Depression Scale; GAM: Generalized additive model; LBW: Low birth weight; NHW: Non-Hispanic White; NPB: Nonparametric Bayes shrinkage; O_3: Ozone; PIP: Posterior inclusion probability; $PM_{2.5}$: Particulate matter with an aerodynamic diameter less than 2.5 microns; SD: Standard deviation; SES: Socioeconomic status; SGA: Small for gestational age.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-022-00934-z.

Additional file 1. Supplemental Materials.

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are available for analyses related to the aims of the study upon reasonable request.

Declarations

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