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Prenatal Environmental Exposures and Associations with Teen Births

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Abstract

Background: Children's prenatal exposure to multiple environmental chemicals may contribute to subsequent deficits in impulse control, predisposing them to risk-taking.

Objective: Our goal was to investigate associations between prenatal exposure mixtures and risk of teen birth, a manifestation of high-risk sexual activity, among 5,865 girls (1st generation) born in southeast Massachusetts from 1992-1998.

Methods: Exposures included prenatal modeled polychlorinated biphenyls (PCBs), ρ,ρ′-dichlorodiphenyl dichloroethylene (DDE), hexachlorobenzene (HCB), lead (Pb), and mercury (Hg). We fit adjusted generalized additive models with multivariable smooths of exposure mixtures, 1st generation infant's birth year, and maternal age at 1st generation birth. Predicted odds ratios (ORs) for teen birth were mapped as a function of joint exposures. We also conducted sensitivity analyses among 1st generation girls with measured exposure biomarkers (n=371).

Results: The highest teen birth risk was associated with a mixture of high prenatal HCB, Hg, Pb, and PCB, but low DDE exposure, with similar associations in sensitivity analyses. The highest OR predicted for girls born in 1995 to mothers of median age (26 years) was at the 95th percentile of

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Conflict of Interest

The authors declare that they have no conflicts of interest.

the HCB and PCB exposure distributions (OR=3.09; 95% confidence interval: 0.29, 32.4). Additionally, girls born earlier in the study period or to teen mothers were at increased risk of teen birth.

Significance: Prenatal environmental chemical exposures and sociodemographic characteristics may interact to substantially increase risk of teen births.

Keywords

environmental mixtures; teen birth; modeled exposures; adolescent behavior; prenatal exposures; organochlorines; metals

Introduction

Full development of the prefrontal cortex and its associated inhibitory functions extends past adolescence into early adulthood (1). Impulsive and reward-driven areas of the brain may dominate adolescents' and young adults' decision-making processes and actions, increasing their susceptibility to engage in high-risk, sensation-seeking activities (2,3). Manifestations of risk-taking behavior in these age groups, such as high-risk sexual behavior and teen birth, constitute major public health problems with high economic and social costs (4). Early age at first sexual intercourse is associated with increased risk of teen pregnancy, sexually transmitted disease, and poor psychosocial and physical health in adulthood (5,6).

In 2010, teen pregnancy and childbirth in the U.S. cost over $9 billion in medical and foster care expenses, lost tax revenues (because of failure of teen mothers to complete high school), and expenses from negative outcomes among children of teen mothers (7). For example, children of teenage mothers are at a greater risk for many negative social and health outcomes, including lower educational achievement, high school dropout, higher morbidity, incarceration during adolescence, teenage pregnancy, and unemployment as a young adult (8). Although rates of teen pregnancy have generally declined since the mid-1990s in most developed countries, the U.S. teen pregnancy rate (composed of miscarriages, abortions, and births) remains relatively high (57 per 1,000 females aged 15-19 in 2010); trend data indicate that the birth rate is lower (34 per 1,000 females aged 15-19 in 2010), with approximately 26% of pregnancies aborted (4,9). Compared to older women, pregnant teens are more likely to experience complications, including obstructed labor, fistula, and preterm delivery, and to give birth to low birth weight infants (10). Further, this is a public health issue of considerable impact as risk of death associated with pregnancy in 15-19 year olds is substantially higher than in 20-24 year olds (11).

Adolescent risk-taking, including high risk sexual activity, is influenced by a complex array of factors including sex, sociodemographic characteristics, peer behavior, and community characteristics (e.g., neighborhood crime and safety) (12). In addition, there is increasing evidence associating prenatal and early life environmental chemical exposures with altered behavioral development during childhood, including maladaptive behaviors that may predispose to risk-taking. Prenatal and early life environmental chemical exposures may also contribute to early pubertal maturation (13,14), which is associated with earlier age at sexual debut and sexual risk-taking (15-17). Impulsivity, in turn, is a demonstrated mediator of the

relation between early pubertal maturation and early sexual initiation (18). Animal models and epidemiologic studies generally support positive associations of early life exposures to polychlorinated biphenyls (PCBs), lead (Pb), and mercury (Hg) with subsequent impairment of impulse control, a core function of the prefrontal cortex and a correlate of risk-taking (19-21). Pb, even at low exposures, is also associated with long-term high-risk behaviors, such as delinquency (22,23). However, except for Pb exposure, most studies to date have focused on behaviors in children before adolescence. As a result, less is known about the role of early life chemical exposures and behavior among adolescents; given their unique susceptibility to risk taking, this is an important developmental window to study.

This study examined associations between mixtures of modeled prenatal environmental chemical exposures and subsequent teen birth, a reflection of high-risk sexual activity, among a large cohort of girls born in New Bedford and surrounding communities in southeast Massachusetts (MA) and identified via state birth records (i.e., MA Birth Record Cohort). New Bedford is a sociodemographically diverse community of approximately 95,000 residents, about 22% of whom live below the poverty level. Local industrial activity and hazardous waste sites contribute to environmental pollution in the region (24). Further, teen birth rates in the New Bedford area consistently rank among the highest in MA (25). To model prenatal environmental exposure, our study leveraged measured biomarkers of prenatal exposure to multiple prevalent and potentially neurotoxic chemicals, including heavy metals and organochlorines collected from a longitudinal birth cohort of infants (the New Bedford Cohort) born from 1993-1998 to mothers residing near the New Bedford Harbor (NBH) Superfund Site (26,27). We conducted sensitivity analyses using measured chemical biomarkers of prenatal exposure available for the New Bedford Cohort girls.

Our overall objective was to identify modifiable exposures that are associated with subsequent teen birth to inform targeted public health interventions in communities like New Bedford where the potential for multiple exposures is high and teen births have a considerable public health impact.

Methods

Massachusetts Birth Record Cohort (MBRC)

Our primary analysis used birth record data from the MA Department of Public Health (MADPH). This MA Birth Record Cohort (MBRC) consisted of all female children born in four towns (Acushnet, Dartmouth, Fairhaven, New Bedford) surrounding the NBH between January 1992 and December 1998 (n=5,865). The MBRC records contain extensive covariate information collected at birth, including parental demographics (birth place, maternal/paternal race/ethnicity), socioeconomic status proxies (education, marital status), pregnancy exposures (smoking, alcohol), pregnancy weight gain, and adequacy of prenatal care, and infant (1st generation) race/ethnicity, birth weight, gestational age, and breastfeeding status at birth. Using geographic information systems (GIS), census tract median household income and residential distances (in meters) to the NBH and to the nearest major roadway were assigned to geocoded birth addresses. The MBRC 1st generation births were followed through age 19 to identify subsequent cases of teen birth by linking the teen's own birth record with the birth record of her child (2nd generation).

MBRC Exposure Measures

Biomarkers of prenatal chemical exposure were available for a subset of the MBRC and were used to model prenatal chemical exposure for the MBRC. Specifically, biomarkers of organochlorine and metal exposures were measured in umbilical cord serum (sum of 4 prevalent PCBs [ΣPCB_4], ρ,ρ′-dichlorodiphenyl dichloroethylene [DDE], hexachlorobenzene [HCB]), umbilical cord blood (Pb), and maternal peripartum hair (Hg) samples collected from 788 mother-infant pairs participating in the New Bedford Cohort (NBC) studies (26,27). The NBC participants are a subset of the larger MBRC cohort and were born in the same four study towns during the study time period. Predictive prenatal exposure models were previously constructed for these biomarkers using data collected from the NBC; sociodemographic characteristics are generally comparable for the NBC and MBRC (Table S1), with high Pearson correlation coefficients ($r \geq 0.60$) for continuous variables and high percentage agreement (≥ 77%) for categorical variables (28). We used these exposure models, which were validated using repeated cross-validation (29), to predict prenatal chemical exposures for all (1st generation) female births in our MBRC study population (Table 1) as a function of maternal characteristics (address at birth, age, race/ethnicity, educational attainment, and country of birth), infant year of birth, residential proximity to the NBH and nearest major roadway, and year home was built (for prenatal Pb). All primary epidemiologic analyses of the MBRC included log-transformed measures of predicted ΣPCB_4, DDE, HCB, Hg, and Pb. The cross-validated R^2 values comparing measured biomarker levels with exposure model predictions for ΣPCB_4, DDE, HCB, Pb, and Hg were 0.54, 0.40, 0.34, 0.46, and 0.40, respectively; interquartile ranges were similar for measured biomarkers in NBC and imputed exposures in the MBRC cohort (28).

MBRC Covariates

The primary epidemiologic analyses of the MBRC included covariates from the 1st generation's birth records. Covariate adjustment was determined by assessing which variables were associated with subsequent teen birth using univariable logistic regression models; variables were included in the epidemiologic models if the univariable model coefficient had a p-value<0.05, if the variable yielded a change in effect size in the univariable model of at least 10% compared to the referent category, or if addition of the variable into the mixture model improved model fit, which was assessed using the Akaike Information Criteria (AIC). Selected categorical covariates included census tract median household income (less than $20,000, greater than or equal to $20,000), maternal education (less than high school, high school graduate or more), paternal education (less than high school, high school graduate or more), maternal marital status (married, unmarried), prenatal care payment source (private insurance, other payment), parity (1, 2, 3, ≥4), maternal race (Non-Hispanic White, Non-Hispanic African American, Hispanic, Non-Hispanic Other), adequacy of prenatal care defined as Adequate on the Kessner Index (yes, no), breastfeeding initiated at hospital (yes, no), year maternal residence built (before 1951, 1951-1970, after 1970), and smoking during pregnancy (any, none). Additional categorical variables tested but not retained in the final mixture model were whether mother was non-U.S.-born (Azores/Portugal, Cape Verde, Other), any alcohol consumption during pregnancy (yes, no), and delivery payment source (private insurance, other payment). Continuous variables included in the final epidemiologic models were maternal age at 1st generation's birth and 1st

generation's year of birth. We also tested infant birthweight, gestational age, maternal weight gain during pregnancy, residential distance to NBH (in meters), and maternal residential distance at 1st generation's birth to nearest major roadway (in meters), although they did not improve the fit of the final mixture model.

MBRC Epidemiologic Models

We fit epidemiologic models of the risk of giving birth as a teen for our MBRC study population, where teen births were defined as those that occurred between ages 13 and 19 years and took place in Massachusetts. Only 1st generation females with complete data were included in epidemiologic analyses (Table 2). Vital record information on 1st generation females when they were born (between 1992-1998) was linked by the MADPH to vital record information from subsequent years to determine who gave birth as teens. Exposure effects were examined in both single and multiple-exposure logistic regression models of teen birth. To analyze the effects of mixtures of exposures and continuous covariates, generalized additive models (GAMs) with a multivariable smooth term for joint exposures were used and odds ratios with 95% confidence intervals estimated. The following model was used for teen birth:

$$\boldsymbol{logit}\,[\boldsymbol{p}(\boldsymbol{x1},\ldots,\boldsymbol{xN})] = \boldsymbol{S}(\boldsymbol{x1},\ldots,\boldsymbol{xN}) + \boldsymbol{b}'\boldsymbol{z}$$

where $logit\,[p(x1,\ldots,xN)]$ is the log odds of teen birth at a mixture of multiple continuous exposures and covariates $(x1,\ldots,xN)]$ $S(x1,\ldots,xN)$ represents a multivariate loess (locally weighted scatter plot smoothing) term; b denotes the vector of parameters; and $\mathbf{z}$ comprises the vector of covariates. The optimal span size, which determines the amount of smoothing, was selected by minimizing the AIC (30-32).

The final mixture model was used to map odds ratios for teen birth by predicting odds ratios (ORs) for four different combinations of two exposures at a time on an X-Y axis, where X-coordinates represented levels of one continuous chemical exposure (e.g., HCB) and Y-coordinates represented levels of another continuous chemical exposure (e.g., ΣPCB_4). The smoothed surface illustrated the ORs at varying levels of the two exposures on the axes, while holding remaining continuous predictors included in the loess and categorical covariates constant. Chemical exposure distributions exhibited skewedness; therefore, predictions were restricted to the 5th to 95th percentiles of the chemical distribution exposures on the axes to minimize edge effects (33). Each odds ratio map was predicted at the median for maternal age (26 years), infant year of birth (1995) and the categorical covariates: maternal/paternal education high school or higher; maternal race non-Hispanic white; no smoking during pregnancy; non-initiation of breastfeeding at hospital; parity of 2; adequate prenatal care; private insurance prenatal care source of payment; maternal residence at birth built in or before 1970; and census tract median household income $20,000 or greater. Maps were predicted at the highest levels for the chemical exposures not on the axes. Odds ratio were calculated using the median predicted log odds of each surface as the referent.

Permutation tests provided a global p-value for statistical significance. A distribution of deviance statistics was generated under the null hypothesis that the smooth term for the mixture is not significant by permuting the variables in the smooth and refitting the model (30,31).

New Bedford Cohort (NBC) Sensitivity Analyses

Our sensitivity analyses examined mixtures of measured prenatal exposures in the NBC, a subset of the MBRC with extensive chemical biomarker measures; questionnaires, psychometric tests, and medical record reviews were used to determine non-chemical and sociodemographic covariates for mothers and 1st generation children. Despite residence in the four towns adjacent to the NBH Superfund site, most NBC biomarker concentrations were consistent with general population samples of infants studied elsewhere (34). Having extensive cohort data on a subset of the MBRC provided a unique opportunity to assess potential differences in associations for measured (versus modeled) prenatal exposure as well as the impact of more comprehensive covariate adjustment. Of the 376 singleton female births included in the NBC and born between 1993-1998 in the four study towns, we linked 371 to MADPH birth records used in the MBRC analysis to identify subsequent cases of teen birth.

As in the MBRC, chemical exposures used in the sensitivity analyses included ΣPCB_4, DDE, HCB, and Pb. Hg was not included due to the large proportion of missing data among NBC girls (33.4%). Details on the collection of NBC biomarker data and analytical methods are described elsewhere (26,27,34). For sensitivity analyses, we followed a similar model-building strategy as in the primary analyses and considered additional covariates (e.g., non-chemical maternal stressors available in the NBC but not the MBRC) to explore the potential for other factors to confound or otherwise impact associations observed between prenatal chemical mixture exposures and teen birth risk in primary analyses. Additional covariates included the Hobel perinatal risk score (35), maternal IQ, maternal depression score on the Beck Depression Inventory (BDI) at time of the child's 15-year exam (36), and Home Observation for Measurement of the Environment (HOME) score, a measure of the quality of parenting and the home environment assessed at approximately age 8 years (37). The final mixture model was adjusted for the following covariates pertaining to the mother of the 1st generation child: depression symptoms, age at child's birth, race/ethnicity, and birth country, as well as household characteristics including HOME score and median household income at child's birth. Information on maternal dietary factors (i.e., consumption of organ meat, seafood, local produce, grains and vitamins during pregnancy) was available and incorporated in additional sensitivity analyses to examine whether beneficial nutrients in dietary sources of chemical exposure (e.g., fish consumption can be a source of organochlorine exposure) may have confounded our main findings (26,27,38).

We fit epidemiologic models of subsequent teen birth for female infants in the NBC, using logistic regression in both single and multiple-exposure models. NBC mother-infant pairs with incomplete data were excluded from sensitivity analyses. In contrast to the MBRC, where all exposures were considered simultaneously in a single model, GAM smooth terms were restricted to two exposures at a time given the small sample size. Mapping of teen birth

odds ratios was done as in the primary analysis, with maps predicted at the median value for all covariates. The covariates in the final model included median values for the following characteristics of the mother of the 1st generation child: age at birth, depression symptom score on the BDI, and HOME score, as well as non-Hispanic white race/ethnicity, whether non-U.S.-born, and median household income $20,000 or greater.

R (version 3.3.3) and ArcGIS were used for data analyses. For spatial analyses and map creation, we used the R MapGAM package (39). This research was approved by the human subjects institutional review boards of the University of California, Irvine, Brigham and Women's Hospital, Boston and the MADPH. For the NBC, all participants signed written informed consent (parental consent and adolescent assent) prior to study data collection.

Results

MA Birth Record Cohort (MBRC)

Population Characteristics and Predicted Chemical Exposures.—Of the 5,865 female infants born in the study area between 1992-1998, 291 (4.96%) subsequently gave birth between 13-19 years of age. Of note, the proportion of girls who subsequently gave birth as teenagers decreased steadily from 7.7% (of those born in 1992) to 2.6% (of those born in 1998). The distribution of predicted prenatal chemical exposures and selected study population characteristics and their univariable associations with subsequent risk of teen birth are presented in Tables 1 and 2. Increased HCB and Pb were associated with higher odds of teen birth, while ΣPCB_4, DDE, and Hg were protective in univariable analyses (Table 1).

As indicated in Table 2, there were some significant differences between 1st generation children with a known teen birth and those without. For example, 1st generation children with a subsequent teen birth tended to have younger mothers compared to 1st generation children without a teen birth (23.4 versus 26.1 years old, respectively). Parents of teen mothers also had lower educational attainment (i.e., 54.3% of 1st generation children with a subsequent teen birth had mothers who did not complete high school compared to 27.4% without a teen birth). The proportion with lower household income at the time of the 1st generation child's birth was also higher for children with a subsequent teen birth (39.2%) compared to those without (21.4%). Teen mothers were also more likely to have been exposed to smoking in utero (32.3% compared to 22.6%).

Exposure Mixture Models.—Five chemical exposures and two non-chemical continuous predictors were included in the final mixture model in two multivariable smooth terms (Table S1). The first smooth term included log cord serum HCB, log maternal hair Hg, log cord blood Pb, and log cord serum ΣPCB_4; the second smooth term included log cord serum DDE, maternal age at birth, and infant year of birth. The continuous variables in the smooths were grouped to minimize correlation between the exposures and continuous predictors (Table S2). The global permutation test based on the deviance statistic indicated that the mixture term was significant in the model ($p<0.001$). Table S3 presents a summary of teen birth odds ratio ranges for selected combinations of chemical exposures on the map axes predicted at fixed levels of the other continuous variables in the smooth terms.

To address sparseness of data at the extremes of the exposure distributions, values on each exposure axis of the OR maps were restricted from the 5th to the 95th percentile (Figures S1 and S2). Higher levels of cord serum HCB and maternal hair Hg (Figure 1A), cord blood Pb (Figure 1B), and cord serum ΣPCB_4 (Figure 1C) were associated with higher risk for subsequent teen birth, although associations were not statistically significant. The ORs predicted for girls born in 1995 to mothers of median age (26 years) at the 95th percentile of the exposure distributions of HCB with Hg, Pb, and ΣPCB_4 were 1.85 (95% confidence interval (CI): 0.15, 22.9; Figure 1A), 2.53 (95% CI: 0.25, 25.5; Figure 1B), and 3.09 (95% CI: 0.29, 32.4; Figure 1C), respectively. However, higher levels of cord serum HCB and cord serum DDE yielded lower risk of teen birth (OR=0.93; 95% CI: 0.1, 12.0; Figure 1D). The protective pattern observed with higher cord serum DDE and HCB remained consistent when predicting and mapping adjusted odds ratios at varying levels of cord serum DDE with the other exposures: maternal hair Hg (Figure S3B), cord blood Pb (Figure S3C), and cord serum ΣPCB_4 (Figure S3D). When associations were plotted on the same color scale for ORs (Figure S4), the greatest variation in risk was observed for associations between cord serum HCB and cord serum ΣPCB_4 (minimum-maximum OR range: 0.13, 3.09).

To assess the effect of the variables included in the mixture smooth at values more representative of the general population in our dataset, Table 3 presents the ORs and 95% confidence intervals for variation in each continuous variable, one at a time, while holding all the other continuous variables constant at the median value. We observed non-linear associations with chemical exposures except for cord serum HCB, which had increasing ORs with increasing exposure values. As was the case with the mapped results, ORs were higher for associations at the highest exposure levels. However, when predicted at median values of other exposures (Table 3) rather than the highest values (Figure 1), lower exposure levels were also associated with increased risk. This may be due to the increased risks observed for girls born to younger mothers who are also likely to have lower levels of most of our targeted exposures (Table S3). Statistically significant elevated ORs were observed for girls born to 14-year-old mothers, the youngest maternal age (OR=4.70, 95% CI: 1.05, 20.97), and for births in 1992, the earliest birth year (OR=2.61, 95% CI: 1.13, 6.02), although with wide confidence intervals.

New Bedford Cohort (NBC) Sensitivity Analyses—Teen birth rates were similar in the NBC and MBRC. Of the 371 NBC girls born in the study area between 1993-1998, 19 (5.12%) had a subsequent teen birth. We observed similar univariable associations with ΣPCB_4 and DDE (Table 1); however, HCB and Pb were also protective in NBC univariable analyses. Predictors of teen birth in the NBC were similar to MBRC with increased risk associated with girls born to younger, single, non-white mothers with less than a high school education who were living in low-income households at the time of their daughter's birth. Mothers of girls who subsequently gave birth as teens also had lower IQ, higher maternal depression symptom scores, and lower HOME scores. Due to the small sample size, GAMs could not be fit with more than two exposures in each mixture smooth. Therefore, we created six mixture models, each of which included a bivariable smooth term with two measured chemical biomarkers: (1) HCB and ΣPCB_4, (2) HCB and Pb, (3) HCB and DDE, (4) ΣPCB_4 and Pb, (5) ΣPCB_4 and DDE, and (6) Pb and DDE. As in the MBRC analysis,

values on each exposure axis were restricted from the 5th to the 95th percentile to address sparseness of data at the extremes of the exposure distributions (Figure S5). Figure 2 presents the ORs for teen births in the NBC across varying levels of exposure combinations. The pattern of associations using the measured biomarkers of exposure, and adjustment for potential confounding covariates only available in the NBC data, were similar to the MBRC results. Of note, lower levels of cord serum DDE also yielded higher risk of teen birth (Figures 2C, 2E, and 2F). Patterns were also similar for models only adjusted for variables available in the MBRC (i.e., excluding maternal depression and HOME score, Figure S6).

To assess the potential for maternal pregnancy diet to negatively confound associations between biomarkers of prenatal DDE exposure and subsequent teen birth, we performed further adjustments. For example, in analyses of DDE and Pb exposure, adjustment for maternal pregnancy organ meat consumption (Figure S7A), seafood consumption (Figure S7B), local produce consumption (Figure S7C), consumption of grains (Figure S7D), pregnancy vitamin use (Figure S7E), and both consumption of local produce and vitamin use (Figure S7F) did not account for DDE's apparent protective association. However, after adjustment for local produce (Figure S7C), vitamin use (Figure S7E) or both (Figure S7F), the apparently monotonic protective association observed with higher DDE shifted so that the highest teen birth risk was now at mid-range DDE levels.

Discussion

By employing a unique and powerful study design, this is among the first studies to assess hypothesized associations between prenatal exposure to environmental mixtures and subsequent teen birth. We focused on a vulnerable population: all girls born in the sociodemographically diverse New Bedford Harbor area of southeastern MA between 1992-1998. We used state-of-the-art approaches to model prenatal chemical exposure in this large study sample and to assess the impact of complex exposure mixtures. Indeed, cross-validated R^2 values for the modeled exposures used in our study showed comparable performance to exposure regression models used in other rigorous epidemiologic studies (40-42). We conducted sensitivity analyses in a subset of girls with measured prenatal exposure biomarkers and additional covariate information for confounding adjustment to assess the robustness of associations observed using modeled exposures.

Increased risk of teen birth was observed among girls with simultaneous prenatal exposure to high levels of multiple organochlorines and metals (Figure 1), an association that would not have been evident in single exposure models (Table 1) or without consideration of the combined impact of multiple co-occurring risk factors (Table 3). Specifically, a mixture of ΣPCB_4, DDE, HCB, Hg, Pb, maternal age at birth, and 1st generation's year of birth were associated with a girl's subsequent risk of teen birth. Risk was greatest among girls with higher prenatal exposures to organochlorines (except DDE) and metals (Figure 1) and who were born earlier in the study period or to younger mothers (Table 3). Increased risk of teen birth among girls born to young mothers is well-documented in previous research (43), and we observed 73 1st generation births to young mothers (< 20 years of age) within our study population (Table S5). We used infant year of birth as a temporal proxy to control for ongoing policies and interventions aimed at reducing teen pregnancy (44,45). In our study

communities, state and regional programs (e.g., Massachusetts Alliance on Teen Pregnancy, Southcoast Hospital Responsible Attitudes towards Pregnancy, Parenting and Prevention Program) have been implemented to address the region's high teen pregnancy rates (46). Study infants were born between 1992 and 1998 so they reached early adolescence (e.g., age 13 years) between 2005 and 2011; teen birth rates declined substantially from 2005 to 2011 (47). For example, between 2007 and 2014, the teen birth rate dropped 42% in New Bedford (48). Temporal declines in teen birth rates among MBRC girls are consistent with these trends.

Associations of modeled prenatal chemical exposures with teen births for the full cohort were generally adverse, as expected, with the exception of DDE, which appeared to have a protective effect (Figures 1 and S3). These results were consistent with sensitivity analyses using the NBC subset with measured prenatal chemical exposures (Figure 2). In other studies of the NBC, associations of prenatal exposure to $\pounds PCB_4$ and DDE with neurobehavior have been negatively confounded by sociodemographic factors and diet (26). Although diets high in fish and fresh produce have been associated with chemical exposures, the neurotoxic effects of prenatal DDE exposure in our analyses may be confounded by the beneficial effects of a healthy maternal diet during pregnancy (49). Availability of maternal diet information during pregnancy in the NBC allowed us to assess whether confounding by maternal diet contributed to the apparent protective effect of DDE. After adjustment for local produce intake and any vitamin use during pregnancy, DDE associations with teen birth became less adverse at lower DDE exposure levels (Figure S7). This supports confounding by maternal diet as a potential contributor to apparent beneficial associations of DDE with teen births; however, residual confounding may still exist.

We did not have measures of postnatal chemical exposures which could also contribute to the risk of teen birth. Prenatal and postnatal exposures may be correlated(50), and our analyses may be confounded if postnatal risk factors are also affected by a shared cause of prenatal exposures that is not explained by the other measured risk factors. Future studies on prenatal exposures and teen birth might benefit from other known or suspected postnatal risk factors.

Maternal substance use (e.g. tobacco, alcohol) during pregnancy, even at low levels, is associated with a range of neurodevelopmental deficits, including behavioral disorders, in offspring (51-53). Any smoking during pregnancy was associated with higher risk of subsequent teen birth in the 1^{st} generation daughters. However, any alcohol consumption showed a protective effect in the univariable analysis, though this may be related to the small number of individuals reporting alcohol use during pregnancy and social desirability bias leading to differential underreporting (54,55).

There is mechanistic support for a role of chemical exposures in risk-taking via alterations in impulse control and reward-driven behaviors. In addition, both organochlorines and metals can act as endocrine disruptors and, in some cases, have been associated with altered pubertal development (56). Alterations in pubertal development, in turn, particularly earlier pubertal development, are associated with earlier age at first sexual intercourse and with the adoption of risky sexual behaviors in adolescence, both of which may result in higher risk of

teen birth (57). Despite this mechanistic support, there are few epidemiologic studies on prenatal chemical exposure mixtures and manifestation of adolescent risk-taking behaviors, particularly teen pregnancy and teen birth. Much of the epidemiologic literature focuses on early life individual and combined exposures and associations with early childhood neurodevelopment and neurobehavioral outcomes, such as ADHD (58,59), although one study found an association between early life Pb exposure and repeat teen pregnancy and tobacco use (60). Taken together, the primary analysis of modeled prenatal exposure mixtures and subsequent teen birth in the MBRC and sensitivity analysis with observed biomarkers in a subset of the population (NBC) add to this critically understudied area of environmental health.

Various statistical approaches to characterizing and assessing mixtures exist, each with their own strengths and limitations (61,62). The extension of generalized additive models to mixtures using the MapGAM package in R allowed us to map cross-sections of odds ratios based on varying levels of two continuous exposures in the mixture, while holding other exposures and covariates constant for interpretation of results. This approach facilitated visualization of complex, multidimensional findings and made relationships among multiple simultaneous exposures readily understandable. In addition, we were able to identify highly susceptible subpopulations, based on both chemical and non-chemical factors, for whom teen birth risk is most extreme (e.g., being born to a teen mother), appreciating that the risk predicted for average population characteristics is expected to be lower. Finally, this method allows for significance testing, in our case, using permutation tests to evaluate the statistical significance of the loess mixture term(s).

Our study focused on teen births as an outcome, as opposed to teen pregnancies. Although studying teen pregnancies would also be meaningful, it was not possible to ascertain whether a 1st generation girl had a pregnancy that did not result in a live birth due to pregnancy termination or miscarriage using birth registry data. Linkage of 1st generation birth records to their subsequent hospitalization records for 2nd generation births restricted the case count to those girls who had a live birth registered through MADPH. Because of missing father's information in MADPH birth records and lack of the identifiers that are required for record linkage, we were unable to ascertain 1st generation boys who may have fathered a pregnancy. Furthermore, linkage for girls was not conducted for those who may have given birth outside of Massachusetts. Thus, there is likely some measurement error in our outcome which could decrease the precision of our findings. Further, rates of engagement in risky sexual activity may be underestimated in our study population. We lacked information on whether the 1st generation child subsequently gave birth multiple times during adolescence or if the birth was a first or later birth, so we could not assess those with repeated teen births, a subset that may be of particular concern (63,64). Covariate adjustment in primary analyses was limited to maternal and infant demographic variables available in MBRC data; therefore, we were unable to adjust for some potential confounders (e.g., quality of home environment, maternal prenatal diet) in those analyses. However, corroboration of our primary findings in sensitivity analyses adjusted for these potential confounders supports the robustness of our main results. Corroboration between results also demonstrates the utility of predictive chemical exposure models derived from a subset of the population to assess health outcomes. This allowed us to conduct mixture analyses in a large population sample that

could accommodate analyses assessing associations between multiple exposures and teen births, a rare outcome that requires a large sample of chemical biomarker exposure estimates not typically available in longitudinal cohort studies.

Our results suggest that prenatal chemical exposures may interact with sociodemographic variables (i.e., mother's age at 1st generation's birth and 1st generation year of birth) to contribute to elevated risk of subsequent teen births in girls born in the southeastern MA study communities. Infants born earlier in the study period to younger mothers demonstrated higher risk of subsequent teen birth at minimum levels of cord serum DDE and maximum levels of HCB, Hg, Pb, and ΣPCB_4. Our analyses leveraged an innovative extension of generalized additive models to characterize and assess hypothesized associations between environmental exposure mixtures and teen births. We combined the power of a large public database (to ascertain sufficient cases of a relatively rare but highly adverse outcome, i.e. teen birth) with a more granular exposure assessment in a cohort study to address a substantial public health issue with long-term, cross-generational implications. Further, we employed exposure mixtures methods that facilitated visualization and clear communication of multidimensional joint exposure effects, thereby identifying and characterizing teen birth risk factors that might otherwise not have been possible with existing analytic tools. Identification of environmental and sociodemographic factors that contribute to highly impactful manifestations of risk-taking behavior, such as teen pregnancy and teen birth, is a public health priority, especially among communities exposed to multiple chemicals. Characterization of vulnerable populations based on combinations of environmental and sociodemographic risk factors could be used to enhance availability of pregnancy risk-reduction and education interventions for those who might benefit most (65). Future research in prospective cohort settings is warranted to ascertain whether the joint exposures examined in this study, and others not examined, elevate teen pregnancy and teen birth risk in other geographic settings and time periods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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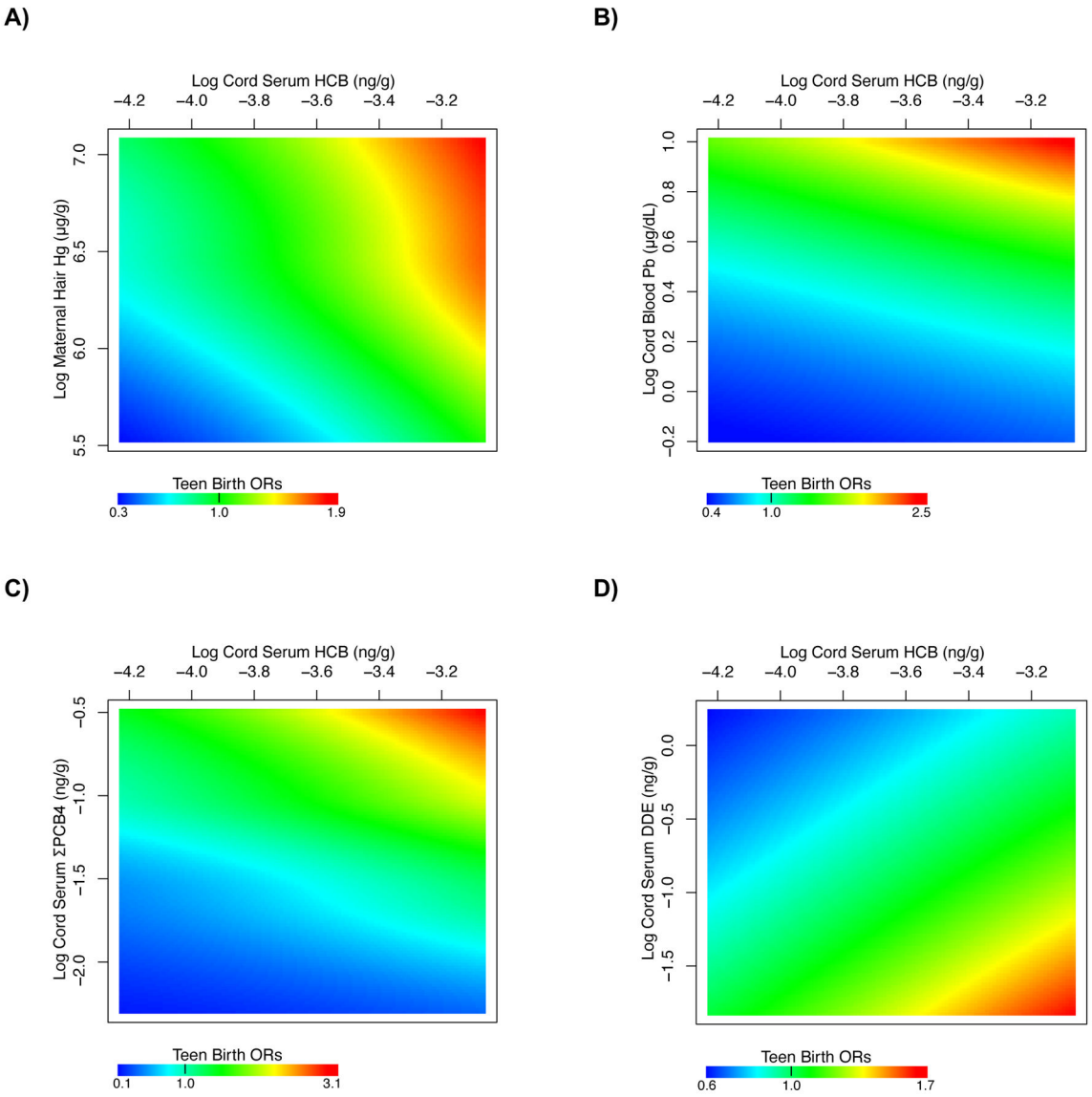

Figure 1. Association between teen birth and prenatal exposure to a mixture of HCB, Hg, Pb, ΣPCB_4, and DDE, as well as maternal age at birth and infant year of birth in Massachusetts Birth Record Cohort (MBRC) female births from 1992-1998 (N=5,865).

Odds ratios for teen birth were predicted for a girl born to a 26-year-old mother in 1995 at varying log cord serum HCB levels on the x-axis and varying log maternal hair Hg (A); log cord blood Pb (B); log cord serum ΣPCB_4 (C); and log cord serum DDE (D) on the y-axis. For each map, exposures not on the axes were held constant at the maximum value, hypothesized to be the greatest risk. Analyses were further adjusted for median household income, parental education, maternal marital status, prenatal care payment source, parity, maternal race, adequacy of prenatal care, breastfeeding initiation at hospital, year maternal residence built, and maternal smoking during pregnancy. Odds ratios were calculated using the median predicted log odds of each surface as the referent.

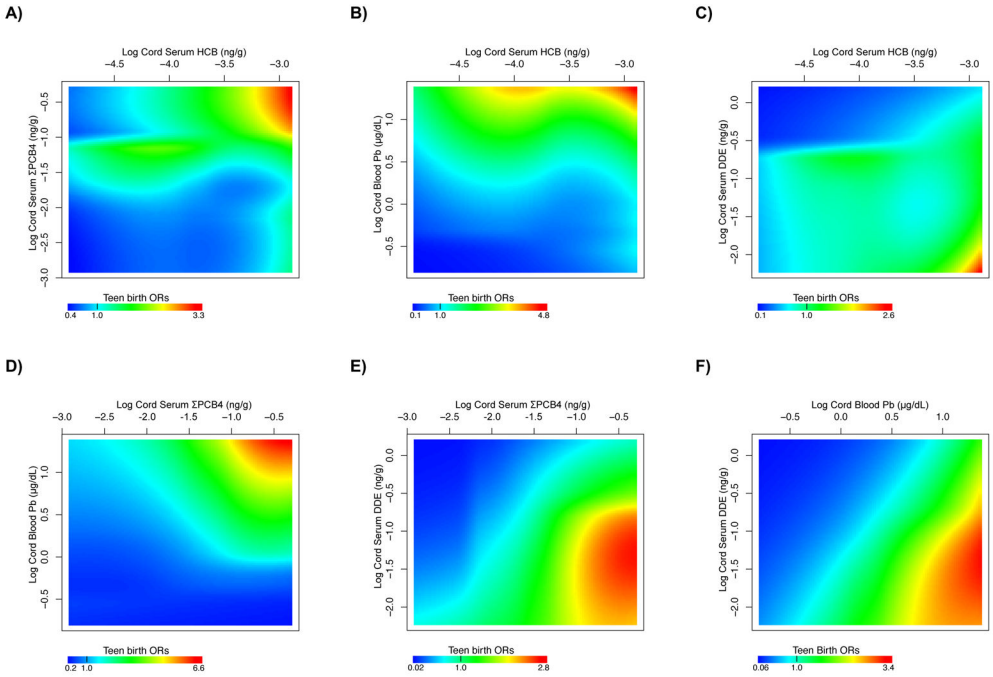

Figure 2. Associations between teen birth and mixtures of measured biomarkers of prenatal exposures among females in the New Bedford Cohort (NBC) study, born 1993-1998 (N=371).

Odds ratios for teen birth were predicted using the median value of covariates and were calculated using the median predicted log odds of each surface as the referent. Analyses were adjusted for maternal depression, maternal age at the girl's birth (1st generation), quality of the home environment, maternal race/ethnicity, whether the mother was non-U.S.-born, and annual household income at the girl's (1st generation) birth.

Table 1.

Distributions of predicted prenatal exposures in the Massachusetts Birth Record Cohort (MBRC)[a] (born 1992-1998, N=5,865), distributions of measured prenatal exposure biomarkers in the New Bedford Cohort (NBC)[b] study (born 1993-1998, N=371), and univariable associations with risk of subsequent teen birth.

	Cord Serum ΣPCB_4 (ng/g)	Cord Serum DDE (ng/g)	Cord Serum HCB (ng/g)	Cord Blood Pb (μg/dL)	Maternal Hair Hg (μg/g)
MBRC gave birth as teen (n=291)					
5th %	0.01	0.14	0.02	1.03	0.24
Median	0.17	0.27	0.03	1.55	0.43
95th%	0.51	1.52	0.05	3.10	1.02
MBRC did not give birth as teen (n=5,574)					
5th%	0.10	0.17	0.01	0.82	0.25
Median	0.21	0.35	0.03	1.42	0.51
95th%	0.61	1.23	0.05	2.69	1.19
MBRC OR (95% CI)	0.58 (0.39, 0.87)	0.61 (0.40, 0.92)	1.70 (1.15, 2.53)	3.33 (2.27, 4.89)	0.64 (0.44, 0.94)
NBC gave birth as teen (n=19)					
5th%	0.04	0.09	0.01	0.26	0.13
Median	0.15	0.27	0.02	1.53	0.25
95th%	0.34	0.49	0.03	3.69	0.67
Missing (n)	0	0	0	0	7
NBC did not give birth as teen (n=352)					
5th%	0.06	0.11	0.01	0.46	0.13
Median	0.19	0.31	0.02	1.13	0.45
95th%	0.75	1.33	0.05	4.12	1.80
Missing (n)	16	16	16	21	117
NBC OR (95% CI)	0.17 (0.03,0.83)	0.14 (0.02,0.79)	0.51 (0.14,1.81)	0.92 (0.28,3.01)	N/A[c]

[a] The MBRC consists of girls born in the New Bedford Harbor study area (towns of New Bedford, Acushnet, Dartmouth and Fairhaven, Massachusetts) between 1992-1998.

[b] The NBC represents a subset of girls born in the New Bedford Harbor study area between 1993-1998.

[c] Hg was not included in the sensitivity analysis due to a large number of missing values in the NBC.

Abbreviations: ΣPCB_4, sum of four prevalent polychlorinated biphenyl (PCB) congeners (118, 138, 153, and 180); DDE, ρ,ρ′-dichlorodiphenyl dichloroethylene; HCB, hexachlorobenzene; Pb, lead; Hg, mercury; CI, confidence interval; OR, unadjusted odds ratio for change from 5th to 95th percentile of exposure.

Table 2.

Maternal and infant demographic, health and lifestyle characteristics[a] and their association with the risk of teen birth among all female infants born in the New Bedford Harbor study area[b], 1992-1998 (N=5,865).

	Gave birth as teen (n=291) n (%)	Did not give birth as teen (n=5,574) n (%)	Univariable OR (95% CI)	Final Mixture OR[c] (95% CI)
Infant's (1st Generation) Characteristics				
Birthweight (g) (mean (sd))	3,263 (508)	3,303 (511)	0.78 (0.54, 1.13)[d]	N/A
Year of birth			0.82 (0.77, 0.87)[e]	S
1992	71 (24.4)	846 (15.2)		
1993	56 (19.2)	809 (14.5)		
1994	60 (20.6)	837 (15.0)		
1995	31 (10.7)	739 (13.3)		
1996	24 (8.2)	750 (13.5)		
1997	27 (9.3)	765 (13.7)		
1998	22 (7.6)	828 (14.8)		
Gestational Age (wks) (mean (sd))	39.6 (1.78)	39.5 (1.81)	1.04 (0.98, 1.13)	N/A
Characteristics of Infant's (1st Generation) Mother				
Age at infant's birth (yrs) (mean (sd))	23.4 (5.4)	26.1 (5.8)	0.91 (0.89, 0.94)	S
Pregnancy weight gain (lbs) (mean (sd))	27.5 (12.6)	29.6 (12.2)	0.98 (0.97, 0.99)	N/A
Race/Ethnicity				
Non-Hispanic White	181 (62.2)	4,386 (78.7)	referent	referent
Non-Hispanic African	18 (6.2)	248 (4.4)	1.76 (1.06, 2.90)	1.12 (0.24, 2.94)
American				
Hispanic	70 (24.1)	553 (9.9)	3.07 (2.30, 4.10)	1.54 (0.87, 2.73)
Non-Hispanic Other	22 (7.5)	367 (6.6)	1.45 (0.92, 2.29)	1.77 (0.66, 4.73)
Missing	0 (0.0)	20 (0.4)		
Country of birth				
Azores/Portugal	70 (24.0)	1,370 (24.6)	0.98 (0.74, 1.30)	N/A
Cape Verde	27 (9.3)	463 (8.3)	1.12 (0.74, 1.69)	N/A
Other	194 (66.7)	3,721 (66.7)	referent	
Missing	0 (0.0)	20 (0.4)		
Any smoking during pregnancy				
Yes	94 (32.3)	1,261 (22.6)	1.63 (1.26, 2.09)	1.17 (0.74, 1.85)
No	197 (67.7)	4,295 (77.1)	referent	referent
Missing	0 (0.0)	18 (0.3)		
Any alcohol use during pregnancy				
Yes	3 (1.0)	102 (1.8)	0.56 (0.18, 1.76)	N/A
No	288 (99.0)	5,447 (94.3)	referent	
Missing	0 (0.0)	25 (8.6)		
Initiated breastfeeding at hospital				
Yes	81 (27.8)	2,271 (40.7)	0.56 (0.43, 0.72)	0.64 (0.41, 0.99)

	Gave birth as teen (n=291) n (%)	Did not give birth as teen (n=5,574) n (%)	Univariable OR (95% CI)	Final Mixture OR[c] (95% CI)
No	210 (72.2)	3,272 (58.7)	referent	referent
Missing	0 (0.0)	31 (0.6)		
Marital status at child's birth				
Married	103 (35.4)	3,296 (59.1)	0.38 (0.29, 0.48)	0.82 (0.49, 1.38)
Unmarried	188 (64.6)	2,278 (40.9)	referent	referent
Missing	0 (0.0)	0 (0.0)		
Maternal education at child's birth				
<High school	158 (54.3)	1,529 (27.4)	3.15 (2.48, 4.00)	1.49 (0.73, 1.70)
≥High school	132 (45.4)	4,023 (72.2)	referent	referent
Missing	1 (0.3)	22 (0.4)		
Parity				
1	110 (37.8)	2,421 (43.4)	referent	referent
2	96 (33.0)	1,848 (33.2)	1.14 (0.86, 1.51)	1.39 (0.86, 2.24)
3	54 (18.6)	825 (14.8)	1.44 (1.03, 2.01)	1.61 (0.89, 2.89)
≥4	31 (10.6)	452 (8.1)	1.51 (1.00, 2.28)	1.26 (0.53, 3.01)
Missing	0 (0.0)	28 (0.5)		
Adequate prenatal care (Kessner Index)				
Yes	270 (92.8)	5,260 (94.4)	0.60 (0.52, 0.87)	0.91 (0.61, 1.36)
No	21 (7.2)	244 (4.4)	referent	referent
Missing	0 (0.0)	70 (1.3)		
Prenatal care source of payment				
Private insurance	65 (22.3)	2,891 (51.9)	0.26 (0.20, 0.35)	0.66 (0.41, 1.07)
Other payment	226 (77.7)	2,647 (47.5)	referent	referent
Missing	0 (0.0)	36 (0.6)		
Delivery source of payment				
Private insurance	65 (22.3)	2,886 (51.8)	0.26 (0.20, 0.35)	N/A
Other payment	225 (77.4)	2,640 (47.4)	referent	
Missing	1 (0.3)	48 (0.8)		
Other Household Characteristics				
Residential distance to NBH (m) (mean (sd))	1,182 (1,329)	1,633 (3,301)	0.38 (0.23, 0.64)[d]	N/A
Residential distance to major road (m) (mean (sd))	111 (147)	194 (391)	0.39 (0.24, 0.65)[d]	N/A
Year maternal residence built				
≤1950	211 (72.5)	3,811 (68.4)	1.69 (1.16, 2.46)	0.90 (0.44, 1.84)
1951-1970	36 (12.4)	604 (10.8)	1.82 (1.12, 2.96)	0.90 (0.51, 1.60)
>1970	32 (11.0)	975 (17.5)	referent	referent
Missing	12 (4.1)	184 (3.3)		
Median household income at child's birth				
<$20,000/year	114 (39.2)	1,192 (21.4)	2.37 (1.86, 3.02)	1.48 (0.96, 2.28)
≤$20,000/year	177 (60.8)	4,382 (78.6)	referent	referent
Missing	0 (0.0)	0 (0.0)		

	Gave birth as teen (n=291) n (%)	Did not give birth as teen (n=5,574) n (%)	Univariable OR (95% CI)	Final Mixture OR[c] (95% CI)
Paternal education at birth				
<High school	154 (52.9)	1,798 (32.3)	2.36 (1.86, 2.99)	1.12 (0.73, 1.70)
≥High school	137 (47.1)	3,776 (67.7)	referent	referent

[a] Ascertained from Massachusetts birth records, i.e., the Massachusetts Birth Record Cohort (MBRC)

[b] Towns of New Bedford, Acushnet, Dartmouth and Fairhaven, Massachusetts.

[c] Missing values were excluded from the analyses

[d] Odds ratio calculated for change from 5th to 95th percentile

[e] Year of birth modeled as a continuous variable

Abbreviations: OR, odds ratio; CI, confidence interval; sd, standard deviation. N/A indicates variable was not included in final mixture model; S indicates variable was in the smooth; NBH, New Bedford Harbor.

Table 3.

Odds ratios (ORs) and 95% confidence intervals (CI) calculated for a range of values of continuous covariates included in the mixture smooths predicting risk of teen birth among 5,685 Massachusetts Birth Record Cohort participants.

Variable	Value		OR[a]	95% CI
Log HCB (ng/g)	Min	−4.78	0.80	(0.19,3.37)
	25th%	−3.82	1.19	(0.52,2.74)
	Median	−3.61	1.34	(0.60,2.98)
	75th%	−3.38	1.54	(0.64,3.68)
	Max	−2.23	3.77	(0.66,21.46)
Log Hg (μg/g)	Min	4.75	2.60	(0.54,12.53)
	25th%	5.91	1.12	(0.64,1.94)
	Median	6.22	1.04	(0.62,1.73)
	75th %	6.58	0.71	(0.40,1.27)
	Max	8.07	1.72	(0.22,13.19)
Log Pb (μg/dL)	Min	−0.83	2.12	(0.38,11.65)
	25th%	0.12	1.33	(0.67,2.68)
	Median	0.36	1.34	(0.60,2.98)
	75th %	0.62	1.33	(0.52,3.40)
	Max	1.82	2.41	(0.23,24.98)
Log £PCB_4 (ng/g)	Min	−2.93	1.48	(0.26,8.36)
	25th%	−1.91	1.12	(0.54,2.31)
	Median	−1.58	1.34	(0.60,2.98)
	75th%	−1.18	1.70	(0.53,5.44)
	Max	0.96	21.91	(1.10,437.50)
Log DDE (ng/g)	Min	−2.30	2.52	(0.63,10.16)
	25th%	−1.44	1.53	(0.64,3.65)
	Median	−1.06	1.34	(0.60,2.98)
	75th%	−0.67	1.25	(0.52,3.04)
	Max	1.87	3.25	(0.25,42.72)
Infant Year of Birth	Min	1992	2.61	(1.13,6.02)
	25th%	1993	2.07	(0.94,4.53)
	Median	1995	1.34	(0.60,2.98)
	75th %	1997	0.89	(0.35,2.26)
	Max	1998	0.74	(0.27,2.09)
Maternal Age (year)	Min	14	4.70	(1.05,20.97)
	25th%	22	1.91	(0.73,5.01)
	Median	26	1.34	(0.60,2.98)
	75th%	31	0.86	(0.39,1.93)
	Max	47	0.65	(0.06,7.06)

[a]Predictions were made varying only the continuous variable of interest. For other variables in the model, each prediction used the median values for continuous variables and categorical variable values were assigned as follows: maternal/paternal education high school or higher; maternal race non-Hispanic white; no smoking during pregnancy; non-initiation of breastfeeding at hospital; parity of 2; adequate prenatal care; private insurance prenatal care source of payment; maternal residence at birth built in or before 1970; and median household income $20,000 or greater.

Abbreviations: DDE, dichlorodiphenyl dichloroethylene; HCB, hexachlorobenzene; Hg, mercury; ΣPCB_4, sum of four prevalent PCB congeners (118, 138, 153, 180); Pb, lead.