A Summary of Recent Findings on Birth Outcomes and Developmental Effects of Prenatal ETS, PAH, and Pesticide Exposures

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Abstract

Inner-city minority populations are high-risk groups for adverse birth outcomes and also more likely to be exposed to environmental contaminants, including environmental tobacco smoke (ETS), benzo[a]pyrene B[a]P, other ambient polycyclic aromatic hydrocarbons (global PAHs), and residential pesticides. The Columbia Center for Children's Environmental Health (CCCEH) is conducting a prospective cohort study of 700 northern Manhattan pregnant women and newborns to examine the effects of prenatal exposure to these common toxicants on fetal growth, early neurodevelopment, and respiratory health. This paper summarizes results of three published studies demonstrating the effects of prenatal ETS, PAH, and pesticides on birth outcomes and/or neurocognitive development [Perera FP, Rauh V, Whyatt RM, Tsai WY, Bernert JT, Tu YH, et al. Molecular evidence of an interaction between prenatal environment exposures on birth outcomes in a multiethnic population. Environ Health Perspect 2004;12:630–62; Rauh VA, Whyatt RM, Garfinkel R, Andrews H, Hoepner L, Reyes A, et al. Developmental effects of exposure to environmental tobacco smoke and material hardship among inner-city children. Neurotoxicol Teratol 2004;26:373–85; Whyatt RM, Rauh V, Barr DB, Camann DE, Andrews HF, Garfinkel R, et al. Prenatal insecticide exposures, birth weight and length among an urban minority cohort. Environ Health Perspect, in press]. To evaluate the effects of prenatal exposure to ETS, PAHs, and pesticides, researchers analyzed questionnaire data, cord blood plasma (including biomarkers of ETS and pesticide exposure), and B[a]P-DNA adducts (a molecular dosimeter of PAHs). Self-reported ETS was associated with decreased head circumference (P = 0.04), and there was a significant interaction between ETS and adducts such that combined exposure had a significant multiplicative effect on birth weight (P = 0.04) and head circumference (P = 0.01) after adjusting for confounders. A second analysis examined the neurotoxic effects of prenatal ETS exposure and postpartum material hardship (unmet basic needs in the areas of food, housing, and clothing) on 2-year cognitive development. Both exposures depressed cognitive development (P < 0.05), and there was a significant interaction such that children with exposure to both ETS and material hardship exhibited the greatest cognitive deficit (7.1 points). A third analysis found that cord chlorpyrifos, and a combined measure of cord chlorpyrifos, diazinon, and propoxur-metabolite, were inversely associated with birth weight and/or length (P < 0.05). These results underscore the importance of policies that reduce exposure to ETS, air pollution, and pesticides with potentially adverse effects on fetal growth and child neurodevelopment.

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INTRODUCTION

There is growing evidence of the adverse impact of exposures to ambient and indoor air pollutants on fetal growth and early childhood neurodevelopment (Perera et al., 1999). Human and experimental studies show that the fetus and infant are more sensitive than adults to many environmental toxicants, including environmental tobacco smoke (ETS), polycyclic aromatic hydrocarbons (PAHs), and residential pesticides such as diazinon and chlorpyrifos (Mott et al., 1994; Natural Resources Defense Council, 1993; WHO, 1986; Whyatt and Perera, 1995; Whyatt et al., in press). Exposures to ETS and PAHs are especially high among low-income, urban, and minority populations, both because of the uneven distribution of outdoor pollution sources (Chuang et al., 1999; Wernette and Nieves, 1992) and higher smoking rates in these populations (Brownson et al., 2002; Heritage, 1992; Pirkle et al., 1996; Wasserman et al., 2000; Weitzman et al., 2002; Wernette and Nieves, 1992; Chen and Petitti, 1995; Wagenknecht et al., 1993; Metzer et al., 1995). In addition, these minority populations are also more likely to experience poverty and a range of accompanying hardship, including substandard housing, poor nutrition, and inadequate health care (Adler et al., 1999; Kahn and Kamerman, 2002; Polednak, 1997). Efforts to operationalize the hazards the accompany poverty reveal considerable heterogeneity of hardships within low-income populations (Manfredi et al., 1992). These conditions of daily living may mediate the adverse health effects of poverty (Rogers et al., 1998), translating low income into developmental delay. In New York City, it is estimated that 74% of the children in Central Harlem and 60% in Washington Heights live in fair to poor quality housing, as compared to 38% city-wide (Citizen's Committee for Children of New York, 1997). Across the United States, 10 million children under the age of 6 years are exposed to residential ETS (American Cancer Society, 2001), including exposures in the homes of relatives and caregivers (Hopper and Craig, 2000). Elevated cotinine levels, indicative of ETS exposure, have been reported in 70–80% of inner-city children (Weaver et al., 1996). In addition, 60% of Hispanics and 50% of African Americans, compared to 33% of Caucasians, live in areas failing to meet two or more of the national ambient air quality standards (Metzer et al., 1995; Wernette and Nieves, 1992).

With regard to pesticide exposure, a 1997 study of pesticide use in New York State found that the heaviest application (in gallons and pounds) of legally registered pesticides by licensed applicators occurred not in the agricultural counties but in the boroughs of Manhattan and Brooklyn in New York City (Thier et al., 1998). Chlorpyrifos was the insecticide most heavily applied in New York City, and one of the insecticides most heavily used by pest control operators for the New York City Housing Authority (Landrigan et al., 1999; Thier et al., 1998).

In the first of three analyses set forth in this paper, Perera et al. evaluated the effects of prenatal exposure to two common urban pollutants: environmental PAHs estimated by DNA adducts in white blood cells formed by B[a]P, a representative PAH, and ETS estimated by questionnaire data and plasma concentrations of cotinine (Perera et al., 2004). In addition to being genotoxic and carcinogenic, PAHs such as benzo[a]pyrene (B[a]P) are endocrine disruptors (Bui et al., 1986; Davis et al., 1993; Bostrom et al., 2002). The authors reported earlier that prenatal PAH exposure estimated by personal air monitoring was associated with reduced birth weight and head circumference among African Americans in the present NYC cohort (Perera et al., 2003). ETS, a complex mixture of over 4000 chemicals, including PAH and carbon monoxide (Leikauf et al., 1995), has been shown to adversely affect fetal growth as well as child growth and development (reviewed in Eskenazi et al., 1995; Etzel, 1997; National Research Council, 1986). Adverse effects include deficits in birth weight, birth length, and cognitive functioning at age 3 (Janerich et al., 1990; Martinez et al., 1994; Schuster-Kolbe and Ludwig, 1994; Sexton et al., 1990). Here the hypothesis was that prenatal exposure to these two environmental pollutants alone and/or in combination is negatively associated with birth weight, length, and head circumference, after controlling for the effects of known physical, biologic, and toxic determinants of fetal growth (Perera et al., 2004).

As reported previously, the study cohort has substantial exposure to these contaminants during pregnancy (Whyatt et al., 2001, 2002, 2003; Perera et al., 2002). Specifically, analysis of PAHs in air samples from the first 250 subjects showed that all samples had detectable levels of one or more carcinogenic PAH, ranging over four orders of magnitude (Perera et al., 2002). Almost half of the mothers and infants initially enrolled had cotinine levels indicative of ETS exposure ($\geq$0.05–25 ng/mL). Maternal and newborn plasma cotinine levels were significantly higher for mothers who reported smoking by others in the household than for mothers who reported no smoking in the home ($P <$ 0.001) (Perera et al., 2004).

Adverse socioeconomic conditions with consistent effects on fetal and child neurodevelopment have been demonstrated in a range of populations (Bradley and Corwyn, 2002; DiPietro et al., 1998), and could have been mediated by nutrition, substance abuse, health service delivery, environmental agents, psychosocial stress (Hoffman and Hatch, 1996; Lupien et al., 2000), or other health behavioral pathways (DiPietro, 2000). Such living conditions, brought on by social adversity, may bring about health and developmental problems associated with poverty (Rogers et al., 1998), translating low income into illness and developmental delay. Mechanisms underlying these pathways, however, are unclear (Rauh et al., 2004). In the second analysis described here, Rauh et al. assessed the impact of prenatal exposure to residential ETS at high and low levels of material hardship (a marker for deprivation in the areas of food, housing, and clothing) while adjusting for other toxicant exposures and social risk factors, and excluding women who actively smoked during pregnancy (Rauh et al., 2004). The hypothesis was that prenatal ETS exposure negatively affects early child development and that hardships exacerbate the harmful impact of ETS, after adjustment for other biomedical and demographic risks. The contribution of postnatal ETS exposure to child development, beyond the effects of prenatal exposure, was also assessed (Rauh et al., 2004).

In the third analysis presented here, Whyatt et al. evaluated the association between birth outcomes and levels of chlorpyrifos, diazinon, and propoxur measured in umbilical cord blood samples collected at delivery. The prospective cohort study has shown widespread pesticide use during pregnancy in minority communities in New York City (Whyatt et al., 2002, 2003). Specifically, of the 459 African American and Dominican women initially interviewed, 85% reported using some form of pest control measures during pregnancy and 35% reported using an exterminator. Most of the pesticide use was for cockroach control (Whyatt et al., 2002). All women had detectable levels of at least three insecticides (the organophosphates chlorpyrifos and diazinon and the carbamate propoxur) in personal air samples collected over 48 h during the third trimester. The insecticides were detected in 45–74% of blood samples collected from the mothers and newborns at delivery; maternal and newborn levels were similar and highly correlated, indicating the pesticides had been transferred from the mother to fetus during pregnancy (Whyatt et al., 2003). These findings raise concerns over the potential health effects of residential pesticide use to the developing fetus.

MATERIAL AND METHODS

Study Subjects

The subjects of this report are Dominican and African American women residing in Washington Heights, Central Harlem, and the South Bronx who delivered at New York Presbyterian Medical Center (NYPMC), Harlem Hospital (HH), or their satellite clinics between April 98 and October 2002, and enrolled in a cohort study concerning the impact of indoor and ambient pollutants undertaken by CCCEH (Perera et al., 2002, 2003). Ethnicity was based on self-identification. Non-smoking women (classified by self-report and validated by cotinine levels less than 25 ng/mL), aged 18–35, who self-identified as African American or Dominican, and who registered at the OB/GYN clinics at NYPMC and HH by the 20th week of pregnancy were approached for consent to participate. Eligible women were free of diabetes, hypertension, and known HIV, documented or reported drug or alcohol abuse, and had resided in the area for at least 1 year (Perera et al., 2004). Most of the deliveries were full-term since women were not fully enrolled until environmental measures had been collected during the third trimester and blood samples (from the mother and/or newborn) had been obtained at delivery (Whyatt et al., in press). The mean gestational age at delivery was 39.5 weeks (Perera et al., 2004) and length of gestation was treated as a covariate in most analyses of toxicant effects. Current medical records were available and examined for gestational length and previous history. Women with previous pregnancies were eligible, however, multiple births were excluded. Multiple family members are not included in this sample.

The overall cohort consisted of 588 women who were "fully enrolled", that is, had prenatal monitoring, complete questionnaire data, and contributed a blood sample (from cord, mother or both) at the time of delivery. The retention rate for the full cohort was 89.9% (or 529) at the 2-year follow-up. There was no significant difference between women who were retained in the study versus those who were lost to follow-up with respect to maternal age, ethnicity, marital status, education, income, gestational age, or birth weight of the newborn. Even though all the subjects are drawn from the same parent population, the numbers of subjects in each of the three analyses varied due to differences in the size of the subset with complete measures at the time of each report and the availability of data for each of the different end-points. Therefore, each of the three studies is based on a sub-sample of the

total cohort. The Perera et al. analysis was based on a sub-sample of 214 subjects with adduct measurements in umbilical cord blood samples (in some cases the amount of blood collected was inadequate for the assay), and complete questionnaire and medical record data used as covariates in the multi-regression models. Rauh et al. utilized data from 226 subjects from the cohort, with developmental outcomes measured at 24 months postnatally. Whyatt et al. analyzed data on birth outcomes and insecticide levels in blood samples collected at delivery from 314 newborns.

Personal Interview

A trained bilingual interviewer administered a 45-min questionnaire during the last trimester of pregnancy, at 6, 12, and 24 months postpartum. The content included: socioeconomic and demographic information, residential history, maternal education level, living conditions during the current pregnancy (including housing quality and material hardship), history of exposure to active and passive smoking, alcohol, drugs, and PAH-containing foods (frequency of consumption of blackened meat, chicken or fish). ETS exposure was measured by a set of questions about timing, frequency, and amount of exposure to cigarette, cigar, and pipe smoke in the home. A measure of material hardship, originally developed by Mayer and Jencks (1988), assessed the level of unmet basic needs in the areas of food, housing, and clothing. Material hardship was defined as the amount of unmet basic needs; i.e., going without or having inadequate food, housing or clothing at some point in the past year each counted as one unmet need. Two or more unmet needs were considered 'high hardships', as compared with fewer than two ('low hardships'). The Psychiatric Epidemiology Research Instrument Demoralization Scale (Dohren-wend et al., 1978) was included in the interview as a measure of maternal nonspecific psychological distress. It has been used in previous studies of stressful living conditions (e.g., Dohrenwend, 1981). Information about pesticide use included whether or not any pest control measures were used by an exterminator or by others (the woman herself, other household members or the building superintendent) during pregnancy and if so, what types of measures were used (Perera et al., 2003; Whyatt et al., 2002, 2003).

Prenatal Personal Air Monitoring

As described in detail previously (Perera et al., 2003; Whyatt et al., 2002, 2003), women in the cohort were asked to wear a small backpack during the third trimester of pregnancy holding a personal ambient air monitor during the daytime hours for two consecutive days and to place the monitor near the bed at night. The personal air sampling pumps operated continuously at 4 L/min (LPM) over this period, collecting particles of ≤2.5 microns in diameter on a pre-cleaned quartz microfiber filter and collecting semivolatile vapors and aerosols on a polyurethane foam (PUF) cartridge back-up. Analyses for pesticide levels were carried out at Southwest Research Institute as described (Perera et al., 2003; Whyatt et al., 2002, 2003). For quality control (QC), each personal monitoring device was coded as to accuracy in flow rate, time, and completeness of documentation; and samples with unacceptable QC scores were excluded from analyses. The personal monitoring took place between February, 1998 and May, 2002.

Biologic Sample Collection and Analysis

For all three analyses, maternal blood (30–35 mL) was collected within 1 day postpartum, and umbilical cord blood (30–60 mL) was collected at delivery (Rauh et al., 2004). Samples were transported to the laboratory immediately, where buffy coat, packed red blood cells, and plasma samples were separated and stored at $-70\,^{\circ}C$. A portion of each sample was shipped to the Centers for Disease Control (CDC) for analysis of plasma cotinine using high-performance liquid chromatography atmospheric-pressure ionization tandem mass spectrometry (Bernert et al., 1994). The limit of detection for cotinine was 0.05 ng/mL. The maternal and cord plasma concentrations of cotinine were significantly correlated ($r = 0.88$, $P < 0.001$). Lead in umbilical cord blood was analyzed by Zeeman graphite furnace atomic absorption spectrometry, using a phosphate/Triton X-100/nitric acid matrix modifier. B[a]P-DNA adducts in extracted white blood cell (WBC) DNA from maternal and cord blood, were analyzed by the HPLC/fluorescence method of (Alexandrov et al., 1992), which uses an HPLC method to detect B[a]P tetromers. For chlorpyrifos and diazinon, the parent compound was measured in plasma and for propoxur, the chemical-specific metabolite, 2-isopropoxyphenol was measured (Whyatt et al., 2003).

Measures of Fetal Growth and Child Development

Gestational age, birth weight, birth length, and head circumference data were abstracted from maternal and infant medical records by trained research workers. In

the Rauh et al. analysis, the Bayley Scales of Infant Intelligence-II were used to assess cognitive development at 24 months of age (Bayley, 1993). Each child was tested by a bilingual research assistant, trained and checked for reliability, under controlled conditions at the Children's Center offices (Rauh et al., 2004). Each scale provides a Developmental Quotient (raw score/ chronological age), which generates a Mental Development Index (MDI) and a corresponding Psychomotor Development Index (PDI); only the results of the MDI were used for the present report. Bayley Scales have been shown to be sensitive to the effects of toxic exposures such as low-level intrauterine lead (Bellinger et al., 1987). In the present Rauh et al. analysis, the inter-rater reliability for the 24-month MDI was $r = 0.92$, based on double scoring of a random 5% of the sample. In addition to the continuous MDI score, Rauh et al. also used the standardized cut-point to classify children as significantly delayed (<80) (Rauh et al., 2004).

Statistical Analysis

To exclude active smokers for all three studies discussed, subjects with cotinine levels >15 ng/mL were excluded (Perera et al., 2003). Adducts were used both as a continuous variable and as a dichotomous one. Perera et al. defined high adducts as greater than 0.36 adducts/10^{-8} nucleotides (the median of the detectable adduct values or the upper 20%) (Perera et al., 2004). As in our prior study (Perera, 2000), in the analysis of the relationship between adducts and birth outcomes, cord blood adducts were used as the independent variable. Samples with non-detectable levels of cotinine were assigned a value equal to LOD/2. The maternal and cord plasma concentrations of cotinine were significantly correlated ($r = 0.887$, $P < 0.001$ by Spearman's rank). Therefore, in the 30 cases where the umbilical cord cotinine levels were not available, the mothers' values were used. High/low cotinine was dichotomized using the median of all samples as the cutpoint (0.0435 ng/mL).

Perera et al. analyzed the relationships between the exposure variables and the birth outcomes by multiple regression, adjusting for known or potential confounders. In addition to cord blood adducts dichotomized as high/low and self-reported ETS (yes/no smokers in the home), the final regression model included covariates representing known or suspected risk factors that were associated with birth outcomes ($P \leq 0.1$ by linear regression). These variables are defined in Table 1 (Perera et al., 2004). Birth outcomes were log transformed to provide a better fit to the data and/or to

Table 1

Associations between all covariates and birth outcomes by multiple linear regression[a] (Perera et al., 2004)

		Birth weight	Birth length	Head circumference
B[a]P-DNA	β	0.020	−0.005	0.007
	P	0.49	0.64	0.39
Environmental tobacco smoke[b]	β	−0.003	−0.007	−0.005
	P	0.90	0.32	0.43
Interaction	β	−0.088	−0.014	−0.032
	P	0.05	0.39	0.01
Ethnicity[c]	β	−0.004	0.015	−0.012
	P	0.85	0.03	0.04
Gender[d]	β	0.011	0.011	0.017
	P	0.55	0.07	0.002
BMI	β	0.005	0.001	0.001
	P	<0.001	0.01	0.01
Dietary PAH	β	−0.006	−0.002	0.001
	P	0.04	0.05	0.26
Gestational age[e]	β	1.416	0.526	0.387
	P	<0.001	<0.001	<0.001
Caesarian	β			0.003
	P			0.63
	n	214	208	207

[a] Covariates included ethnicity (African American or Dominican), gender of newborns, maternal BMI (weight (kg)/height (m)^2), dietary PAH (frequency of eating fried, broiled or barbecued food during the last 2 weeks), gestational age. For head circumference, the model also included Caesarian section (yes or no).
[b] ETS in the home (0 = no; 1 = yes).
[c] African American = 1; Hispanic = 0.
[d] Male = 0; female = 1.
[e] Birth outcomes were log (ln) transformed.

approximate the normal distribution and stabilize the variance. Model 1 to model 3 evaluated the main effects of self-reported ETS, high/low cotinine, and high/low B[a]P-DNA, adjusting for potential confounders including ethnicity, body mass index (BMI), gestational age, dietary PAHs, infant gender, and Caesarian delivery (a predictor of head circumference). Income ($<10,000$ or $\geq 10,000$ per household), parity (0 or ≥ 1 live birth), social adversity (a composite score based on marital status, income, education, and whether currently on assistance), alcohol consumption (yes/no) were not significant predictors of outcomes ($p > 0.1$) and were not included. The other variables, including dietary PAH, were included as covariates. The final models tested the interaction between adducts and ETS (or cotinine) using appropriate interaction terms (Perera et al., 2004).

Rauh et al. used Chi-square analysis and logistic regression of self-reported ETS exposure on cotinine assay levels as tests of association for biological ver-

ification of the ETS measure (Rauh et al., 2004). Intrauterine lead levels (umbilical cord blood samples) ranged from non-detectable to 7.6 µg/dL, with a mean of 1.209 µg/dL, and were log (ln) transformed to approximate the normal distribution. Analysis of variance and Chi-square analysis were used to evaluate the construct validity of the material hardship measure against poverty and the Psychiatric Epidemiologic Research Instrument Demoralization Scale. Consistent with the literature linking psychological distress with measures of SES, regression of demoralization on hardships showed that total number of hardships was significantly and positively associated with demoralization ($P < 0.001$), after adjustment for income and race/ethnicity. Based on the correlations between the measures of demoralization, poverty, and material hardships, both cross-sectionally and over time, we concluded that: (1) material hardship was moderately, not highly, associated with poverty (r's ranged from 0.08 [NS] to 0.24 [$P < 0.001$]), and associations were strongest at the same time point (all P-values <0.001); (2) material hardship was relatively stable over time, as indicated by significant correlations of repeated measures from pregnancy through the child's second year (r's ranged from 0.24 to 0.42, all P-values <0.001); (3) maternal psychological distress was a function of material hardship (all P-values <0.001) to a greater degree than it was related to the income measure of poverty (r's ranged from 0.05 to 0.27, some P-values <0.001), suggesting that some of the conditions that accompany poverty may be more important determinants of maternal adjustment than income alone.

Stability of socioeconomic indicators over time was determined by correlational analysis. The relationship between exposures and cognitive development was analyzed by multiple linear regression (for predicting continuous developmental scores) and logistic regression (for predicting risk of significant developmental delay), adjusted for known or potential confounders, and including all tests of two-way interactions between exposures and sociodemographic conditions. The hardship measure was categorized into high/low hardships for inclusion in multivariate tests of interactions with ETS. Criteria for selection of confounders were based on significant associations with either toxicant exposure (ETS or PAH) or cognitive development. Additional biomedical and demographic variables that were significantly associated with cognitive development in the present sample were included as covariates to reduce the error term (Rauh et al., 2004).

Whyatt et al. used multiple regression analyses to measure the contribution of antenatal insecticide expo-sure to birth outcomes. Covariates included in the final models were race/ethnicity, gestational age, parity, maternal pre-pregnancy weight, and net weight gain during pregnancy (maternal pregnancy weight gain minus the newborn's weight), maternal self-reported environmental tobacco smoke in the home, gender of the newborn, and season of delivery. Models for head circumference also included whether or not the delivery was by Caesarian section.

As described previously (Perera et al., 2003; Whyatt et al., 2003) pesticide levels in maternal and umbilical cord plasma samples were highly correlated ($r = 0.76$ for chlorpyrifos, $r = 0.68$ for diazinon, and $r = 0.53$ for 2-isopropoxyphenol, $P < 0.001$, Spearman's rank). Therefore, in cases where the umbilical cord blood sample was not collected, the mother's values were used based on the formulas derived from regression analyses.

Pesticide levels blood samples were log-trans-formed prior to statistical analyses to normalize positively skewed distributions. To evaluate the combined effects of chlorpyrifos and diazinon on birth outcomes, diazinon levels were converted to chlorpyrifos equivalents based on the ratio of the chlorpyrifos and diazinon relative potency factors calculated by the EPA (US Environmental Protection Agency; Office of Pesticide Programs, 2002).

When the models indicated a significant association between a pesticide and one or more of the birth outcomes in a regression equation, the pesticide levels were also categorized into four exposure groups in order to evaluate the dose–response relationships (Whyatt et al., in press). Stratified analyses were also conducted to evaluate the effects of the pesticide exposures on birth outcomes among newborns born before versus on or after January 1, 2001. Results in all three studies are considered statistically significant at $P < 0.05$ (two-tailed) (Whyatt et al., in press).

RESULTS

Perera et al. Analysis

Demographic and exposure characteristics for the subjects included in the present analysis are provided in Table 2 together with summary data on cord blood B[a]P-DNA, and cotinine (Perera et al., 2004). ETS exposure was associated with smaller head circumference ($\beta = -0.01$, $P = 0.04$) after adjusting for potential confounders. Cotinine was significantly associated with birth length ($\beta = -0.01$, $P = 0.05$). By Spearman's

Table 2
Demographic and exposure characteristics of the population[a] (Perera et al., 2004)

	All (n = 214)[a]	African American (n = 84)	Dominican (n = 130)
Maternal age (year)[b]	24.3 (4.7)[b]	23.8 (4.4)	24.7 (4.9)
Maternal education			
Less than high school	32%	31%	32.2%
High school	45%	44%	46%
Higher than high school	23%	25%	22.8%
Maternal ETS (no. who report a smoker in the home)	39.3%	47.6%[*]	33.8%
Maternal alcohol consumption (no. who drank alcohol during pregnancy)	27.8%	22%	31.7%
Maternal height (cm)[b]	162.6 (8.1)	165.1 (8.4)[**]	161 (7.6)
Maternal pre-pregnancy weight (kg)[b]	67.4 (17.5)	71.9 (19.8)[**]	64.5 (15.2)
Gestational age (weeks)[b]	39.5 (1.3)	39.2 (1.4)[**]	39.6 (1.2)
Newborn birth weight (g)	3445.6 (475.3)	3386.6 (502.4)[d]	3483.8 (454.8)
Newborn birth length (cm)[b]	51 (2.4)	51.1 (2.8)[d]	50.9 (2.2)
Newborn head circumference (cm)[b]	34.2 (1.4)	34 (1.6)[d]	34.4 (1.2)
Gender of newborn (% females)	53.7%	51.2%	55.4%
Plasma cotinine (ng/mL)[bc] (% of detectable)	50%	78.1%[**]	31.9%
Mean of detectable (S.D.)	0.41 (0.92)	0.34 (0.30)	0.52 (1.44)
% in the third tertile		54.8%	19.5%
Newborn B[a]P-DNA adducts (adducts/10^{-8} nucleotides)	0.22 (0.14)	0.23 (0.15)	0.22 (0.13)

[a] Subjects with B[a]P-DNA cord blood sample(s), complete questionnaire data, and birth outcome data. There were no significant differences between the overall parent population and the present subset in terms of demographic, questionnaire-derived, and birth outcome variables shown in Table 1. Six babies were missing reliable data on birth length and seven were missing reliable data on head circumference.

[b] Mean (standard deviation). Arithmetic means are presented for ease of comparison with other studies; however, the reported analyses are based on log-transformed data.

[c] As mentioned, subjects with cotinine >15 ng/mL were excluded from analysis. Cotinine represents the level in cord blood or, if unavailable, the level in maternal blood.

[d] By multivariate Hotelling's t-test, at least one of these outcomes (weight, length, head circumference) was significantly lower in African Americans than in Dominicans ($P < 0.01$).

[*] $P \leq 0.05$ for African American vs. Dominican (Chi-square test for maternal ETS).

[**] $P \leq 0.01$ for African American vs. Dominican. (Student's t-test for maternal height, pre-pregnancy weight, and gestational age.)

Test, B[a]P-DNA adducts were not significantly correlated with ETS, cotinine, or dietary PAH. B[a]P-DNA alone (either as a continuous or dichotomous variable) was not significantly associated with birth outcomes, however, the interaction between high/low adducts and ETS was significant using either adduct variable. There was a 233 g (6.8%) reduction of birth weight and 1 cm (2.9%) reduction of head circumference in the high B[a]P-DNA/ETS+ compared with the low B[a]P-DNA/ETS− group.

Rauh et al. Analysis

Prenatal ETS exposure in the home was highly prevalent, occurring in 40.2% of the children with 24-month Bayley scores (Rauh et al., 2004). The mean unadjusted 2-year cognitive development score of children who were exposed to prenatal ETS (mean = 82.02; S.D. = 13.01) was significantly lower than the mean score for children who were not exposed (mean = 86.61; S.D. = 12.30) ($F = 7.41$, $p = 0.007$). Total number of material hardships in the postpartum period was significantly associated with 24-month development ($P < 0.05$) and income ($\chi^2 = 13.658$, $P < 0.05$). Gender, gestational age, and infant age at test administration together accounted for 11.1% of the variance in 24-month Bayley MDI scores and were included as covariates. The reported frequency of dietary PAHs (ingestion of blackened or charred foods) was low and was not significantly associated with either airborne exposures or developmental outcome. Cord blood lead was not significantly associated with airborne exposures or developmental outcome. As shown in Table 3, prenatal ETS exposure was significantly associated with a number of demographic variables, such that prevalence of self-reported ETS exposure was higher among African Americans ($\chi^2 = 5.24$, $P < 0.05$), unmarried women ($\chi^2 = 4.30$, $P < 0.05$), younger women ($F = 7.44$, $P < 0.01$), and those with lower income ($\chi^2 = 7.28$, $P < 0.01$) (Rauh et al., 2004). Postnatal ETS exposure over the first 2 years of life was reported by 37.6% of mothers ($n = 85$), both pre and postnatal exposure was reported by 26.5% ($n = 60$), and 11.1% ($n = 25$) had postnatal ETS exposure only.

Table 3
Characteristics of the study population by ETS exposure (n = 226) (Rauh et al., 2004)

Characteristic	Prenatal environmental tobacco smoke exposure level				
	Exposed (n = 91)		Unexposed (n = 135)		p-value
	%	Mean (S.D.)	%	Mean (S.D.)	
Maternal characteristics					
Ethnicity					
African American	49.0		51.0		<0.05
Latino	33.8		66.2		<0.01
Annual income <$10,000	53.6		38.1		<0.01
Age (year)		23.62 (05.0)		25.22 (4.98)	
Primiparous	55.2		46.2		
Married	17.1		28.1		<0.05
Psychological distress score[a]		30.78 (19.0)		28.95 (16.4)	NS
More than 12 years of education	23.8		33.2		p = 0.07
One or more material hardships[b]	24.8		21.3		NS
Prenatal	39.5		36.0		NS
12 months	28.2		25.9		NS
24 months	24.4		21.2		NS
Infant characteristics					
Birth weight (grams)		3355.8 (491.5)		3416.2 (487.6)	NS
Birth length (cms)		50.67 (2.49)		51.00 (2.83)	NS
Birth head circumference (cms)		33.94 (1.47)		34.21 (1.51)	NS
5-min Apgar (% ≥9)	86.6		90.9		NS
Gestational age (week)		39.34 (1.30)		39.36 (1.53)	NS
Male	50.0		47.4		NS
Birth complications (5 min Apgar)		8.90 (0.44)		8.95 (0.50)	NS
Age at 24-month testing (week)		24.46 (1.52)		24.47 (1.28)	NS
24-month Bayley mental development score (MDI)		82.02 (13.0)		86.61 (12.3)	<0.01
Developmentally delayed (<80 on MDI)	41.9		25.9		<0.01
Exposures					
Airborn PAH[c] (ng/m³)		3.66 (3.04)		3.51 (4.03)	NS
Dietary PAH (charred food)	4.9		4.9		NS
Cord blood lead (ug/dL)		1.39 (1.17)		1.19 (0.81)	NS
Postnatal ETS[d]	65.9		18.5		<0.001
Alcohol consumption (beer, wine or liquor)[e]	1.8		2.3		NS

[a] Psychiatric Epidemiology Research Instrument; 27-item scale; Dohrenwend et al., 1978.
[b] Total unmet needs in areas of food, housing, clothing; categorized into high = 1; low = 0.
[c] Natural log total PAH.
[d] Defined as any ETS in the home in the first 2 years; yes = 1; no = 0.
[e] Defined as ≥ one drink per day throughout pregnancy (includes high & moderate exposure).

The multivariate model and results are presented in Table 4 (Rauh et al., 2004), where model 1 includes only main effects and model 2 tests the significance of interaction term(s). In model 1, the main effect of ETS was highly significant (P = 0.005), such that exposure was associated with a 4.8-point deficit in Bayley MDI score. Maternal education/training beyond high school (>12 years) was significantly associated with cognitive development, and married status was positively associated, with borderline significance (P = 0.099). Total number of material hardships was negatively, yet only marginally, associated with MDI (P = 0.064). Maternal psychological distress was not significant in the model and not included in the final multivariate model. The main adverse effect of ETS remains significant when material hardship is included in the model, suggesting that both risk factors contribute independently to cognitive deficit. In model 2, the interaction between ETS and material hardship was tested and found to be significant, such that the adverse impact of prenatal ETS exposure on child development was greater among children whose mothers reported greater material hardship (P = 0.03), resulting in a cognitive deficit of approximately 7 points.

By a logistic regression analysis evaluating the impact of exposures and covariates on the risk of developmental delay (<80 on the Bayley), the main effect of ETS was again significant (OR = 2.36; 95% CI

Table 4
Regression models testing main and interactive effects of prenatal ETS, postnatal ETS, and material hardships on 24-month Bayley cognitive development score, adjusted for race, gender, marital status, maternal age, lead, PAH, gestational age, and age at test administration in an inner-city minority sample (n = 226) (Rauh et al., 2004)

Variable	Model 1: no interaction			Model 2: interaction		
	β	S.E.	P-value	β	S.E.	P-value
Prenatal chemical exposures						
ETS[a]	−4.777	1.58	0.003	−2.647	1.86	0.155
Airborne PAH[b]	0.824	1.12	0.492	0.799	1.11	0.517
Lead[c]	1.061	1.06	0.317	0.984	1.05	0.350
Covariates						
Race/ethnicity[d]	6.518	1.71	<0.001	6.488	1.69	<0.001
Gender[e]	6.457	1.54	<0.001	6.551	1.53	<0.001
Gestational age (week)	1.599	0.53	0.003	1.560	0.53	0.004
Age at test administration	1.212	0.48	0.013	1.195	0.48	0.014
Maternal education[f]	3.329	1.63	0.042	3.138	1.62	0.054
Married[g]	3.322	1.75	0.099	3.545	1.73	0.042
Material hardship[h]	−3.230	1.74	0.064	−0.421	2.17	0.846
Interaction term						
Material hardship × ETS				−7.116	3.33	0.034
r^2		0.250			0.266	

  [a] Prenatally exposed = 1; not exposed = 0.
  [b] Natural log total PAH.
  [c] Natural log cord blood lead.
  [d] African American = 1; Hispanic = 0.
  [e] Male = 0; female = 1; please note that the sign of the coefficient has been altered from the original manuscript for consistency in coding.
  [f] Additional education/training beyond the high school degree: >HS = 1; ≤HS = 0.
  [g] Married = 1; unmarried = 0.
  [h] Total unmet needs in areas of food, housing, clothing; categorized into high = 1; low = 0.

= 1.22, 4.48), such that children with ETS exposure were more than twice as likely to show developmental delay as compared to unexposed children. The interaction of ETS and material hardships just missed significance at the 0.05 level.

Whyatt et al. Analysis

Demographics, birth outcomes, and exposure characteristics are presented in Table 5 (Whyatt et al., in press). As discussed in detail previously (Whyatt et al., 2003), with the exception of diazinon in blood samples, the insecticide levels were substantially lower among infants born after 1/1/01 ($P \leq 0.001$, independent t-test). A significant inverse association was seen between birth weight and length and levels of the organophosphates in umbilical cord plasma. Specifically, birth weight decreased by 42.6 g (95% CI −81.8 to −3.8, P = 0.03) and birth length decreased by 0.24 cm (95% CI −0.47 to −0.01, P = 0.04) for each log unit increase in cord plasma chlorpyrifos levels. Birth weight and length also decreased with increasing levels of cord plasma (ln) diazinon and the effect size was similar to that seen for chlorpyrifos, but the standard error was larger and the results were not

significant. However, when chlorpyrifos and diazinon levels were summed (after adjusting for relative potency), birth weight decreased significantly by 49.1 g (95% CI −91.3 to −6.9, P = 0.02) and birth length by 0.27 cm (95% CI −0.52 to −0.02, P = 0.03) for each log unit increase in the sum of the insecticides in chlorpyrifos-equivalents. The median level of chlorpyrifos was 2.3 pg/g and the range was 0.4–63 pg/g (Whyatt et al., in press).

Table 6 shows results of the regression analyses of birth weight and length among infants stratified into four exposure groups based on increasing levels of chlorpyrifos and diazinon in cord plasma (Whyatt et al., in press). The effects were principally seen among newborns with the highest exposures (group 4). Birth weight averaged 150.1 g less (95% CI −287.7 to −12.5) among newborns with group 4 compared to group 1 chlorpyrifos exposures (p = 0.03) and birth length averaged 0.75 cm less (95% CI −1.6 to 0.06, P = 0.07). Birth weight averaged 186.3 g less (95% CI −327.2 to −45.4) among newborns with group 4 compared to group 1 combined exposures to chlorpyrifos and diazinon (in chlorpyrifos-equivalents, adjusted for relative potency) (P = 0.01) and birth length averaged 0.8 cm less (95% CI −1.6 to 0.02, P = 0.056). By

Table 5
Demographics, birth outcomes, and exposure characteristics of the populations (n = 314) (Whyatt et al., in press)

Maternal age (years)[a]	24.6 ± 4.9	Maternal net weight gain during pregnancy (kg)[a]	12.8 ± 7.0
Ethnicity (%)		Gestational age of newborn (week)[a]	39.3 ± 1.4
African American	42%	Sex of the newborn (% female)	53%
Dominican	58%	Newborn birth weight (g)[a]	3382.1 ± 485.8
Maternal education (%)[b]		Newborn birth length (cm)[a]	50.9 ± 2.6
<High school degree	34%	Newborn head circumference (cm)[a]	34.1 ± 1.5
High school diploma or GED	45%	Parity (% nullaparous)	51%
>High school	21%	Personal air pesticide levels (ng/m^3)[d]	
Maternal ETS		Chlorpyrifos	15.3 ± 31.8
% Reporting smoker in home	38%	Diazinon	117.2 ± 523.4
Maternal alcohol consumption[b]		Propoxur	53.6 ± 113.2
% Reporting any drinking during pregnancy	25%	Umbilical cord blood pesticide levels (pg/g)[e]	
% Reporting regular[c] drinking	2%	Chlorpyrifos	4.0 ± 6.1
Maternal height (cm)[a]	162.6 ± 7.9	Diazinon	1.1 ± 1.3
Maternal pre-pregnancy weight (kg)[a]	68.3 ± 17.7	2-Isopropoxyphenol	3.1 ± 2.8

[a] Mean ± standard deviation.
[b] Missing data: maternal age, n = 1; education, n = 7; alcohol, n = 10; maternal height, n = 11; birth length, n = 5; head circumference, n = 16.
[c] One alcohol drink or more per day during any trimester.
[d] Pesticide levels in maternal air samples were available for chlorpyrifos, n = 271; for propoxur, n = 271; and for diazinon, n = 269.
[e] For chlorpyrifos, levels in umbilical cord blood samples were available for n = 256 infants and were imputed from the mothers' values for n = 31 infants; for diazinon levels in umbilical cord blood samples were available for n = 257 infants were imputed from the mothers' values for n = 45 infants; and isopropoxyphenol levels in umbilical cord blood samples were available for 257 infants and were imputed from the mothers' values for 45 infants.

Table 6
Differences in birth weight (g) and birth length (cm) by cord plasma organophosphate exposure groups[a] (Whyatt et al., in press)

	Chlorpyrifos		Chlorpyrifos and diazinon[b]	
	β ± S.E.	P-value	β ± S.E.	P-value
I. Birth weight				
Group 1 vs. group 2	39.2 (−107.3 to 185.7)	0.60	−78.5 (−225.5 to 68.5)	0.29
Group 1 vs. group 3	−50.9 (−188.2 to 86.3)	0.47	−33.1 (−173.7 to 107.4)	0.64
Group 1 vs. group 4	−150.1 (−287.7 to −12.5)	0.03	−186.3 (−327.2 to −45.4)	0.01
I. Birth length				
Group 1 vs. group 2	0.17 (−0.70 to 1.0)	0.71	−0.06 (−0.93 to 0.81)	0.89
Group 1 vs. group 3	−0.21 (−1.0 to 0.61)	0.61	−0.005 (−0.84 to 0.82)	0.99
Group 1 vs. group 4	−0.75 (−1.6 to 0.06)	0.07	−0.80 (−1.6 to 0.02)	0.056

[a] Newborns were categorized into four exposure groups based on cord plasma organophosphate levels. Group 1 includes infants with insecticide levels below the limit of detection; group 2 includes infants with the lowest third of detectable insecticide levels; group 3 includes infants with in the middle third of detectable insecticide levels; and group 4 includes infants with the highest third of detectable insecticide levels. Dummy variables were used in the regression analyses to compare birth outcomes among newborns in exposure group 1 to birth outcomes among newborns in exposure groups 2, 3, and 4. Covariates included in the regression models were gestational age of the newborn (in week), maternal pre-pregnancy weight, and weight gain during pregnancy (in pounds), newborn gender (0 = male; 1 = female), parity (0 = nulliparous; 1 = at least one prior live birth), ethnicity (0 = Dominican; 1 = African American), ETS in the home (0 = no; 1 = yes) and season of delivery (dummy variable 1: 0 = summer; 1 = winter; dummy variable 2: 0 = summer; 1 = spring; dummy variable 3: 0 = summer; 1 = fall).
[b] Sum of chlorpyrifos and diazinon in chlorpyrifos-equivalents adjusted for relative potency.

contrast, there were no significant differences in birth outcomes among newborns in the second and the third exposure groups compared to those in the first exposure group (Whyatt et al., in press).

Among newborns born prior to 2001, the association between (ln) 2-isopropoxyphenol and birth length was statistically significant (β = −0.73 cm/unit, P = 0.01). Among newborns born after 1/1/01, the association remained inverse but the magnitude of the effect was less and no longer significant (β = −0.30 cm/unit, P =

0.56). No association was seen between infant head circumference and levels of propoxur or its metabolite in cord blood samples (data not shown) (Whyatt et al., in press).

DISCUSSION

These three analyses provide new molecular epidemiologic evidence that exposure to common environ-

mental pollutants (PAH and ETS, ETS, and material hardship, and household insecticides) at levels currently encountered in New York City can act in combination to adversely affect fetal development and/or child cognitive development. After adjusting for potential confounders, the association between ETS and ETS in combination with B[a]P-DNA adducts and/or decreased birth weight and smaller head circumference (Perera et al., 2004), as well as the inverse association between prenatal chlorpyrifos exposure and birth weight and length (Whyatt et al., 2004), are of potential concern because several studies have reported that reduction in birth weight correlates with lower IQ as well as poorer cognitive functioning and school performance in childhood (Chaikind and Corman, 1991; Matte et al., 2001; Desch et al., 1990). Furthermore, Rauh et al. found that children exposed to both prenatal ETS and material hardship scored on average, 7.1 points lower on the Bayley MDI as compared to those with neither ETS nor hardship (Rauh et al., 2004).

The finding of a significant interactive effect between ETS and B[a]P-DNA adducts, along with the observed lack of correlation between adducts and ETS, suggests that the effect of ETS is largely due to other non-PAH constituents of tobacco smoke and that the adducts may be largely reflecting other environmental sources of PAH as well as individual susceptibility to them. The combination of high B[a]P-DNA adducts and ETS exposure was associated with a 7% reduction of birth weight and a 3% reduction of head circumference (Perera et al., 2004). The results are consistent with ecologic studies showing associations between ambient levels of air pollutants (including total suspended particulate matter) and low birth weight (Bobak, 2000; Chen and Omaye, 2001; Ha et al., 2001).

Although this analysis is based on individual prenatal exposure data from biomarkers, as well as extensive medical records and questionnaire data, it is limited by the modest sample of subjects (214) for whom data from all relevant domains are currently available (Perera et al., 2004).

Rauh et al. found a significant inverse relationship between prenatal ETS exposure in the home and 24-month Bayley MDI scores (Rauh et al., 2004). These findings provide evidence of a developmentally toxic effect of secondhand smoke during pregnancy. After adjusting for confounders and covariates, the mean development score for infants who were prenatally exposed was approximately 5 points below the unexposed group mean, and those infants with prenatal ETS

exposure were twice as likely to be classified as significantly delayed when compared to infants with no prenatal ETS exposure. In this sample, the mean MDI scores was 84.31 (S.D. = 12.91), and African American children had significantly higher mean MDI scores (mean = 87.55, S.D. = 12.31) than Dominican children (mean = 82.77, S.D. = 12.68, $P < 0.01$). Lower scores on the Bayley Scales by Dominican children were largely a function of failed language items, possibly related to bilingual practices in the home.

The adverse impact of fetal exposure to ETS may be due to mechanisms exerted by the ETS constituents, such as alteration of receptor-mediated cell signaling in the brain (Slotkin, 1998), anti-estrogenic effects (Bui et al., 1986), induction of P450 enzymes (Manchester et al., 1987), DNA damage resulting in activation of apoptotic pathways (Nicol et al., 1995), (Wood and Youle, 1995), and/or agents that bind to receptors for placental growth factors resulting in decreased exchange of oxygen and nutrients (Dejmek et al., 2000).

A limitation of the present analysis is the failure to measure the possible compensatory effects of family resources and supports. It is possible that material hardship is merely a marker for exposure to other unmeasured toxicants so that the interaction with ETS reflects a biological synergism with other pollutants (Rauh et al., 2004). Rauh et al. also cite poor maternal dietary practice as a possible third common risk factor shared by children with prenatal ETS and conditions of material hardship, and may explain the apparent interaction effect. In the present sample, co-exposure to both ETS and material hardship may be a marker for the most extreme dietary deficiencies, resulting in the greatest neurodevelopmental deficits in this group (Rauh et al., 2004). In the present study, material hardship likely serves as a marker for multiple economic and psychosocial disadvantages, any one of which might be considered a risk factor for aberrant child development. Some of the pathways by which socioeconomic disadvantage may affect child health and development have been extensively reviewed elsewhere (Adler et al., 1999). The finding of a strong relationship between material hardship and psychological distress is consistent with other studies (e.g., Linares et al., 2001). Although maternal distress did not appear to have a mediational role in this population (no direct association between distress and cognitive development, and no reduction in the magnitude of the hardship effect with distress in the model), maternal distress is undoubtedly an important part of the caretaking environment and may play a role in the mod-

ulation of the prenatal toxicant effect, as seen for example in the cocaine literature (Frank et al., 2002).

While the adjusted mean MDI scores of the ETS-exposed and unexposed groups differed by only five points, the proportion of children in the ETS-exposed group with cognitive scores <80 was two times greater than among unexposed children. This suggests that twice as many exposed children may need (and are eligible for) early intervention services-an intervention designed for children who are at potential risk for early school failure (Rauh et al., 2004).

The Rauh et al. results suggest that cautions against antenatal maternal smoking should be extended to include fetal exposure to secondhand smoke. In this predominantly low-income minority population, especially among those with high material hardship/deprivation, even a small increase in risk associated with ETS exposure was sufficient to move significant numbers of children into the developmentally delayed range, resulting in greater need for early intervention services and perhaps special education classes in the early school years. Although there exist multiple types of educational disadvantages experienced by children in northern Manhattan, residential tobacco smoke exposure does appear to be a source of significant, highly prevalent, and largely preventable risk for child cognitive delay in this population (Rauh et al., 2004).

Results from Whyatt et al. confirmed the association between cord plasma chlorpyrifos and decreased birth weight and length and found this effect principally among newborns with the highest 25% of exposure levels. By 2001, due to USEPA regulatory action of chlorpyrifos, high exposure levels to newborns drastically decreased and the association between cord plasma chlorpyrifos levels and birth weight and length was no longer inverse or significant (Whyatt et al., 2004).

The study also found that even though associations between cord plasma diazinon levels and birth weight and length were not significant, the effect was similar to that seen for chlorpyrifos so that with increasing diazinon exposures, birth length and weight decreased (Whyatt et al., 2004). In addition, the magnitude of the effect on birth weight was greater than that for chlorpyrifos alone. These findings are consistent with the synergistic and harmful effect on the developing fetus caused by combined ETS and PAH exposure as found by Perera et al. (2004).

The results are important especially since combined exposures to diazinon and chlorpyrifos were common among the current cohort, and experimental evidence has linked chlorpyrifos and diazinon exposures during gestation or the early postnatal period to adverse neurodevelopmental sequelae in the offspring (reviewed in Eskenazi et al., 1999; Landrigan et al., 1999). Nonetheless, since this is among the first studies to report an association between umbilical cord plasma chlorpyrifos and diazinon levels and reduced birth weight and length, further studies are required for confirmation. Results from this study suggest that the USEPA regulatory action may well have improved birth outcomes among minority residents in New York City and implies important benefits for children's health. The differences in fetal growth are comparable to the magnitude of those observed with maternal smoking during pregnancy (U.S. Public Health Service; Office of the Surgeon General, 1990).

The results from the three analyses described above support a causal relationship between prenatal environmental toxicant exposure and the adverse effects on fetal growth and child development, and demonstrate the interaction between physical toxicants and psychosocial factors. The findings underscore the importance of continued research on the combined effects of toxicant exposures since environmental exposure to multiple pollutants and co-exposures to adverse social conditions are the norm rather than the exception. In terms of health policy, the studies cited in this report have generated significant findings that have important implications for the development of public health policies to advance the health and development of children in New York City and nationwide.

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