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# Prenatal Polycyclic Aromatic Hydrocarbon (PAH) Exposure and Child Behavior at age 6-7

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Abbreviations: B[*a*]P, benzo[a]pyrene; CBCL, Child Behavior Checklist; CCCEH, Columbia Center for Children's Environmental Health; CI, confidence intervals; ETS, environmental tobacco smoke, HOME, Home Observation for Measurement of the Environment; PAH, polycyclic aromatic hydrocarbons; PUF, polyurethane foam; QC, quality control

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Abstract

Background: Airborne polycyclic aromatic hydrocarbons (PAH) are widespread urban air pollutants from fossil fuel burning and other combustion sources. We previously reported that a broad spectrum of combustion-related DNA adducts in cord blood was associated with attention problems at age 6-7 in the Columbia Center for Children's Environmental Health (CCCEH) longitudinal cohort study.

Objectives: We have evaluated the relationship between behavioral problems and two different measures of prenatal exposure—both specific to PAH-- in the same cohort.

Methods: Children of nonsmoking African-American and Dominican women in New York City (NYC) were followed from *in utero* to 6-7 years. Prenatal PAH exposure was estimated by personal air monitoring of the mothers during pregnancy as well as by the measurement of DNA adducts specific to benzo[a]pyrene (B[a]P), a representative PAH, in maternal and cord blood. At age 6-7 child behavior was assessed using the Child Behavior Checklist (CBCL) (N=253). Generalized linear models were used to test the association between prenatal PAH exposure and behavioral outcomes.

Results: In multivariate analyses, high prenatal PAH exposure, whether characterized by personal air monitoring (greater than the median of 2.27 ng/m$^3$) or maternal and cord adducts ($\geq$detectable), was positively associated with symptoms of Anxious/Depressed and Attention Problems (p value $\leq$ 0.05).

Conclusion: These results provide additional evidence that environmental levels of PAH encountered in NYC air can adversely affect child behavior.

Introduction

Polycyclic aromatic hydrocarbons (PAH) such as benzo[a]pyrene (B[a]P) are released to air during incomplete combustion of fossil fuel, tobacco and other organic material (Bostrom et al. 2002). In New York City (NYC) and other urban areas, traffic and residential heating are major sources. Urban, minority populations in the U.S. often have disproportionate exposure to air pollution and are at greater risk for adverse health and developmental outcomes (Olden and Poje 1995; Perera et al. 2002). Illustrating widespread exposure to these pollutants, 100% of the mothers in the Columbia Center for Children's Environmental Health (CCCEH) NYC cohort had detectable levels of PAH in prenatal personal air samples. In addition, 40% reported environmental tobacco smoke (ETS) exposure during pregnancy (Perera et al. 2003).

Because of the heightened susceptibility of the fetus and infant, exposures to PAH and other environmental pollutants during the prenatal and early postnatal stages are of particular concern (Anderson et al. 2000; Grandjean and Landrigan 2006; National Research Council 1993; Perera et al. 2004a; World Health Organization 1986). In particular the prenatal period is thought to be highly sensitive to neurotoxic effects of environmental contaminants (Nijland et al. 2008; Rodier 2004). Laboratory experiments have indicated that the fetal brain and nervous system may be particularly sensitive to PAH (Brown et al. 2007; McCallister et al. 2008; Wormley et al. 2004). PAH are transferred across the placenta and the fetal blood brain barrier (reviewed in (Brown et al. 2007; Hood et al. 2000). Following gestational exposure in humans, DNA adducts formed by benzo[a]pyrene (B[a]P) and other PAH have been detected in maternal and cord blood samples in a range of populations, (Perera et al. 2005). PAH exposure has also been linked to epigenetic effects (Perera et al. 2009a). In studies in laboratory animals, B[a]P exposure also

been associated with AhR up-regulation in gestationally exposed rats suggesting possible endocrine disruption (Wu et al. 2003).

In the CCCEH NYC cohort, prenatal exposure to PAH has previously been associated with multiple adverse effects including developmental delay at age 3 (Perera et al. 2006) and reduced IQ at age 5 (Perera et al. 2009b). Experimental studies exposing laboratory animals to PAH during the prenatal and neonatal periods have reported neurodevelopmental and behavioral effects including impairment of memory and ability to learn (Brown et al. 2007; Wormley et al. 2004), anxiety, and depression-like symptoms in the absence of overt toxicological effects (Saunders et al. 2006; Saunders et al. 2002; Saunders et al. 2003; Takeda et al. 2004; Wormley et al. 2004; Yokota et al. 2009). Anxiety and depression are internalizing problems that can affect learning (Emslie 2008; Wood 2006).

We have previously found that a wide spectrum of bulky/hydrophobic DNA adducts, including those formed by PAH, nitro-PAH and aromatic amines, detected by the $^{32}$P-postlabeling assay in umbilical cord blood from cohort children were associated with symptoms of anxiety/depression and attention problems during childhood (Perera et al. 2011). Here, in addition to prenatal PAH air monitoring, we have used a chemical- specific biomarker of exposure (B[a]P–DNA adducts) to examine the relationship between prenatal PAH exposure and child behavior. The B[a]P–DNA adducts are specific to a representative member of the PAH class and therefore more directly complement the prenatal air monitoring of B[a]P and other PAH than the $^{32}$P-radiolabelled adducts, which represent an array of pollutants in addition to PAH.

We have examined children's behavior at age 6-7 in relation to prenatal exposure to PAH and B[a]P DNA adducts using the Child Behavior Check List (CBCL) (Achenbach and Rescorla 2001). We focused on the syndromes and problems of *a priori* interest (anxious/depressed and attention problems) based on the experimental findings for PAH (Saunders et al. 2006; Saunders et al. 2002; Saunders et al. 2003; Takeda et al. 2004; Wormley et al. 2004; Yokota et al. 2009). This is the first report of associations between child attentional and behavioral problems, on the one hand, and two complementary specific measures of prenatal PAH exposure: monitored air concentrations of PAH and a PAH-specific biomarker of exposure.

## Methods

*Sample selection:* A complete description of the NYC cohort and study design appears elsewhere (Perera et al. 2003; Perera et al. 2006). Briefly, African-American and Dominican women who resided in Washington Heights, Harlem, or the South Bronx in New York City, (NYC) U.S. were recruited between 1998 and 2003 through the local prenatal care clinics into a prospective cohort study. To reduce the potential for confounding, enrollment was restricted to women who were non-active cigarette smokers in the age range of 18-35, nonusers of other tobacco products or illicit drugs, free of diabetes, hypertension, or known HIV, and had initiated prenatal care by the $20^{th}$ week of pregnancy. Postnatal interviews were administered to the mothers in person at 6 months and annually thereafter to determine changes in children's health, residence and ETS exposure. Developmental status was assessed every 1-2 years. The Institutional Review Board of the New York Presbyterian Medical Center approved the study; the mothers provided informed consent for themselves and their children under 7 years of age, while children over 7 years provided assent.

A total of 617 mother/child pairs had complete prenatal PAH monitoring and prenatal questionnaire data. By the time of this analysis, 431 children had reached age 7 and 294 children had the CBCL completed at age 6-7. The sample included in the present analysis was composed of 253 of those children who also had available data on explanatory or potential confounding variables of interest. Table 1 compares characteristics of this sample with those subjects who were not included due to missing covariates or CBCL data (N=364). The two groups were similar with respect to level of PAH and ETS exposure, gestational age, maternal education, and maternal demoralization measured by the PERI Demoralization Scale (Dohrenwend et al. 1978); however, they differed with respect to the home caretaking environment measured by the HOME Inventory (Bradley 1994) (p-value=0.03), sex of the child (p-value=0.05), and ethnicity (p-value <0.0001). Specifically, the group included in the analysis had a higher proportion of girls, African-Americans, and a more favorable home environment.

*Personal Interview:* A 45-minute questionnaire was administered by a trained bilingual interviewer during the last trimester of pregnancy to obtain demographic information, residential history, and health and environmental data such as active smoking (to confirm non-active smoking status) and passive smoking. In this cohort, self-reported exposure to ETS was correlated with cotinine measured in cord blood (r=0.44, p-value<0.0001). The questionnaire also elicited information on dietary PAH (consumption of broiled, fried, grilled or smoked meat), and socioeconomic information related to income and education (Perera et al. 2003). Postnatal interviews were administered in person at 6 months and annually thereafter to determine changes in residence, exposure to ETS, and health and environmental conditions. The quality of the proximal care-taking environment was assessed at child age 3 using Caldwell and Bradley's Home Observation for Measurement of the Environment (HOME) (Bradley 1994).

*Prenatal personal PAH assessment:* Personal monitoring was carried out during the third trimester of pregnancy as previously described (Perera et al. 2003). Vapors and particles of ≤2.5 μm in diameter were collected on a precleaned quartz microfiber filter and a precleaned polyurethane foam (PUF) cartridge backup. The samples were analyzed at Southwest Research Institute (SWRI) for B[a]P, benz[a]anthracene, chrysene, benzo[b]fluroanthene, benzo[k]fluroanthene, indeno[1,2,3-cd]pyrene, dibenz[a,h]anthracene, and benzo[g,h,i]perylene. For quality control (QC), each personal monitoring result was assessed as to accuracy in flow rate, time, and completeness of documentation. Samples not meeting QC criteria for adequacy were not included in the analysis.

We have validated 48-hour personal monitoring as an indicator of longer-term, integrated exposure in two ways. In a subset of the NYC cohort (N=84), indoor air was monitored over a 6-week period during the 3rd trimester concurrent with the personal air monitoring: the prenatal personal air concentrations were significantly correlated with indoor levels of PAH (sum of the 8 PAH) ($r=0.58$, p-value<0.001) (Rundle et al. [in press] ). In addition, among a subset of pregnant women (N=80) participating in a parallel birth cohort study in Poland and simultaneously monitored for personal, indoor, and outdoor airborne PAH, all three measurements were found to be highly correlated (pair-wise Spearman's coefficients $\geq 0.84$, p-value< 0.01) (Choi et al. 2008 ), supporting the use of personal monitoring to integrate indoor and outdoor exposure. A caveat is that the air concentrations of PAH in the Polish study were 10-times higher than in the NYC cohort (Jedrychowski et al. 2005).

*Biomarkers*: Adducts in white blood cells reflect individual variation in exposure, absorption, metabolic activation, and DNA repair, providing a biologic dosimeter and marker of potential risk. We collected umbilical cord blood at delivery and maternal blood (30–35 mL)

generally on the first day after delivery and transported the samples to the CCCEH Molecular Epidemiology Laboratory within several hours of collection. The buffy coat, packed red blood cells, and plasma were separated and stored at –70°C. B[a]P–DNA adducts in extracted white blood cell DNA were analyzed using the high performance chromatography (HPLC)/ fluorescence method of Alexandrov et al. which detects B[a]P tetraols (Alexandrov et al. 1992). The method has been described previously (Perera et al. 2004b).

*Behavioral outcomes:* The CBCL is a widely used instrument shown to be sensitive to diverse prenatal environmental exposures, including stress events, smoking during pregnancy, and exposure to various pollutants (Axtell et al. 2000; Rauh et al. 2006; Robinson et al. 2008; Wasserman et al. 2001). Research workers trained in neurodevelopmental testing administered the 118 item CBCL for children ages 6-18 (Achenbach and Rescorla 2001) to the mothers in English or Spanish. Specifically, the mothers completed the CBCL with guidance as needed from the research workers. The syndrome scores were computed for the two *a priori* domains of interest (Anxious/Depressed and Attention Problems) by summing the scores on the specific items, yielding a continuous raw score. The raw scores were also converted to standardized T-scores, generated according to the procedure of Abramowitz and Stegun (1968). The T score is truncated (Petersen et al. 1989): a score of 50 is assigned to those with percentiles of raw scores $\leq$ 50 based on a reference population (Achenbach and Rescorla 2001), while children with raw score percentiles > 50 are assigned an actual T-score.

The CBCL also yields scales derived from the *Diagnostic and Statistical Manual (DSM) of Mental Disorders* (2000) that are intended to approximate clinical diagnoses. The DSM scores are dichotomized using a borderline or clinical cut-point corresponding to the 93$^{rd}$ percentile in a reference population for each domain (Achenbach and Rescorla 2001). Children were thus

classified as in the borderline or clinical range (T score ≥ 65) or in the normal range (T score < 65) for the DSM oriented Anxiety Problems and for Attention Deficit/Hyperactivity Problems.

Because maternal intelligence is a known predictor of child neurodevelopment across populations, the Test of Non-Verbal Intelligence-Second Edition (TONI-2) (Brown et al. 1990) was administered to the mothers at about child age 3. The TONI-2 is a 15-minute, language-free measure of general intelligence, relatively stable and free of cultural bias. The quality of the proximal care-taking environment is also a predictor of child neurodevelopment, therefore Caldwell and Bradley's Home Observation for Measurement of the Environment (HOME) (Bradley 1994), was administered at about 3 years to assess physical and interactive home characteristics. Because ambient PAH concentrations are higher in the winter months (heating season), we adjusted for season of monitoring (heating vs. non heating season).

*Statistical Analysis:* As in prior analyses (Perera et al. 2003), a composite PAH variable was computed as the sum of the eight intercorrelated PAH air concentration measures (r values ranging from 0.38-.96; all p-values <0.001 by Pearson's correlation). This variable was dichotomized at the median for the parent population (2.273ng/$m^3$) to obtain a measure of high/low exposure. In separate analyses, PAH were log transformed and treated as a continuous variable. B[a]P-DNA adduct data were available on 223 maternal samples and 148 cord blood samples. Adduct levels were dichotomized as detectable/non-detectable, with detectable levels found in 87 maternal and 56 cord blood samples.

Covariates were selected based on whether they were significant contributors to the model (at $p \leq 0.1$) for at least one of the outcomes. They included maternal self report of ETS exposure during pregnancy, sex of child, gestational age of the child, mother's intelligence,

mother's completed years of education prior to birth of the child, maternal prenatal demoralization, child's age at assessment, the quality of the early home caretaking environment assessed at around 3 years of age, and season at time of monitoring (heating vs. non-heating) (see Table 1). Dietary PAH was not a predictor of outcomes at a $p \leq 0.1$ and was not included in the model. Gestational age was based on medical record data for almost all subjects. In order to adjust for postnatal exposure to PAH, further analyses included change of residence prior to the age of testing as a proxy for possible change in PAH exposure or PAH metabolites measured in child urine collected at age 3. We also adjusted for maternal reported postnatal ETS exposure prior to the age of testing. Correlations between continuous airborne PAH and ETS and dietary PAH, respectively, were not significant using Spearman rank-order correlation and Pearson correlation: ($r=-0.01$, p-value=0.82 and $r=0.09$, p-value=0.18, n=238, respectively). The correlation between PAH and cord lead levels, measured at the Centers for Disease (CDC) using inductively coupled plasma mass spectrometry (Centers for Disease Control and Prevention/Division of Laboratory Science 2003), was not significant using Pearson correlation ($r=-0.01$, p-value=0.77, n=168) in the limited subset with both measurements.

We used continuous raw scores and dichotomized T-scores in the analyses of the CBCL syndrome scores. We applied the Poisson model on the raw syndrome scores as they are counts data with a right skew. The syndrome T-scores were dichotomized at 65 (the cutoff for the borderline and clinical range) (Achenbach and Rescorla 2001) and analyzed using a logistic model. Similarly, we used logistic regression to analyze the dichotomized DSM-oriented Anxiety Problems and Attention Deficit/Hyperactivity Problems.

This analysis involved multiple comparisons. Although the Bonferroni method can be overly conservative (Westfall and Young 1993), we report both the uncorrected and corrected p-

values. The Bonferroni- adjusted significance level was $\alpha = 0.05/6 = 0.0083$ (six outcomes tested).

Results

Using Personal Air Monitoring Data as the Exposure Measure. Table 2 provides the distribution of CBCL scores, while Table 3 shows the distribution of children in the normal and borderline or clinical range for logistic models. In simple Poisson regression (without adjustment for covariates), the children of women with higher monitored prenatal exposure to PAH had significantly higher scores, thus more symptoms of Anxious/Depressed and Attention Problems at 6-7 years compared to children with lower prenatal PAH exposure. In the full Poisson model after adjusting for possible confounders, higher monitored PAH exposure was associated with a significantly higher symptom score of Anxious/Depressed (1.45 times that of the low PAH exposure group, 95% confidence interval (CI): [1.22-1.72]; p-value<0.0001) and with the symptom score of Attention Problems (1.28 times that of the low PAH exposure group, 95% CI: [1.10, 1.48]; p-value=0.001, after adjustment using the Bonferroni method) (Table 4).

In logistic regression on the syndrome scales, higher PAH exposure was significantly associated with both Anxious/Depressed and Attention Problems (Table 4). However, as fewer than 5 children were in the borderline or clinical range in the low-exposure group for Anxious/Depressed, these results are less reliable.

In logistic regression after adjustment, higher PAH exposure was associated with higher odds of DSM-oriented Anxiety Problems (OR 4.59, 95% CI: [1.46-14.27]; p-value=0.009) (Table 4). In contrast, high PAH exposure was not significantly associated with DSM-Oriented Attention Deficit/Hyperactivity Problems (OR 2.30, 95% CI: [0.79, 6.70]).

In separate models with log transformed continuous PAH as the independent variable, monitored PAH exposure was positively associated with the syndrome score of Anxious/Depressed (1.20 times that of the low PAH exposure group, 95% CI: [1.06-1.37], p-value=0.004). Log transformed PAH exposure was also positively associated with DSM-oriented anxiety (OR 2.03 for a one unit increase in log PAH, 95% CI: 0.97-4.26; p-value=0.060) and with Attention Problems (OR 1.54, 95% CI: [0.70,-3.40]; p-value=0.283).

Prenatal ETS was a significant predictor of Anxious/Depressed and Attention Problems at age 6-8. Maternal prenatal demoralization was also a significant predictor of most of the outcomes evaluated. Using change of residence prior to the age of testing as a proxy for variation in PAH exposure between the pre- and postnatal periods, the significance of the associations between higher prenatal PAH and outcomes was materially unchanged: both for symptoms of Anxious/Depressed (1.45 times that of the low PAH exposure group, 95% CI [1.22-1.72], p-value<0.0001) and for DSM-oriented Anxiety Problems (OR= 4.36, 95% CI [1.41-13.44], p-value=0.011). The same was true for Attention Problems (1.27 times that of the low PAH exposure group, 95% CI: [1.10-1.47], p=0.001). After controlling for urinary PAH metabolites at age 3 in the subset with available biomarker data (N=191) the association between prenatal PAH and syndrome scores became stronger (Anxious/Depressed 1.72 times that of the low PAH exposure group, 95% CI [1.40-2.10], p-value=<0.0001, Attention Problems 1.38 times that of the low PAH exposure group, 95% CI: [1.16-1.64], p-value=0.0002). Controlling for postnatal exposure to ETS prior to age of testing did not materially influence the results (data not shown).

In separate analyses, we adjusted for ETS exposure using log-transformed cord cotinine as a continuous variable in a subset of the sample with available data (n=194). Associations with PAH were similar to those adjusted for self-reported ETS exposure: Anxious/Depressed 1.40

times that of the low PAH exposure group, 95% CI: [1.15-1.71], p-value=0.001, Attention Problems 1.24 times that of the low PAH exposure group, 95% CI: [1.04-1.47], p-value=0.016. The odds ratio for DSM-oriented Anxiety Problems was closer to the null, though still positive (OR=2.9, 95% CI: [0.81-10.43] with a p-value=0.1); this may be due to reduced sample size.

In separate models, we further controlled for other neurotoxic environmental exposures measured in the CCCEH cohort including bisphenol A (BPA), the pesticide chlorpyrifos, and phthalates using a summary score for the number of these co-exposures that were above the median level for the cohort. The associations between PAH and CBCL Anxious/Depressed and Attention Problems syndrome scores remained similar when adjusting for the summary scores of these other pollutants; however, the sample size was reduced to n=110 (Anxious/Depressed 1.63 times that of the low PAH exposure group, 95% CI: [1.22-2.17], p-value=0.001, Attention Problems 1.54 times that of the low PAH exposure group, 95% CI: [1.22-1.94], p-value=0.0002, DSM oriented Anxiety Problems (OR=7.19, 95% CI: [0.88-58.48], p-value=0.065, DSM oriented ADHD Problems (OR=4.77, 95% CI: [0.74-30.58], p-value=0.100). The summary score was not a significant independent predictor of any of the outcomes.

Using PAH (B[a]P)-DNA Adducts as the Exposure Measure. We analyzed the relationship between cord and maternal B[a]P-DNA adducts and CBCL outcomes, using the same approach as for monitored PAH, with adjustment for the same covariates.

As shown in Table 4, in the Poisson model detectable levels of PAH adducts in both maternal blood and cord blood were associated with significantly higher scores on the CBCL syndromes of Anxious/Depressed (1.23 times that of the non-detectable adducts group, 95% CI [1.04-1.46] p-value=0.019 for maternal and 1.46 times that of the non-detectable adducts group

95% CI [1.19-1.78], p<0.001 for cord). The same was true for Attention Problems (1.25 times that of the non-detectable adducts group, 95% CI [1.08-1.45], p=0.003 for maternal and 1.32 times that of the non-detectable adducts group, 95% CI [1.11-1.58], p=0.002 for cord). Thus, the two measures (personal monitoring and PAH (B[a]P)-specific DNA adducts) gave similar results for the CBCL symptom scores in the Poisson model. In logistic regression on the dichotomized syndrome scales, although detectable levels of cord adducts were associated with Attention Problems, fewer than 5 children were in the borderline or clinical range in the low-exposure group making these results less reliable.

Similar to monitored PAH, cord and maternal adducts were not associated with DSM Oriented Attention Deficit/Hyperactivity Problems. In contrast to monitored PAH, logistic regression did not show significant associations between B[a]P-DNA adducts in either maternal or cord blood with DSM-oriented Anxiety Problems. The results were materially unchanged following adjustment for postnatal exposures to PAH or ETS. Parameter estimates and confidence intervals for all variables included in final models for ambient PAH, maternal adducts and cord adducts are provided in Supplemental Material Tables 1, 2, and 3 respectively.

## Discussion

This is the first report of an association between child behavioral problems, and two complementary measures specific to prenatal PAH exposure: prenatally monitored air concentrations of PAH and a PAH-specific biomarker of exposure (B[a]P-DNA adducts) in cord blood. The finding of significant associations between two complementary measures of prenatal exposure to PAH and indicators of both Anxious/Depressed and Attention Problems in children is consistent with prior experimental research and with our previous reports indicating that fetal

exposure to PAH is associated with impaired cognitive development of children in the cohort (Perera et al. 2009b; Perera et al. 2006). However, the results with the PAH (B[a]P)-specific adducts measured here by HPLC in cord and maternal blood differ somewhat from those reported by us previously using a broader spectrum of adducts measured in cord blood by $^{32}$P-postlabelling (Perera et al. 2011). Although the associations with symptoms of attention problems were similar using all three measures (monitored PAH and the two different types of adducts), the broader spectrum of adducts measured by $^{32}$P-postlabelling was not significantly associated with symptoms of anxiety/depression at age 7; it was, however, significantly and positively associated with symptoms of anxiety/depression at age 5. This divergence is not unexpected given that the $^{32}$P-postlabelling method detects adducts formed by a range of hydrophobic aromatic hydrocarbons in addition to PAH, such as nitro-aromatic compounds (e.g., 3-nitrobenzanthrone) (Arlt et al. 2001) and heterocyclic amines (e.g., 4-aminobiphenyl) (Munnia et al. 2007). In contrast, the HPLC method detects the adducts formed by B[a]P. B[a]P is considered a representative PAH and in our study was highly correlated with the other 7 genotoxic PAH measured in prenatal air (r=.80 to .96, p-value=.001 except for dibenz(a,h)anthracene, r=.53, p-value<.001).

While in the logistic model only monitored PAH was significantly associated with DSM-oriented Anxiety Problems, most of the other associations between symptom scores and measured of PAH are consistent. It is likely that PAH are operating through mechanisms in addition to direct genotoxicity evidenced by DNA adduct formation. In fact, a number of pathways have been suggested including endocrine disruption (Archibong et al. 2002; Bui et al. 1986; Takeda et al. 2004), binding to receptors for placental growth factors resulting in decreased exchange of oxygen and nutrients (Dejmek et al. 2000), binding to the human Ah

receptor to induce P450 enzymes (Manchester et al. 1987), DNA damage resulting in activation of apoptotic pathways (Meyn 1995; Nicol et al. 1995; Wood and Youle 1995), oxidative stress due to inhibition of the brain antioxidant scavenging system (Saunders et al. 2006), or epigenetic alterations affecting gene expression (Perera and Herbstman 2011; Wilson and Jones 1983). Fetal B[a]P exposure also influenced the expression of nuclear transcription factors that mediate the onset of neuronal cell differentiation, suggesting that there may be widespread effects of this agent in the developing brain, ultimately contributing to neurobehavioral impairment (Hood et al. 2000). It should be noted that, while the exposures/doses in the animal studies are higher than those in the NYC cohort, a number of laboratory studies have observed depression-like symptoms and impaired memory in experimental animals exposed gestationally to PAH at doses below those causing overt toxicologic effects (Saunders et al. 2002; Wormley et al. 2004).

The children in the CCCEH cohort are being followed to age 12 years; therefore subsequent testing will provide a picture of the longer term developmental outcomes of children in the cohort. The strengths of the study include the fact that we were able to account for a number of factors other than PAH exposure that are known to affect child neurobehavioral development, drawing upon individual prenatal exposure data from personal monitoring, biomarker data, and extensive medical record and questionnaire data. We were also able to confirm our findings from prenatal PAH monitoring using B[a]P-DNA adducts as our dosimeter.

We acknowledge a number of limitations of this epidemiologic study. First, unmeasured factors such as other pollutants and stress may have contributed to residual confounding. Further, a single 48-hour prenatal monitoring during the second or third trimester was used as a basis for estimating exposure. However, this single personal air measurement has been associated with adverse health and developmental outcomes in two cohorts (Choi et al. 2006; Edwards et al.

2010; Perera et al. 2009b; Perera et al. 2003; Perera et al. 2006) and has been correlated with indoor PAH concentrations monitored over a 6-week period as well as with indoor and outdoor PAH concentrations monitored during the same 48-hour time period (Rundle et al. [in press] ). We therefore consider the single monitoring time point to be a useful indicator of prenatal exposure to PAH via inhalation. In addition, other studies have found that ETS exposure has been associated with behavioral problems (Fergusson et al. 1993; Weitzman et al. 1992). Although we have adjusted for the possible confounding effects of ETS, there is always the possibility that some residual confounding remains, possibly due to measurement error or the shared variance between ETS and PAH measures. As cord blood cotinine was only available on a subset of participants, we used self-reported ETS exposure as a measure of passive smoking. We note, however, that in the smaller sample with cotinine measurements in cord blood, results were similar. Finally, children born severely preterm would not have been included in our analysis because PAH monitoring was carried out in the third trimester, and we excluded active smokers, illicit drug users, and women with preexisting disease. Our findings may therefore not be generalizable to more at risk populations.

## Conclusion

In conclusion, this study provides evidence that prenatal exposure to environmental PAH at levels encountered in the air of New York City may influence child behavior. The results suggest an adverse impact of prenatal PAH exposure on child behavior that could impact cognitive development and ability to learn. Anxiety, depression, and attention problems, which were associated with PAH exposure and B[a]P-DNA adducts in our study population, have been shown to affect subsequent academic performance (Emslie 2008; Wood 2006). PAH are

widespread in urban environments worldwide largely as a result of fossil fuel combustion. Fortunately, it is possible to reduce airborne PAH concentrations using currently available pollution controls, greater energy efficiency, the use of alternative energy sources and regulatory intervention to remove highly polluting sources.

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Table 1. Characteristics of sample

| | Subjects in the analysis (n=253) | | Subjects not included[a] (n=364) |
|---|---|---|---|
| Variables | Mean +/- SD or % | N | Mean +/- SD or % |
| PAH (ng/m$^3$) | 3.23 +/-2.76 | 364 | 3.13+/-4.10 |
| Prenatal ETS[b] | 37.55% | 364 | 32.14% |
| % female[c] | 56.52% | 364 | 48.35% |
| Gestational age[d] | 39.51 +/-1.57 | 364 | 39.59 +/-1.35 |
| Maternal demoralization score[e] | 1.15 +/-0.62 | 324 | 1.15+/-0.65 |
| Maternal education[f] | 11.80 +/-2.04 | 364 | 11.85 +/-2.31 |
| Maternal TONI score[g] | 20.87 +/-8.96 | 232 | 20.57 +/-8.62 |
| Home environment [c,h] | 39.87 +/-5.66 | 215 | 38.60 +/-6.82 |
| Ethnicity (AA%)[c,i] | 49.04% | 364 | 30.22% |
| Heating season[j] | 56.92% | 362 | 58.01% |
| Change of residence prior to the age of testing | 64.03% | 67 | 64.18% |

[a] Some subjects were not included due to missing CBCL or information on at least one covariate.
[b] Prenatal ETS exposure in the home (yes/no)
[c] Significantly different between the two groups based on the Pearson's Chi-square test
[d] Gestational age in weeks
[e] Maternal demoralization during pregnancy
[f] Maternal education in years of school
[g] Non-verbal intelligence measured by the TONI
[h] HOME Inventory as a measure of the home caretaking environment
[i] Percent African American; the rest are Dominican
[j] Third trimester in heating season (yes/no)

Table 2. Distribution of outcomes in n=253 children with PAH measurements

| Outcome | Score range | | Mean of scores | | Percent in borderline or clinical range[a] |
|---|---|---|---|---|---|
| | T-score[b] | Raw score | T-score | Raw score | |
| Anxious/Depressed | 50-82 | 0-17 | 55.54 | 2.55 | 6.32% |
| Attention Problems | 50-83 | 0-16 | 56.19 | 3.34 | 6.72% |
| Anxiety Problems (DSM) | | 0-9 | | 1.53 | 9.48% |
| Attention Deficit Hyperactivity Problems (DSM) | | 0-14 | | 3.28 | 7.91% |

[a] The syndrome T-scores were dichotomized at T=65 as the cutoff for the borderline and clinical range; the DSM-Oriented Anxiety Problems scale was also dichotomized at 93rd percentile.
[b] The T-score is truncated (Petersen et al. 1993); that is, a score of 50 is assigned to those with percentiles of raw scores ≤ 50 based on a reference population(Achenbach and Rescorla 2001).

Table 3. Distribution of dichotomized CBCL outcomes for logistic models

| | Anxious/Depressed | | Attention Problems | | DSM Anxiety Problems | | DSM Attention Deficit/Hyperactivity Problems | | |
|---|---|---|---|---|---|---|---|---|---|
| | Normal range | Borderline or clinical | Normal range | Borderline or clinical | Normal range | Borderline or clinical | Normal range | Borderline or clinical | Total |
| PAH | 237 | 16[a] | 236 | 17 | 229 | 24 | 233 | 20 | 253 |
| Maternal Adducts | 212 | 11 | 208 | 15 | 204 | 19 | 205 | 18 | 223 |
| Cord adducts | 136 | 12 | 137 | 11[a] | 130 | 18 | 137 | 11 | 148 |

[a] In these cells, fewer than 5 children were in the borderline or clinical range in the low-exposure group making these results less reliable

Table 4. Associations between all measures (PAH exposure, maternal and cord PAH (B[a]P)-DNA adducts measured via HPLC, and cord PAH (B[a]P)-DNA adducts measured via $^{32}$P) and CBCL Syndrome and DSM Oriented outcomes in children ages 6-7[a]

| Exposure | Syndrome Scales Anxious /Depressed | | | | | | Syndrome Scale Attention Problems | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Poisson Raw | | | Logistic Dichotomized T | | | Poisson Raw | | | Logistic Dichotomized T | | |
| | Exp beta | 95% CI | p-value | OR | 95% CI | p-value | Exp beta | 95% CI | p-value | OR | 95% CI | p-value |
| PAH (high/low) (n=253, n1=16) | 1.45 | (1.22, 1.72) | <.0001 | 8.89 | (1.70, 46.51) | 0.010[b] | 1.28 | (1.10, 1.48) | 0.001 | 3.79 | (1.14, 12.66) | 0.030 |
| Maternal HPLC adducts[c] (n=223) | 1.23 | (1.04, 1.46) | 0.019 | 1.42 | (0.38, 5.35) | 0.603 | 1.25 | (1.08, 1.45) | 0.003 | 2.24 | (0.74, 6.77) | 0.153 |
| Cord HPLC adducts[c] (n=148) | 1.46 | (1.19, 1.78) | <0.001 | 2.56 | (0.69, 9.43) | 0.159 | 1.32 | (1.11, 1.58) | 0.002 | 4.06 | (0.99, 16.63) | 0.051[b] |
| *Cord $^{32}$P adducts[d] (n=205)* | *-0.03* | *(-0.22, 0.16)* | *0.773* | *1.42* | *(0.45, 4.46)* | *0.544* | *0.22* | *(0.06, 0.38)* | *0.009* | *3.30* | *(1.22, 12.54)* | *0.022* |

| Exposure | DSM-Oriented Scales Anxiety Problems | | | DSM-Oriented Scales Attention Deficit/ Hyperactivity Problems | | |
|---|---|---|---|---|---|---|
| | Logistic Model | | | Logistic Model | | |
| | OR | 95% CI | p-value | OR | 95% CI | p-value |
| PAH (high/low) (n=253) | 4.59 | (1.46, 14.27) | 0.009 | 2.30 | (0.79, 6.70) | 0.129 |
| Maternal HPLC adducts[c] (n=223) | 2.19 | (0.79, 6.07) | 0.133 | 1.84 | (0.66, 5.12) | 0.243 |
| Cord HPLC adducts[c] (n=148) | 2.53 | (0.84, 7.65) | 0.100 | 2.64 | (0.68, 10.26) | 0.161 |
| *Cord $^{32}$P adducts[d, e] (n=205)* | *1.26* | *(0.42, 3.82)* | *0.683* | | | |

[a] Covariates in the models include prenatal ETS, sex of child, gestational age, maternal IQ, HOME inventory, maternal education, ethnicity, prenatal demoralization, age at assessment, and heating season.

[b] These categories had fewer than 5 children in each category; therefore these results are less reliable

[c] HPLC adduct levels dichotomized at the detection level (detectable/not detectable), with detection occurring in n=87 maternal and n=56 cord blood samples

[d] $^{32}$P adducts were dichotomized at upper quartile, with 149 children classified as "low" exposure and 56 children classified as "high" exposure. Results in italics were published previously (Perera et al. 2011)

[e] The earlier publication did not analyze DSM-Oriented Attention Deficit/Hyperactivity Problems