Prenatal Exposure to Air Pollution, Maternal Psychological Distress, and Child Behavior

WHAT'S KNOWN ON THIS SUBJECT: Prenatal exposures to diverse pollutants and psychosocial stressors have been shown independently to adversely affect child development. Less is known about the potential interactions between these factors, although they commonly co-occur, especially in disadvantaged populations.

WHAT THIS STUDY ADDS: The combination of high prenatal exposure to environmental polycyclic aromatic hydrocarbons and maternal demoralization adversely affects child behavior, and maternal demoralization has a greater effect among children with high prenatal polycyclic aromatic hydrocarbon exposure for a majority of behavioral symptoms.

abstract

BACKGROUND: Airborne polycyclic aromatic hydrocarbons (PAHs) are pollutants generated by combustion of fossil fuel and other organic material. Both prenatal PAH exposure and maternal psychological distress during pregnancy have each been associated with neurodevelopmental problems in children. The goal was to evaluate potential interactions between prenatal exposure to airborne PAHs and maternal psychological distress during pregnancy on subsequent behavioral problems in children.

METHODS: In a longitudinal birth cohort study, 248 children of nonsmoking white women in the coal-burning region of Krakow, Poland, were followed from in utero until age 9. Prenatal PAH exposure was measured by personal air monitoring during pregnancy, maternal demoralization during pregnancy by the Psychiatric Epidemiology Research Instrument–Demoralization, and child behavior by the Child Behavior Checklist.

RESULTS: Significant interactions between maternal demoralization and PAH exposure (high versus low) were identified for symptoms of anxious/depressed, withdrawn/depressed, social problems, aggressive behavior, internalizing problems, and externalizing problems. The effects of demoralization on syndromes of anxious/depressed, withdrawn/depressed, rule-breaking, aggressive behavior, and the composite internalizing and externalizing scores were seen only in conjunction with high PAH exposure. Fewer significant effects with weaker effect sizes were observed in the low-PAH-exposure group.

CONCLUSIONS: Maternal demoralization during pregnancy appears to have a greater effect on child neurobehavioral development among children who experienced high prenatal PAH exposure. The results provide the first evidence of an interaction between prenatal exposure to maternal demoralization and air pollution on child neurobehavioral development, indicating the need for a multifaceted approach to the prevention of developmental problems in children. *Pediatrics* 2013;132:e1284–e1294

AUTHORS: Frederica P. Perera, DrPH, PhD,^{a,b} Shuang Wang, PhD,^{b,c} Virginia Rauh, ScD,^{b,d} Hui Zhou, MS,^c Laura Stigter, MA,^b David Camann, MS,^e Wieslaw Jedrychowski, PhD,^f Elzbieta Mroz, MSc,^f and Renata Majewska, MSc^f

^aDepartment of Environmental Health Sciences, Mailman School of Public Health, ^bColumbia Center for Children's Environmental Health, and Department of ^cBiostatistics and ^dHeilbrunn Department of Population and Family Health, Mailman School of Public Health, Columbia University, New York, New York; ^eSouthwest Research Institute, San Antonio, Texas; and ^fDepartment of Epidemiology and Preventive Medicine, Jagiellonian University, Krakow, Poland

KEY WORDS

prenatal, PAH, air pollution, child behavior, maternal psychological distress, demoralization

ABBREVIATIONS

CBCL—Child Behavior Checklist

DSM—Diagnostic and Statistical Manual of Mental Disorders

ETS—environmental tobacco smoke, PAH, polycyclic aromatic hydrocarbon

PERI-D—Psychiatric Epidemiology Research Instrument–Demoralization

Dr Perera conceptualized and designed the study, directed data analysis, and drafted the initial manuscript; Dr Wang advised Dr Perera on data analysis and reviewed and revised the manuscript; Dr Rauh advised on the selection of the behavioral test and demoralization scale and reviewed and revised the manuscript; Mr Zhou assisted Dr Perera with data analysis and reviewed the manuscript; Ms Stigter assisted with the coordination of the project and reviewed the manuscript; Mr Camann analyzed the air samples for polycyclic aromatic hydrocarbons and reviewed the manuscript; Dr Jedrychowski coordinated and supervised data collection in Poland and reviewed the manuscript; Ms Mroz and Ms Majewska assisted Dr Jedrychowski, maintained the cohort in Poland, and conducted neurodevelopmental testing in the children; and all authors approved the final manuscript as submitted.

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Address correspondence to Frederica P. Perera, DrPH, PhD, Mailman School of Public Health, Columbia University, 722 W 168th St, 12th floor, New York, NY 10032. E-mail: fpp1@columbia.edu

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Prenatal exposures to diverse pollutants and psychosocial stressors have been shown independently to adversely affect child development. Less is known about the potential interactions between these factors that may put children at greater risk of cognitive or behavioral problems that can affect learning and academic success. This is an important gap in research because these factors commonly co-occur, especially in disadvantaged populations.¹ A better understanding of their joint effects could lead to multifaceted prenatal interventions to prevent developmental disorders in children.

Many studies show heightened biological and psychological susceptibility of the developing fetus to environmental pollutants and/or psychosocial stressors.^{2–6} Socioeconomic and psychosocial factors, including poverty, maternal education, and maternal psychological distress, are important determinants of fetal and child development.^{6–17} In addition, prenatal maternal stress and maternal psychological distress, reflective of maternal affective or emotional functioning, have also been associated with child behavioral development.^{6,13–15}

Polycyclic aromatic hydrocarbons (PAHs) including benzo[a]pyrene, a representative PAH, are ubiquitous air pollutants generated by combustion sources that include diesel- and gasoline-powered motor vehicles, coal-fired power plants, residential coal and oil heating, and tobacco smoking.¹⁸ PAHs are lipid soluble and accumulate in adipose tissue; they are transferred across the placenta and fetal blood-brain barrier.^{19,20} Laboratory studies in experimental animals have revealed neurodevelopmental and behavioral effects of PAH exposure during the prenatal and neonatal periods, including anxiety, depressionlike symptoms, and memory impairment.^{20–26} Our previous research in a New York City

birth cohort and in the present Krakow birth cohort revealed that prenatal exposure to PAH was associated with adverse cognitive outcomes at age 5 years^{27,28} and with behavioral problems, including anxiety and depression, at ages 6 to 7 years in New York City.²⁹ Although there is some previous human evidence of interactions between socioeconomic factors and pollutants,^{30–34} this is the first study assessing the interaction of PAHs and maternal psychological distress on neurobehavioral outcomes.^{30–33}

METHODS

Sample Selection

The present analysis was undertaken within a longitudinal birth cohort study in a white population in Krakow, Poland. The study was approved by the ethics committee of the Jagiellonian University and the institutional review board of the New York Presbyterian Medical Center. Informed consent was obtained from all subjects. Nonsmoking, pregnant women were recruited between November 2000 and March 2003.³⁵ Pregnant women were eligible if they met the following criteria: were not currently smoking; were registered at prenatal health care clinics in either of the 2 target areas; had lived at the present address for at least 1 year before the initial interview; were between the 8th and 24th weeks of gestation; were >18 years of age; had no current occupational exposure to PAHs or other known developmental toxicants; had no history of illicit drug use, pregnancy-related diabetes, or hypertension; and had an estimate of gestational age based on last menstrual period.

A major source of PAH air pollution during the study period was coal-burning in small furnaces for domestic heating.³⁶ Automobile traffic emissions and coal combustion for industrial

activities were less important contributors.³⁷

Personal Interview, Medical Record, and Biomarker Data

Between the 20th and 30th week of pregnancy, research workers administered an in-depth health, lifestyle, and environmental exposure questionnaire to all women in their homes. The questionnaire elicited information on environmental tobacco smoke (ETS) exposure during pregnancy (presence/absence of smokers in the household during pregnancy), dietary PAH intake (frequency of consumption of broiled, fried, grilled, or smoked meat during pregnancy), and socioeconomic information related to income and education. After delivery, data on pregnancy and delivery were obtained from the mothers' and infants' medical records.

Postnatal interviews were administered to mothers every 6 months after birth to determine any changes in residence, exposure to ETS, or other health or environmental conditions. To validate self-reported exposure to ETS during pregnancy, cotinine in cord plasma was analyzed at the Centers for Disease Control and Prevention.²⁸ PAH metabolites in child urine collected at age 3 years were also analyzed by the Centers for Disease Control and Prevention and used as a measure of postnatal PAH exposure.^{28,38}

Prenatal Personal PAH Assessment

Forty-eight-hour personal air monitoring was carried out during the second or third trimester, and concentrations of 8 PAHs, including benzo[a]pyrene, were analyzed as described previously.³⁹ The 48-hour personal monitoring was validated as an indicator of integrated exposure by simultaneously monitoring a subset of pregnant women ($n = 80$) for personal, indoor, and outdoor airborne PAH concentrations. These 3 measurements were found to

be highly correlated (pairwise Spearman's coefficients ≥ 0.84 , $P < .01$),⁴⁰ supporting the use of personal monitoring as an integrated measure of exposure.

Psychiatric Epidemiology Research Instrument–Demoralization Scale and Maternal Intelligence

The Psychiatric Epidemiology Research Instrument–Demoralization (PERI-D)⁴¹ is a standardized measure of non-specific psychological distress (demoralization), which has been used in a large number of previous studies of stressful living conditions.⁴² Demoralization denotes nonspecific psychological distress, with high demoralization indicating an individual's inability to cope with stressful situations.^{41,42} The PERI-D was administered to the mothers during the second trimester to evaluate maternal psychological demoralization over the last year. In the current sample, demoralization was computed as the mean of 25 different variables. The Cronbach coefficient for these 25 variables was 0.89, showing high internal consistency.

Maternal intelligence was assessed by using the Test of Nonverbal Intelligence–Third Edition, a language-free measure of general intelligence considered to be relatively free of cultural bias.⁴³

Behavioral Outcomes

The Child Behavior Checklist (CBCL)^{44,45} has been widely used and has been shown to be sensitive to diverse prenatal exposures, including stress events during pregnancy, smoking during pregnancy, and exposure to PAHs, pesticides, methylmercury, and tobacco smoke.^{46–48} A research worker trained in neurodevelopmental testing administered the CBCL to the mothers at child ages 6 to 9 years. The CBCL syndromes include problems and complaints in the areas of anxious/depressed,

withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, aggressive behavior, and the summary composite scales of internalizing and externalizing problems. The syndrome scores are computed for each domain of interest by summing the scores on the specific items, with higher scores indicating more symptoms. Table 2 shows the distribution of behavioral symptoms in the sample. The syndrome scores were converted into T scores by assigning a score of 50 to those with percentiles of raw scores ≤ 50 based on a reference population,^{44,49} then dichotomized by using a “borderline or clinical” cutoff corresponding to the 93rd percentile for each domain. The small number of children in the category of “borderline or clinical” for certain syndrome T scores (see Table 2) precluded analysis for some of these outcomes. The CBCL further yields scales derived from the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*⁵⁰ (2000) that are intended to approximate clinical diagnoses. The DSM scores are dichotomized by using a “borderline or clinical” cutoff corresponding to the 93rd percentile for each domain.^{44,49} For both the syndrome and the DSM scores, children are classified in the borderline or clinical range (T score ≥ 65 ; DSM score ≥ 65) or in the normal range (T score < 65 ; DSM score < 65). Table 6 shows the percentage and number of children in the category of “borderline or clinical” with respect to DSM.

Statistical Analysis

As in previous analyses,^{28,39} a composite (total) PAH variable was computed from the 8 intercorrelated PAH air concentration measures (r values ranging from 0.34 to 0.94; all P values $< .001$ by Spearman's rank). The primary PAH-exposure variable in the analysis was total PAHs dichotomized

at the median value in the parent population (22.11 ng/m³) to obtain a measure of high/low exposure. The dichotomized PAH variable was considered preferable to the continuous variable because it is less vulnerable to extremes of exposure. Continuous PAH (log-normal transformed) was used in a secondary analysis of the interaction to compare results using the 2 different variables. Maternal demoralization was treated as a continuous variable.

Analyses of the relation between maternal demoralization, maternal education, and income were conducted to assess whether any of these factors could be associated with maternal demoralization; Pearson correlation, Spearman's rank order correlation, and χ^2 was used as appropriate depending on whether continuous or categorical variables were analyzed.

The Poisson regression model was applied on the raw (untransformed) CBCL syndrome scores and internalizing and externalizing problems because they are count data that sum the scores on the specific items within each scale or group of scales, and the score distribution for each syndrome is right-skewed. Dichotomized T scores and DSM scores were analyzed by using logistic regression, where the numbers permitted. Only results from domains with $> 5\%$ of subjects in the borderline or clinical range were summarized and interpreted. Covariates were selected if they were of a priori interest based on the literature or our previous studies and also significant contributors to at least 1 of the outcomes.

The covariates included child's age at assessment (in months), season at the time of monitoring (heating [October through April] versus nonheating season [May through September]), gestational age, ETS exposure during pregnancy, gender, and mother's education (completion

of lyceum or high school before birth of the child). As in previous analyses, maternal education was used as a proxy for socioeconomic status.²⁸ Dietary PAH exposure was not correlated with monitored PAHs and was not a significant predictor of CBCL scores ($P < .1$) and thus was not included as a covariate. Because prenatal PAH exposure was found previously to be associated with reduced birth weight in this cohort,^{39,51} we evaluated the potential of birth weight as a confounder by including birth weight in separate models. Maternal intelligence is a known correlate of child cognitive development^{52,53} but was available only in a subset of the children; therefore, it was included with the other covariates in a separate analysis. We also adjusted for postnatal PAH exposure by using the sum of creatinine-adjusted PAH metabolites in urine collected at 3 years of age or a measure of postnatal change of residence as an indicator of likely, although unmeasured, change in exposure to airborne PAHs after birth. We further adjusted for maternal report of postnatal exposure to ETS in the home. These latter models were limited by the smaller numbers of participants with data on these additional covariates.

We investigated the interaction between the 2 exposures of interest, prenatal PAH exposure (dichotomous) $\times$ maternal demoralization (continuous), in Poisson regression models. This method allowed us to examine the differential effects of demoralization within the high- versus low-PAH-exposure groups. Subsequent stratified analyses were also conducted to assess the effects of maternal demoralization within the high- and low-PAH-exposure subgroups. We did not adjust for multiple comparisons because such adjustment is considered overly conservative in an initial study of a novel hypothesis.

All effect estimates and P values (α set at .05) were generated by using SAS (version 9.1.0.3; SAS Institute Inc, Cary, NC).

RESULTS

Four hundred twenty-three participants had complete PAH monitoring data, medical records, and questionnaire data. Of these children, 248 had complete questionnaire and CBCL data at ages 6 to 9 years and were included in the present analysis. Table 1 shows the characteristics of the subset of the 248 children. There were no significant differences in these characteristics between the children who were included in the analysis and those not included because they had not reached the age of 9 years, had missed this particular developmental assessment, or were lost to follow-up ($n = 75$). All mothers in the study had detectable levels of PAHs in prenatal personal air samples, whereas 35.5% reported ETS exposure during pregnancy.²⁸ Exposure to PAHs was highly variable among women in the study as evidenced by personal air monitoring during pregnancy (mean: 20.7 ng/m³; range: 1.8–323.76 ng/m³).³⁹ The monitored levels mainly reflected ambient

concentrations of the pollutants.⁵⁴ The mean PAH concentration was higher in the winter/heating season than the summer/nonheating season. For example, the winter mean concentration of BaP was 4.9 ng/m³ compared with 0.9 ng/m³ in the summer.⁵⁵

Table 2 shows the distribution of behavioral symptom outcomes in the sample analyzed. A total of 1% to 13% of children had syndrome scores in the borderline or clinical range. PAH exposure and maternal demoralization treated as continuous variables were not significantly correlated ($r = 0.016$, $P = .80$). Maternal education was not significantly correlated with PAH ($P > .2$). Maternal education (in years) was inversely correlated with demoralization ($r = -0.12$, $P = .057$).

Correlations between airborne PAHs and ETS exposure and between airborne PAHs and dietary PAH were not significant ($P < .12$). As reported previously,²⁸ self-reported ETS exposure during pregnancy was significantly correlated with cotinine in both cord blood and maternal blood at delivery ($r = 0.30$ and 0.34 , respectively), supporting self-reported ETS as a reliable measure of ETS exposure.²⁸

TABLE 1 Characteristics of Children Included and Not Included in the Analysis

Variable	Subjects Included in the Analysis ($n = 248$)	Subjects Not Included in the Analysis ^a ($n = 175$)	P for Difference ^b
Total PAH, mean $\pm$ SD, ng/m ³	40.8 $\pm$ 53.6	48.7 $\pm$ 58.2	.15
Gestational age, mean $\pm$ SD, wk	39.4 $\pm$ 1.6	39.4 $\pm$ 1.4	.73
Maternal psychological distress score ^c , mean $\pm$ SD	1.0 $\pm$ 0.4	1.1 $\pm$ 0.5	.23
Age at assessment, mean $\pm$ SD, mo	87.4 $\pm$ 11.8	NA	NA
Smoking at home ^d , %	22.6	19.4	.44
Female, %	51.2	47.4	.44
Mother with high school education or greater, %	91.5	89.7	.52
Heating season ^e , %	52.8	61.5	.08

NA, not available.

^a Of 423 children with valid prenatal monitoring and questionnaire data, 248 had CBCL data at age 6 to 9 years and data on other required covariates. Subjects were not included due to missing data or loss to follow-up.

^b Statistical differences between the 2 groups were based on a 2-sample t test or a χ^2 test.

^c Maternal psychological distress during pregnancy (PERI-D).

^d Prenatal ETS exposure in the home from smokers other than the mothers who are nonsmokers.

^e Monitoring during the heating season (yes/no). $n = 174$ subjects not included in the analysis.

TABLE 2 Distribution of Behavioral Outcomes (Behavioral Symptoms) in the Sample Analyzed

Domain	Score Range		Mean of Scores		Percentage in Borderline or Clinical Range (<i>n</i>) ^b
	T Score ^a	Raw (Untransformed) Score	T Score	Raw (Untransformed) Score	
Anxious/depressed	50–82	0–17	56.59	4.32	13.3 (33)
Withdrawn/depressed	50–76	0–8	54.63	1.35	6.9 (17)
Somatic complaints	50–72	0–8	54.36	1.31	4.8 (12)
Social problems	50–73	0–11	54.14	2.41	3.6 (9) ^c
Thought problems	50–75	0–11	52.23	1.08	1.2 (3) ^c
Attention problems	50–71	0–13	54.24	3.54	3.6 (9) ^c
Rule-breaking behavior	50–70	0–7	54.67	1.90	4.0 (10) ^c
Aggressive behavior	50–75	0–20	54.49	4.92	6.0 (15)
Internalizing problems	33–80	0–31	53.29	6.98	14.1 (35)
Externalizing problems	33–71	0–24	51.64	6.83	3.6 (9) ^c

N = 248.

^a The T score is truncated⁵¹; that is, a score of 50 was assigned to those with percentiles of raw scores ≤ 50 based on a reference population.⁴⁵

^b The syndrome T scores are dichotomized at *T* = 65 as the cutoff for the borderline and clinical range. Internalizing and externalizing problems are analyzed continuously and therefore do not have a dichotomized value.

^c There were too few children in this category to permit meaningful analysis.

In the Poisson regression model, a significant interaction was observed between prenatal PAH exposure (high/low dichotomized at the median) and maternal demoralization (continuous measure) on the symptoms of anxious/depressed ($\beta = 0.35$, $P = .023$), withdrawn/depressed ($\beta = 0.81$, $P = .003$), social problems ($\beta = 0.4$, $P = .051$), aggressive behavior ($\beta = 0.50$, $P = .0004$), internalizing problems ($\beta = 0.45$, $P = .0002$), and externalizing problems ($\beta = 0.48$, $P < .0001$) (Table 3). (Here the β s are regression coefficients of the

interaction terms, which refer to the difference between the effect of demoralization in the high- versus low-PAH-exposure groups.)

Figure 1 displays the interactions more clearly by showing the effects of maternal demoralization within the high- and low-PAH-exposure groups, separately. Within the high-PAH-exposure subgroup, we found significant effects of maternal demoralization for all the problems mentioned above ($P < .001$) and for somatic complaints ($\beta = 0.88$, $P < .0001$), attention problems ($\beta = 0.31$,

$P = .028$), and rule-breaking behavior ($\beta = 0.47$, $P = .009$) (Table 3). In contrast, among the low-PAH-exposure subgroup, only somatic complaints ($\beta = 0.38$, $P = .038$), social problems ($\beta = 0.32$, $P = .016$), and attention problems ($\beta = 0.25$, $P = .014$) were significantly associated with maternal demoralization (Table 3). Main effects of PAH were seen on withdrawn/depressed, social problems, aggressive behavior, internalizing problems, and externalizing problems; and main effects of maternal demoralization were seen on all of the problems except for thought problems.

Adjustment for maternal intelligence limited the sample size ($n = 199$) but strengthened the interaction effects, as shown in Table 4. Our secondary analyses adjusting for change of residence after the infant's birth as an indicator of potential change in air pollution exposure ($n = 241$) showed that the previously observed interactions remained significant. Furthermore, adjusting for postnatal ETS and postnatal urinary PAH metabolites at age 3 years, the associations remained the same except for symptoms of anxious/depressed, which were no longer significant ($P = .15$), probably due to decreased sample size ($n = 112$) (Table 4).

In logistic regression with dichotomized T scores, significant interactions were

TABLE 3 Interaction Between PAH (High/Low) and Maternal Psychological Distress Overall and the Effect of Maternal Psychological Distress Within the High- Versus Low-PAH-Exposure Groups

Domain	Maternal Psychological Distress ^b					
	Interaction ^a (<i>N</i> = 248)					
	$\beta_{\text{interaction}}$	<i>P</i>	Within the High-PAH Group (<i>n</i> = 114)		Within the Low-PAH Group (<i>n</i> = 134)	
			β	<i>P</i>	β	<i>P</i>
Anxious/depressed	0.35	.023*	0.53	<.0001**	0.16	.13
Withdrawn/depressed	0.81	.003*	0.83	<.0001**	−0.05	.77
Somatic complaints	0.36	.20	0.88	<.0001**	0.38	.038*
Social problems	0.40	.051*	0.70	<.0001**	0.32	.016*
Thought problems	0.17	.59	0.20	.40	0.003	.99
Attention problems	0.08	.64	0.31	.028*	0.25	.014*
Rule-breaking behavior	0.42	.06	0.47	.009*	0.03	.87
Aggressive behavior	0.50	.0004*	0.56	<.0001**	0.01	.92
Internalizing problems	0.45	.0002*	0.65	<.0001**	0.16	.048*
Externalizing problems	0.48	<.0001**	0.54	<.0001**	0.01	.85

Results of analysis of dichotomized T scores are provided in the text and in Table 5.

^a Prenatal PAH dichotomized at the median (22.11 ng/m³). Models adjusted for prenatal ETS, gender, maternal high school completion, gestational age, maternal psychological distress during pregnancy (continuous measure), age at assessment, and heating season at time of monitoring.

^b Effect of maternal psychological distress (continuous) within the specified PAH-exposure group.

* $P < .05$.

FIGURE 1

The relationship between maternal psychological distress and behavioral symptom score within the high- and low-PAH groups, respectively (solid lines represent high PAH exposure; dashed lines represent low PAH exposure). Anx/Dep, anxious/depressed; Prob, problems; With/Dep, withdrawn/depressed.

found between prenatal PAH exposure and maternal demoralization on symptoms in the borderline or clinical range for somatic complaints ($\beta = 4.37$, $P = .021$), aggressive behavior ($\beta = 3.31$, $P = .04$), and externalizing problems ($\beta = 6.14$, $P = .019$) (Table 5). Also using dichotomized T scores, within the high-PAH-exposure group but not the low exposure group, maternal demoralization was significantly associated with anxious/depressed ($\beta = 1.84$, $P = .011$), somatic complaints ($\beta = 6.28$, $P = .004$), aggressive behavior ($\beta = 3.56$, $P = .019$), and internalizing problems ($\beta = 1.68$, $P = .019$).

Table 6 shows the distribution of *DSM* outcomes in the sample analyzed. In the logistic model for *DSM* scores, no significant interactions were found.

The same analysis of the interaction of PAHs $\times$ demoralization on behavioral

symptoms using the continuous measure of PAH (log-normal PAH) gave results consistent with those based on the dichotomous PAH measure.

DISCUSSION

The present analysis suggests that maternal demoralization during pregnancy interacts significantly with prenatal PAH airborne exposure level on neurobehavioral outcomes, including more symptoms of anxiety and depression. Even in this more advantaged population with modest levels of socioeconomic stress, these factors appear to combine to adversely affect children's development. The results are relevant to other populations. Although Krakow has relatively high ambient concentrations of PAHs from coal-burning, levels are within the range seen in other urban areas worldwide.^{56–59}

Mechanisms by which stressors such as material hardship, PAHs, or their combination exert effects on the developing brain are not well understood. However, laboratory studies have identified changes in N-methyl-D-aspartate receptor expression, reduced brain-derived neurotrophic factor mRNA,⁶ and epigenetic changes^{60,61} in response to stress. In humans, increases in prenatal maternal cortisol⁶ and transfer of cortisol to the fetus play a role.⁶² At high concentrations, cortisol may inhibit growth and differentiation of the developing nervous system, and induce neuronal cell death, which is mediated by a decrease in brain-derived neurotrophic factor. Cortisol also affects myelination in the developing brain (reviewed in ref 6).

TABLE 4 Interaction Between PAH (High/Low) and Maternal Psychological Distress on CBCL Symptom Scores With Further Adjustment for Change of Residence After Delivery, Postnatal ETS and PAHs, and Maternal Intelligence

Domain	Interaction ^a With Additional Adjustment for Change of Residence After Delivery (<i>n</i> = 241)		Interaction With Additional Adjustment for Postnatal ETS and Postnatal PAH Urinary Metabolites (<i>n</i> = 112)		Interaction With Additional Adjustment for Maternal Intelligence (<i>n</i> = 199)	
	$\beta_{\text{interaction}}$	<i>P</i>	$\beta_{\text{interaction}}$	<i>P</i>	$\beta_{\text{interaction}}$	<i>P</i>
Anxious/depressed	0.35	.022*	0.30	.15	0.52	.002*
Withdrawn/depressed	0.83	.0040*	0.87	.016*	0.93	.0016*
Somatic complaints	0.36	.20	0.64	.11	0.63	.038*
Social problems	0.39	.058*	0.94	.001**	0.58	.0083*
Thought problems	0.16	.62	0.33	.41	0.50	.16
Attention problems	0.07	.67	0.030	.90	0.18	.33
Rule-breaking behavior	0.41	.07	0.67	.038*	0.52	.036*
Aggressive behavior	0.48	.0007*	0.50	.010*	0.64	<.0001**
Internalizing problems	0.49	<.0001**	0.45	.0053*	0.63	<.0001**
Externalizing problems	0.55	<.0001**	0.53	.0012*	0.61	<.0001**

^a Prenatal PAH dichotomized at the median (22.11 ng/m³). Model adjusted for prenatal ETS, gender, maternal high school completion, gestational age, maternal psychological distress during pregnancy (continuous measure), age at assessment, and heating season at time of monitoring.

* *P* < .05.

The putative mechanisms by which prenatal exposure to environmental toxicants such as PAHs might affect the developing brain include fetal toxicity caused by endocrine disruption,^{24,63,64} binding to receptors for placental growth factors resulting in decreased exchange of oxygen and nutrients,⁶⁵ binding to the human Ah (aryl hydrocarbon) receptor to induce P450 enzymes,⁶⁶ DNA damage resulting in activation of apoptotic pathways,^{67–69} epigenetic effects,⁷⁰ and oxidative stress due to inhibition of the brain antioxidant

scavenging system.²¹ Regarding the specific effects of gestational PAH exposure on neurodevelopment in laboratory animals, potential mechanisms include impairment in N-methyl-D-aspartate receptor-1 (NMDAR1) subunit expression and impaired long-term potentiation (LTP) generation (reviewed in ref 71).

The mechanisms by which maternal prenatal psychological distress might interact with PAH exposure on neurodevelopmental effects in children have not been characterized. The hypothesized

mechanism for these interaction effects is that social stress “interferes with normal functioning of protective toxicokinetic and toxicodynamic processes in ways that impair individual resilience and ability to recover from toxic insults.”^{72,73} Psychological stressors and physical toxicants may potentiate each other through common physiologic pathways, such as inflammation.⁷² Alternatively, interactions might result from the action of these exposures on different pathways (induction of genotoxic damage versus epigenetic alterations) that together affect the developing brain. A better understanding of these complex interdependencies may help explain and ultimately prevent health disparities.

The strengths of this analysis include the ability to account for a number of factors other than PAH exposure that are known to affect child neurobehavioral development and to draw on individual prenatal exposure data from personal monitoring, biomarker data, and extensive medical record and questionnaire data. Because the Krakow population is white and genetically homogeneous, competing explanations such as race/ethnicity and genetic variation were effectively ruled out. Because the study included only nonsmoking

TABLE 5 Interaction Between PAH (High/Low) and Maternal Psychological Distress on CBCL Dichotomized T Scores for Symptoms and Effects of Maternal Psychological Distress Within Each PAH-Exposure Group

Domain	Maternal Psychological Distress ^b					
	Interaction ^a (<i>N</i> = 248)		Within the High-PAH Group (<i>n</i> = 114)		Within the Low-PAH Group (<i>n</i> = 134)	
	$\beta_{\text{interaction}}$	<i>P</i>	β	<i>P</i>	β	<i>P</i>
Anxious/depressed	0.67	.513	1.84	.011*	0.89	.25
Withdrawn/depressed	1.04	.418	0.96	.291	−0.16	.86
Somatic complaints	4.37	.021*	6.28	.004*	0.06	.951
Social problems ^c	—	—	—	—	—	—
Thought problems ^c	—	—	—	—	—	—
Attention problems ^c	—	—	—	—	—	—
Rule-breaking behavior ^c	—	—	—	—	—	—
Aggressive behavior	3.31	.04*	3.56	.019*	0.09	.91
Internalizing problems	1.07	.262	1.68	.019*	0.46	.495
Externalizing problems ^c	—	—	—	—	—	—

^a Prenatal PAH dichotomized at the median (22.11 ng/m³). Model adjusted for prenatal ETS, gender, maternal high school completion, gestational age, maternal psychological distress during pregnancy (continuous measure), age at assessment, and heating season at time of monitoring.

^b Effect of maternal psychological distress (continuous) within the specified PAH-exposure group.

^c There were too few children with scores in the borderline or clinical range to permit meaningful analysis (see Table 2).

* *P* < .05.

TABLE 6 Distribution of *DSM* Outcomes in the Sample Analyzed

Outcomes	Score Range	Mean of Scores	Percentage in Borderline or Clinical Range (<i>n</i>) ^a
Affective disorder	0–11	2.23	8.5 (21)
Anxiety disorder	0–12	3.16	10.1 (25)
Pervasive developmental disorder	0–22	3.10	6.9 (17)
Attention-deficit/hyperactivity disorder	0–10	4.16	4.4 (11)
Opposition disorder	0–9	3.49	4.8 (12)

There were too few children in this category to permit meaningful analysis.

^a The *DSM* scores are dichotomized by using a “borderline or clinical” cutoff corresponding to the 93rd percentile for each domain.

women, active maternal smoking was also not a factor; and ETS exposure was included as a covariate in the models.

There are a number of limitations to this study. The Home Observation for Measurement of the Environment Inventory, a measure of the child's proximal caretaking environment,⁷⁴ is not widely used in central Europe and was not administered in the Polish cohort. However, analyses adjusted for maternal education which partially accounts for the important role of the mothers in stimulating the child.^{52,53,75} In the current study, personal airborne PAH levels were not correlated with total years of education completed by the mother, mitigating concern that unmeasured differences in socioeconomic status may have confounded our findings on PAH exposure. Relying on a single measurement of prenatal air for our exposure measure is limiting, but simultaneous personal, indoor, and outdoor monitoring of a subset of the cohort showed that the 3 measurements were highly correlated.⁴⁰ Moreover, because measurements during the second and third trimesters were correlated,⁴⁰ we consider the single monitoring time point to be a reasonable indicator of prenatal exposure via inhalation over the last 2 trimesters of pregnancy. Regarding the

potential effect of season on our results, monitoring was evenly distributed across seasons (*n* = 86, 81, 85, and 92 mothers monitored in spring, summer, fall, and winter, respectively) and we adjusted for season in the analysis.

Although the fetal window is considered to be the most vulnerable to psychological stress as well as to toxic pollutants, postnatal exposures can be important. However, we did not obtain postnatal measures of demoralization that could affect both child behavior and mother's perception of her child's behavior. We lacked postnatal PAH air-monitoring data. However, as measures of postnatal air pollution exposure, we were able to use levels of PAH metabolites in child urine or change in location of neighborhood of residence as a proxy for likely change in air pollution exposure postnatally.

We note that the prevalence of symptoms of anxious/depressed in the borderline or clinical range (13%) was high relative to other domains but at the lower end of the range reported for anxiety (15%–20%) in American children and adolescents.⁷⁶

Finally, the population characteristics gave us an opportunity to assess

modification of PAH effects by maternal psychological distress within a population not experiencing extreme disadvantage or extreme psychological distress. The levels of demoralization were also moderate. Also, in addition to being homogeneous with respect to race/ethnicity, the population was relatively homogeneous with respect to education and marital status.

CONCLUSIONS

This study provides evidence that the combination of high prenatal exposure to environmental PAHs and maternal demoralization during pregnancy adversely affects child behavior and that maternal prenatal demoralization has a greater effect among children with high prenatal exposure than among those with lower PAH exposure for a majority of behavioral symptoms. These results are of concern because neurobehavioral problems such as reported here may affect subsequent academic performance and well-being. Given the importance of women's mental health during pregnancy for fetal and child development,⁷⁷ the findings suggest the need to screen women early in pregnancy to identify those in need of psychological or material support as part of a multifaceted approach that also includes policy interventions to reduce air pollution exposure in urban areas.

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