Relationships among Polycyclic Aromatic Hydrocarbon–DNA Adducts, Proximity to the World Trade Center, and Effects on Fetal Growth

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Polycyclic aromatic hydrocarbons (PAHs) are toxic pollutants released by the World Trade Center (WTC) fires and various urban combustion sources. Benzo[*a*]pyrene (BaP) is a representative member of the class of PAHs. PAH–DNA adducts, or BaP–DNA adducts as their proxy, provide a measure of chemical-specific genetic damage that has been associated with increased risk of adverse birth outcomes and cancer. To learn whether PAHs from the WTC disaster increased levels of genetic damage in pregnant women and their newborns, we analyzed BaP–DNA adducts in maternal ($n = 170$) and umbilical cord blood ($n = 203$) obtained at delivery from nonsmoking women who were pregnant on 11 September 2001 and were enrolled at delivery at three downtown Manhattan hospitals. The mean adduct levels in cord and maternal blood were highest among newborns and mothers who resided within 1 mi of the WTC site during the month after 11 September, intermediate among those who worked but did not live within this area, and lowest in those who neither worked nor lived within 1 mi (reference group). Among newborns of mothers living within 1 mi of the WTC site during this period, levels of cord blood adducts were inversely correlated with linear distance from the WTC site ($p = 0.02$). To learn whether PAHs from the WTC disaster may have affected birth outcomes, we analyzed the relationship between these outcomes and DNA adducts in umbilical cord blood, excluding preterm births to reduce variability. There were no independent fetal growth effects of either PAH–DNA adducts or environmental tobacco smoke (ETS), but adducts in combination with *in utero* exposure to ETS were associated with decreased fetal growth. Specifically, a doubling of adducts among ETS-exposed subjects corresponded to an estimated average 276-g (8%) reduction in birth weight ($p = 0.03$) and a 1.3-cm (3%) reduction in head circumference ($p = 0.04$). The findings suggest that exposure to elevated levels of PAHs, indicated by PAH–DNA adducts in cord blood, may have contributed to reduced fetal growth in women exposed to the WTC event. *Key words:* DNA adducts, fetal growth, newborns, PAHs, World Trade Center. ***Environ Health Perspect* 113:1062–1067 (2005). doi:10.1289/ehp.7908 available via *http://dx.doi.org/* [Online 20 April 2005]**

The destruction and combustion of the World Trade Center (WTC) towers released a complex mixture of toxicants into the New York City environment on and after 11 September 2001 (Lioy et al. 2002; McGee et al. 2003; Offenburg et al. 2003). These included neurodevelopmental toxicants and carcinogens such as polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins, polychlorinated dibenzofurans, polybrominated diphenyl ethers, and various metals (Chen and Thurston 2002; Jeffrey et al. 2003; Lioy et al. 2002; McKinney et al. 2002; Offenburg et al. 2003). The WTC plume contained high levels of PAHs that spiked at a measurement site 1.8 km (1.1 mi) northeast of the WTC site several times in September and October 2001, with a peak on 3 October during an inversion that brought smoke back to ground level (Service 2003). PAHs are also common pollutants in urban air from fossil fuel combustion by motor vehicles, residential heating units, power plants, and industrial activities (Bostrom et al. 2002) and are present in tobacco smoke and in grilled or broiled food [International Agency for Research on Cancer (IARC) 1983; U.S. Environmental Protection Agency (EPA) 1990]. Thus, during the weeks and months after 11 September 2001, the WTC event added to an ongoing background exposure to airborne PAHs. A number of PAHs, including benzo[*a*]pyrene (BaP), are known human mutagens, carcinogens, and/or developmental toxicants. BaP is widely used as a representative PAH because concentrations of individual PAHs in the urban setting are highly intercorrelated (Perera et al. 2003). Therefore, we have used BaP–DNA adducts as a proxy for PAH–DNA adducts. Because they reflect individual variation in exposure, absorption, metabolic activation, and DNA repair, the adducts in white blood cells provide a biologic dosimeter and marker of potential risk (Bartsch and Hietanen 1996; Veglia et al. 2003). These DNA adducts have an estimated half-life of 3–4 months (Mooney et al. 1995). Thus, considering that the main exposure to WTC-related PAHs occurred between 11 September 2001 and 11 November 2001 while the fires were ongoing, adduct measurements in blood samples collected up to June 2002 would reflect that exposure.

This research focuses on possible risks of the WTC disaster to children of women who were pregnant at that time, because of evidence that the fetus is more sensitive than the adult to a range of pollutants including PAHs (National Research Council 1993; Perera et al. 2004b; Whyatt et al. 2001). For example, compared with their mothers, newborns sampled at delivery have evidenced a higher rate of genetic damage from PAHs (in the form of DNA adducts) and demonstrated slower clearance of various toxicants (National Research Council 1993; Perera et al. 2004b; Whyatt et al. 2001). Moreover, the fetal growth effects of ambient PAHs or of PAH–DNA adducts, alone or in combination with environmental tobacco smoke (ETS),

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have been demonstrated in other populations, including those from Eastern Europe and New York City (Dejmek et al. 1999, 2000; Perera et al. 1998, 2004b).

We recently reported results from our parent study showing that infants born to women who lived within a 2-mi radius of the WTC during the month after 11 September 2001 showed significant decrements in term birth weight and birth length, compared with infants born to women living farther away, after controlling for sociodemographic and biomedical risk factors and gestational duration (Lederman et al. 2004). The relation of distance to birth weight and length were similar when a 1-mi radius was used to define the residential group, but the differences were no longer significant. In choosing a distance cutoff, there is a choice between selecting a more highly exposed but smaller group, namely, those living very close (within 1 mi), or a less-exposed but larger group, those living in a wider area (within 2 mi).

To explore the possible contribution to adverse birth outcomes of ambient PAHs after the disaster, we first evaluated whether PAH–DNA adducts were related to proximity to the WTC site. We then evaluated whether, as in a prior study in northern Manhattan/south Bronx, New York (Perera et al. 2004a), PAH–DNA adducts in cord blood adversely affected birth outcomes, alone or in combination with ETS.

Materials and Methods

Recruitment, data collection, and geocoding. This study is a project within the Columbia Center for Children's Environmental Health (CCCEH; www.ccceh.org). The study methods have been described previously (Lederman et al. 2004). Patients were enrolled at Beth Israel, St. Vincent's, St. Vincent's affiliated Elizabeth Seton Childbearing Center, and New York University Downtown Hospitals, selected because of their close proximity to the WTC site. Singleton pregnant women were enrolled at the time of labor. Eligible women were between 18 and 39 years old, pregnant on 11 September 2001 based on delivery within 41 weeks of 11 September, had not smoked during pregnancy, and reported no diabetes, hypertension, HIV infection or AIDS, or use of illegal drugs in the preceding year. Enrollment began on 12 December 2001, as soon as institutional review board approval was obtained, and ended on 26 June 2002. Women were briefly screened for eligibility, recruited, enrolled, consented (before delivery), and interviewed after delivery by bilingual interviewers in their preferred or native language (English, Spanish, or Chinese). Of 738 women initially screened for eligibility, 369 women were eligible and gave consent for participation; 329 contributed at least one blood sample (cord or maternal blood), medical record information, and a complete postpartum interview, all of which were required for full enrollment in the study. Information on the pregnancy, delivery, and birth outcomes was collected from the medical records of the mother and newborn (Lederman et al. 2004). A 30- to 45-min interview was administered to each mother to elicit information on demographics; reproductive history; background environmental exposures including dietary PAH exposure via grilled, smoked, and barbecued foods; and the location of the woman's residences and workplaces during each of the 4 weeks after 11 September 2001. Residential and work addresses were geocoded at the Center for International Earth Science Information Network of Columbia University's Earth Institute; the geocoded linear distance from the WTC site was computed for each residence and work site (GIS software, including ArcGIS 8.3 and the StreetMap 2003 extension; Environmental Systems Research Institute, Redlands, CA). Figure 1 shows the location of residences and workplaces of subjects included in the analysis of adducts.

Blood collection and adduct analysis. Umbilical cord blood (mean 30.7 mL) was collected at delivery and maternal blood (30–35 mL) generally on the first day after delivery. Samples were transported 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. As noted, BaP–DNA adducts were used as a proxy for PAH–DNA adducts. BaP–DNA adducts in extracted white blood cell DNA were analyzed using the high-performance liquid chromatrography (HPLC)/fluorescence method of Alexandrov et al. (1992), which detects BaP tetraols (Alexandrov et al. 1992; Rojas et al. 1994), modified as described (Perera et al. 2004b). Briefly, about 100 µg DNA was used for each analysis. Many precautions were taken to avoid the presence of fluorescent contaminants. DNA samples (each ~100 µg) were dissolved in 0.1 N HCl, and acid hydrolysis was carried out at 90°C for 6 hr. The resulting solution was analyzed in a Shimadzu HPLC system with RF-10Axl spectrofluorometric detector. The Shimadzu (Kyoto, Japan) SIL-10A automatic sample injector (Shimadzu, Kyoto, Japan) was used to minimize any batch effect. The tetraol concentrations were calculated by comparing the samples analyzed with an external calibration curve, generated from the fluorescence peak of a known amount of authentic benzo[*a*]pyrene diol epoxide (BPDE) tetraol standard, every time a set of samples was analyzed. Calibration was carried out with DNA from calf thymus alone (background) and spiked with 2, 4, and 8 pg *anti*-BPDE tetraol. These standard solutions were then treated in the same way as the tested samples. The correlation coefficient was 0.98, and the mean coefficient of variation for analyses repeated on different days was 12%. The detection threshold of *anti*-BPDE tetraols [r-7,c-10,t-8,t-9-tetrahydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (BaP tetraol I-1) and r-7,t-9,t-10,t-8-tetrahydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (BaP tetraol I-2)] was 0.25 pg (signal-to-noise ratio > 3) so that, in the present study, with 100 µg DNA, this assay could detect 0.25 adducts/10^8 nucleotides. Assays were performed on all samples that were of adequate quantity and quality for analysis.

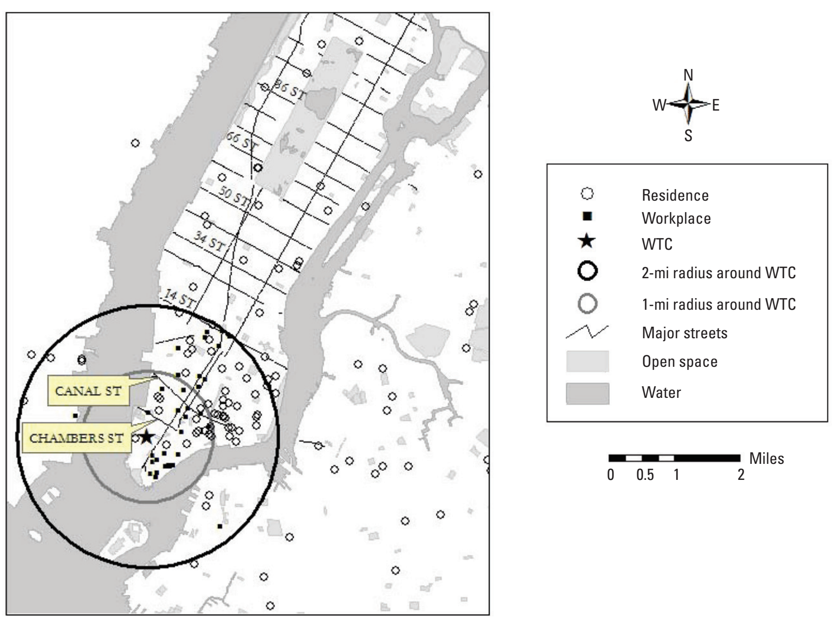

Figure 1. Location of residences and workplaces of subjects included in the analysis of adducts. Map provided by the Center for International Earth Science Information Network (CIESIN), Columbia University.

All subjects who had available adduct data for the mother and/or child were included in the present analyses. In some excluded cases, a blood sample could not be collected; in others, the amount of DNA isolated was inadequate for analysis. Usable adduct data were obtained for a total of 170 maternal blood samples and for 203 cord blood samples.

Description of the sample. The parent study population was diverse, reflecting the mixed residential and commercial nature of lower Manhattan and the broader area served by the delivery hospitals (Lederman et al. 2004). Table 1 shows the demographic characteristics of the 203 women whose newborns had cord adduct data. In the analysis of the effect of cord blood adducts on birth outcomes, as in the prior report on proximity to the WTC site and birth outcomes (Lederman et al. 2004), we excluded women who were not pregnant on 11 September 2001 (n = 11) or who had a preterm delivery (< 258 days of gestation, n = 6) to reduce variability due to medically indicated preterm births unrelated to the exposure of interest. Thus, the sample in this analysis was 186. The subset of 203 mothers with newborn cord blood adduct data did not differ from the 126 mothers without cord adduct measurements with respect to maternal age, income, education, ethnicity, gestational duration, exposure to ETS, or proportion residing within 1 or 2 mi of the WTC site (see Table 1). A total of 170 mothers had adduct measurements in their peripheral blood (102 women had both maternal and cord adducts measured). The subset of 170 mothers was comparable with the full sample on all demographic indicators (data not shown). The subset with cord adduct data who met the inclusion criteria for the birth outcome analysis (n = 186) differed from those who were excluded (n = 17) only with respect to gestational age, birth weight, and head circumference (p < 0.01), reflecting the fact that preterm pregnancies were excluded.

Statistical methods. Adduct levels were treated in the analyses both continuously and categorically (detectable or nondetectable). As in prior studies (Perera et al. 2004a), samples with nondetectable PAH–DNA adducts were given a value of one-half the limit of detection (LOD/2 = 0.125). Because of their distributional properties, adducts were log transformed but means are presented in arithmetic scale for ease of interpretation. In the analysis of the relationship between proximity to the WTC site and adduct levels, subjects were classified into three groups: those who at some time in the 4 weeks after 11 September 2001 resided within 1 mi of the WTC site (residential group), those who worked but did not live within 1 mi of the WTC during this time period (employed group), and those who neither worked nor lived within this radius at any time during the 4 weeks after 11 September 2001 (reference group). This classification was based on the fact that women who resided within a 1-mi radius of the WTC spent significantly more hours in the area each day in the month after 11 September 2001 than did women who were employed in those areas. Thus, the potential for exposure to air pollution from the WTC was much greater among the residential group. A similar classification was made using a 2-mi radius for proximity to the WTC to more fully examine the effect of distance.

We tested differences in adduct levels between the various exposure groups by t-test and Wilcoxon rank sum. Fisher's exact test was used to test differences in the percentages of subjects with detectable adducts in each group. In addition, proximity was evaluated as a continuous measure of linear distance from the site using Spearman's correlation. In the correlation analysis, subjects living > 20 mi from the WTC site were excluded. We examined trends across the three exposure groups using linear regression (for means) or logistic regression (for percentages).

We used multiple regression to assess the effect of PAH–DNA adducts, alone and combined with ETS, on birth weight, birth length, and head circumference (all log transformed), ponderal index, and sex-specific small size for gestational age (SGA) among term deliveries (Alexander et al. 1996), adjusting for known or potential confounders. As in the prior report (Lederman et al. 2004), maternal age; parity; prepregnancy weight; height; ethnicity; Medicaid status as an indicator of poverty; medical complications including diabetes, hypertension, and pre-eclampsia; trimester of pregnancy on 11 September 2001 (first trimester vs. other); length of gestation; cesarean section (for head circumference analyses only); and sex of newborns were included in the analyses because they are known risk factors and/or potential confounders. All statistical analyses were carried out using SPSS software (version 11.5; SPSS Inc., Chicago, IL).

Results

Relationship between proximity to the WTC site and adducts. Given the above, we hypothesized that *a*) subjects who lived near the WTC during the month after 11 September 2001 would have the highest levels of adducts and the highest percentage of cord and maternal blood samples with detectable adducts, subjects who neither lived nor worked near the WTC (reference group) would have the lowest adduct levels and percentage of detectable adducts, and the values for subjects who were employed near the site but did not live there would be intermediate; *b*) the levels of adducts in cord and maternal blood of residents near the WTC would be inversely related to linear distance from the WTC site; and *c*) the adducts among subjects living near the WTC would be higher than those reported previously from subjects in northern Manhattan/south Bronx, almost all sampled before 11 September 2001 (Perera et al. 2004a). Table 2 shows the mean adduct levels and percentages of detectable adducts in cord blood (n = 203) and maternal blood (n = 170) in each of the three groups defined by the 1-mi radius. A pattern emerged whereby the mean cord and maternal blood adducts were highest in the residential group, intermediate in the employed group, and lowest in the reference group (trend across the three groups in mean maternal blood adducts, p = 0.02). There was also a significant trend in the percentages of maternal samples with detectable adducts (p = 0.05). The cord adduct value in the residential group was higher compared with the reference group (0.28 per 10^8 vs. 0.23 per 10^8, p = 0.06 by t-test, p = 0.07 by Wilcoxon rank sum).

Using the 2-mi radius to define proximity, the absolute value for cord adducts was lower for the reference group (0.23 per 10^8) than for the other two groups (both 0.24 per 10^8), but the differences were not statistically significant. With respect to maternal adducts, using the 2-mi radius to define the groups, the means in both the residential and employed groups were higher than the mean in the reference group, but the differences were not significant. Adducts in maternal blood were inversely but not significantly correlated with linear distance from the WTC site. Overall, cord blood adducts (n = 203) were not significantly correlated with a continuous measure of linear distance of residence (from 0.31 to 19.1 mi). However, the correlation was significant among the newborns of women residing within a 1-mi radius of the site (n = 12, r = –0.66, p = 0.02 by Spearman correlation). Maternal and cord adduct levels for the women who lived within 1 mi of the WTC exceeded the levels for women within 2 mi (0.30 vs. 0.23 adducts/10^{-8} nucleotides, for maternal levels and 0.28 vs. 0.24 adducts/10^{-8} nucleotides, for cord levels; both not significantly different).

We also compared the mean cord adduct levels (n = 203) in this study to the levels reported previously from the Northern Manhattan/South Bronx cohort (n = 218), 91.3% of whom were sampled before the WTC event (Perera et al. 2004a). The mean cord adduct level (0.28 ± 0.08) and the percentage of detectable cord adducts (83.3%) were higher for the WTC study newborns whose mothers lived within 1 mi of the WTC in any of the 4 weeks after 11 September 2001 than in newborns from the northern Manhattan/south Bronx cohort (mean 0.23 ± 0.14, 42.8%

detectable, $p = 0.02$ by *t*-test, $p = 0.11$ by Wilcoxon rank sum, $p = 0.01$ by Fisher's exact test for percent detectable). Similarly, using a 2-mi cutoff to include a larger number of subjects in the exposed group, albeit with diluted exposure, the mean cord adduct level (0.24 ± 0.09) and the percentage of samples with detectable adducts in cord blood (68.6%) were both significantly higher in the WTC sample compared with newborns in the northern Manhattan/south Bronx study ($p = 0.05$, by *t*-test for mean, $p = 0.2$ by Wilcoxon rank sum, $p < 0.01$ by Fisher's exact test for percent).

With respect to maternal blood adducts, the mean level (0.30 ± 0.16) and the detectable percentage (80%) for the women who lived within 1 mi of the WTC site were also higher than the corresponding values for the women in the northern Manhattan/south Bronx study (0.22 ± 0.14, 36.9%; $p < 0.01$ by *t*-test, $p < 0.05$ by Wilcoxon rank sum test, $p = 0.01$ by Fisher's exact test for percent).

Consistent with prior reports in other populations (Perera et al. 2005), adducts in cord blood and maternal blood were not significantly correlated with self-reported ETS or dietary PAH exposure during pregnancy. Nor were adducts correlated with elapsed time between 11 September 2001 and blood sample collection. Maternal adducts were not significantly correlated with adducts in cord blood ($r = 0.08$, $p = 0.41$, Spearman correlation).

Relationship between cord adducts and birth outcomes. Table 3 shows the characteristics of the 186 subjects used for the birth outcomes analyses. We hypothesized *a priori* that *a*) as in all subjects with adduct data, adducts in the newborns of women meeting the eligibility criteria for the birth outcomes analysis would be related to proximity of the mother's residence to the WTC site; and *b*) increased cord blood PAH–DNA adducts, alone or in combination with prenatal exposure to ETS, would be associated with newborn weight, length, and head circumference, as previously reported in our northern Manhattan/south Bronx cohort study (Perera et al. 2004a).

When the sample was limited to term deliveries for birth outcomes analyses, the mean cord adduct level, as in the larger sample used above for the distance analyses, was highest in the residential group (0.28 per 10^8), intermediate in the employed group (0.24 per 10^8), and lowest in the reference group (0.23 per 10^8). The mean in the residential group was significantly higher than in the reference group ($p = 0.04$ by *t*-test, $p = 0.06$ by Wilcoxon rank sum). As observed in the comparison of the mothers, newborns whose mothers lived within 1 mi of the WTC after 11 September 2001 had a higher mean adduct level than did newborns in the northern Manhattan/south Bronx study ($p = 0.02$ by *t*-test, $p = 0.11$ by Wilcoxon rank sum). Among the subjects who resided within 1 mi of the WTC site, distance of residence from the site was negatively associated with cord adducts ($n = 9$, $r = -0.92$, $p < 0.01$ by Spearman correlation).

Cord adducts, ETS, and birth outcomes. As noted, birth outcome analyses included only term deliveries to women who were pregnant on 11 September 2001 in order to reduce variability due to medically indicated preterm births unrelated to the exposure of interest (WTC air pollution). ETS was not correlated with cord adduct levels ($r = 0.03$, $p = 0.71$ by Spearman correlation). As shown in Table 4, there were no significant main effects of cord adducts or ETS exposure on birth weight, length, or head circumference. However, the effect of the interaction between adducts treated as a continuous variable and ETS (yes/no) was significant on birth weight ($p = 0.03$) and head circumference ($p = 0.04$). The effect of the interaction between adducts treated as a categorical variable (detectable/nondetectable) and ETS was also significant on

Table 1. Characteristics of subjects with cord blood adduct data and without cord adduct data.

Characteristic	Subjects with cord adduct data ($n = 203$)	Subjects without cord adduct data ($n = 126$)
Maternal age (years)	30.06 ± 5.19	30.62 ± 5.24
Household income (US$)[a]	22,596 ± 17,679	22,715 ± 15,980
Maternal education (%)		
< High school	19.2	17.5
High school	17.2	16.7
> High school	63.5	65.9
Race (%)		
Asian	37.4	29.4
Black	13.8	17.5
White	40.4	40.5
Maternal exposure to ETS (% reporting smoker in the home)	17.7	18.3
Resided within 1 mi in any of the 4 weeks after 11 September 2001 (%)	5.9	5.6
Resided within 2 mi in any of the 4 weeks after 11 September 2001 (%)	25.1	27.8
Gestational duration (days)	276.7 ± 9.41	276.9 ± 10.66
Newborn birth weight (g)	3,421 ± 450	3,418 ± 500
Newborn birth length (cm)	50.7 ± 3.1	50.9 ± 2.4
Newborn head circumference (cm)	34.2 ± 1.4	34.3 ± 1.7

Values are mean ± SD unless otherwise noted.
[a]Income based on midpoint of each of 10 household income categories, ranging from < \$10,000 to > \$90,000. The midpoint of the first category was set at \$5,000 and that of the last category was set to \$95,000. Some women did not report income.

Table 2. Mean adduct levels and percentages of detectable adducts in newborns and mothers residing within 1 mi of the WTC site, employed within 1 mi, or in the reference group.

	Resided within 1 mi in any of the 4 weeks after 11 September 2001	Employed within 1 mi in any of the 4 weeks after 11 September 2001	Reference group
Newborn BaP–DNA adducts ($n = 203$)	($n = 12$)	($n = 23$)	($n = 168$)
Adducts/10^8 nucleotides* (mean ± SD)	0.28 ± 0.08	0.24 ± 0.12	0.23 ± 0.10
Detectable (%)	83.3	52.2	58.9
Maternal BaP–DNA adducts ($n = 170$)	($n = 10$)	($n = 27$)	($n = 133$)
Adducts/10^8 nucleotides** (mean ± SD)	0.30 ± 0.16	0.25 ± 0.11	0.22 ± 0.10
Detectable (%)***	80.0	66.7	52.6

*$p = 0.06$, difference in mean cord adducts between residents and reference group by *t*-test, $p = 0.07$ by Wilcoxon rank sum; **$p = 0.02$, trend in maternal adduct means across groups; ***$p = 0.05$, trend in percentage of detectable adducts in maternal blood.

Table 3. Characteristics of study subjects in the birth outcomes analysis ($n = 186$).

Characteristic	Value
Maternal age (years)	30 ± 5.2
Household income (US$)[a]	23,270 ± 17,783
Maternal education (%)	
< High school	18.3
High school	16.1
> High school	65.6
Race (%)	
Asian	36.6
Black	14.5
White	41.4
Maternal ETS (% reporting smoker in the home)	17.7
Resided within 1 mi in any of the 4 weeks after 11 September 2001 (%)	4.8
Resided within 2 mi in any of the 4 weeks after 11 September 2001 (%)	23.7
Gestational duration (days)	277.9 ± 8.0
Newborn birth weight (g)	3,453 ± 439
Newborn birth length (cm)	50.8 ± 3.2
Newborn head circumference (cm)	34.3 ± 1.4

Values are mean ± SD unless otherwise noted.
[a]Income based on midpoint of each of 10 household income categories, ranging from < \$10,000 to > \$90,000. The midpoint of the first category was set at \$5,000 and that of the last category was set to \$95,000. Some women did not report income.

birth weight (p = 0.04) and marginally significant on head circumference (p = 0.06). We estimate that among ETS-exposed subjects a doubling of PAH–DNA adducts within the observed range corresponds to an average 8% [95% confidence interval (95% CI), 1–14%] reduction in birth weight of 276 g (95% CI, 31–480 g) and an average 3% (95% CI, 0.5–5%) decrement in head circumference of 1.03 cm (95% CI, 0.2–2 cm). The estimated decrements attributable to having detectable versus nondetectable adducts among those with ETS exposure were 297 g (95% CI, 6–564 g) or 9% (95% CI, 0.2–16%) in birth weight and 1.0 cm (95% CI, 0.02–2 cm) or 3% (95% CI, 0.1–6%) in head circumference. There were no significant effects of adducts, ETS, or their interaction on gestational age, ponderal index, or SGA.

Discussion

The first major finding is that pregnant women who were most likely to have been exposed to PAHs released by the fires during the 4 weeks after 11 September 2001, namely, those living within 1 mi of the WTC site, had increased levels of PAH–DNA adducts in cord blood and maternal blood. Specifically, the mean level of PAH–DNA adducts in cord and maternal blood were higher among subjects who resided within 1 mi of the WTC site, compared with those who worked within 1 mi of the site but did not live there, and especially compared with the reference group of women who neither worked nor lived within 1 mi. This is consistent with data collected 6 weeks after the WTC event showing the rapid drop-off with increasing distance in levels of PAHs, polybrominated diphenyl ethers, and PCBs in organic films on window surfaces, reaching background levels within 2.2 mi from the WTC site (Butt et al. 2004).

Compared with a northern Manhattan/south Bronx cohort exposed to background pollution in New York City (Perera et al. 2005), the subjects who lived within 1 mi of the WTC in any of the 4 weeks after 11 September 2001 had significantly higher mean cord and maternal blood adduct levels and percentage of cord and maternal blood samples with detectable adduct levels. The observed relationships are consistent with the fact that exposure to PAHs in air pollution emitted during the WTC destruction on 11 September and the subsequent fires was likely to have been substantial for those pregnant women who spent large portions of each day near the site during the month after the tragedy.

The second major finding is that PAH–DNA adducts, in conjunction with ETS exposure, were significantly associated with reduced birth weight and head circumference (p < 0.05), consistent with our prior findings in the northern Manhattan/south Bronx cohort (Perera et al. 2005). The estimated average decrements in birth weight (276 g, 8%) and head circumference (1.03 cm, 3%), corresponding to a doubling in cord blood adduct concentrations among ETS-exposed babies, were greater than those observed in the northern Manhattan/south Bronx cohort (138 g or 4% decrement in birth weight and 0.34 cm or 1% decrement in head circumference). In light of the finding that adducts were related to proximity of residence to the WTC site during the month after 11 September 2001, these data suggest that increased PAH–DNA adducts as a result of the WTC disaster adversely affected fetal growth.

Traffic in the area of the WTC, particularly during the recovery and cleanup operations, may have contributed to the air pollution and PAH adducts. Analysis of PAHs in archived samples of fine particles collected in the WTC area between 23 September 2001 and 27 March 2002 indicated that for 3 months after 11 September, fire was the predominant PAH source but that diesel (truck) sources predominated for the next 3 months (Pleil et al. 2004). Women in our cohort who were working or residing in the area in the month after 11 September probably had continued exposure to traffic-generated PAHs after that period, because both residence and employment locations were quite stable.

Table 4. Results of regression analyses of adducts, ETS, and birth outcomes.

	Birth weight[a] (n = 181)		Birth length[a] (n = 177)		Head circumference[a] (n = 177)	
	B	*p*-Value	*B*	*p*-Value	*B*	*p*-Value
(Constant)	5.233	< 0.01	3.152	< 0.01	2.852	< 0.01
Adducts in cord blood[a]	0.03	0.18	0.001	0.96	0.01	0.27
ETS	–0.15	0.06	0.01	0.79	–0.04	0.12
Cord adducts × ETS	–0.11	0.03[b]	0.01	0.53	–0.04	0.04[c]
Sex of newborns (girl 0, boy 1)	0.05	< 0.01	0.03	< 0.01	0.02	< 0.01
Parity (0, ≥ 1)	0.05	0.01	0.01	0.25	0.01	0.03
Medicaid	0.03	0.15	0.02	0.06	0.01	0.49
Maternal prepregnancy weight (lb)	0.00001	0.82	–0.0003	0.07	–0.00001	0.90
Maternal height (cm)	0.01	< 0.01	0.002	0.01	0.001	0.02
Asian	0.002	0.91	–0.04	0.00	–0.01	0.40
Black	–0.02	0.47	–0.02	0.12	–0.01	0.21
Maternal medical complications	–0.03	0.33	–0.07	< 0.01	–0.004	0.66
First trimester on 11 September	–0.01	0.44	0.02	0.08	–0.001	0.81
Maternal age	–0.001	0.66	0.0005	0.65	–0.00003	0.97
Length of gestation (days)	0.01	< 0.01	0.001	0.02	0.002	< 0.01
Cesarean section					0.013	0.0

[a]Adducts and birth outcomes both natural log transformed. [b]Interaction corresponds to an estimated 276 g (or 8%) average decrease per doubling in adducts among ETS-exposed subjects. [c]Interaction corresponds to an estimated 1.03 cm (or 3%) decrease per doubling in adducts among ETS-exposed subjects.

The observed effects of PAHs and ETS on fetal growth are biologically plausible and consistent with prior research. Mechanisms by which PAHs or PAH–DNA adducts acting in combination with ETS can affect fetal growth include antiestrogenic effects (Bui et al. 1986), binding to the human aryl hydrocarbon 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), binding to receptors for placental growth factors resulting in decreased exchange of oxygen and nutrients (Dejmek et al. 2000), or interference with transcription, DNA replication, or protein synthesis (Bostrom et al. 2002). ETS is a complex mixture of > 4,000 chemicals, including PAHs and carbon monoxide (Leikauf et al. 1995). Prenatal exposure to tobacco smoke has been associated with deficits in birth weight and birth length (Janerich et al. 1990; Martinez et al. 1994; Schuster-Kolbe and Ludwig 1994; Sexton et al. 1990).

The lack of a significant correlation between adducts and ETS or dietary PAH consumption probably reflects individual variation in adduct formation due to coexposures, as well as nutritional, and genetic factors that modulate adduct formation. Although group-level differences in adducts are generally found between exposure groups, few studies have found a direct correlation between PAH–DNA adducts and estimated individual PAH exposure levels (Lunn et al. 1999).

A major strength of the present study is the prepartum enrollment of exposed and unexposed women from a common clinical population. All women delivered at one of three lower Manhattan hospitals during the same time period. In addition, enrollment occurred before delivery, before the outcome of the pregnancy was known, so that women's decision to participate was not based on their knowledge of their own birth outcome. The potential sample selection bias introduced by volunteerism of women who experienced worrisome birth outcomes was thus avoided. Recruitment procedures ensured a wide range of race/ethnicity, income, education, and other characteristics, improving the generalizability of our findings. In addition, the subjects were geographically well dispersed during pregnancy with respect to the WTC site, providing a basis for comparing subjects with differential exposure.

A limitation of the study is the modest number of subjects with adduct measurements and the fact that, because of the time required to obtain institutional review board approval from the participating hospitals, recruitment did not begin until December. With respect to the adduct-distance analysis, another limitation is the small number of subjects living or working within 1 mi of the WTC and therefore likely to have been most intensely exposed to pollutants emanating from the WTC site. Given the time lapse of 1–7 months between exposure to WTC pollutants in the 2 months after 11 September and blood collection at delivery, and given the estimated 3- to 4-month half-life of PAH–DNA adducts in white blood cells (Mooney et al. 2005), the measured adduct values may underestimate the effect of the event on the biomarker. We were also unable to assess effects of exposure in the third trimester, or preterm deliveries, stillbirths, or spontaneous abortions possibly resulting from toxic exposures, preventing the study of outcomes of women who may have been at excess risk. Further, our sample size prevented us from examining whether outcomes differed depending on the week (or weeks) of exposure during pregnancy.

In conclusion, the finding that PAH–DNA adducts were associated with proximity to the WTC site and, in combination with ETS, adversely affected both birth weight and head circumference in this cohort has potential implications for the subsequent health and cognitive development of the children. Lower birth weight, even in the normal range, has been associated with increased fetal, neonatal, and infant mortality (Arias et al. 2003; Rees et al. 1996; Seeds and Peng 2000), subsequent poorer health and delayed physical and cognitive development (Barker 1996; Dietz 1994; Matte et al. 2001; Rice and Barone 2000; Richards et al. 2002), and increased susceptibility to stress in adulthood (Nilsson et al. 2001).

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