# Brief Report

# Maternal Occupational Exposure to Polycyclic Aromatic Hydrocarbons and Craniosynostosis among Offspring in the National Birth Defects Prevention Study

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**Background:** Evidence in animal models and humans suggests that exposure to polycyclic aromatic hydrocarbons (PAHs) may lead to birth defects. To our knowledge, this relationship has not been evaluated for craniosynostosis, a birth defect characterized by the premature closure of sutures in the skull. We conducted a case-control study to examine associations between maternal occupational exposure to PAHs and craniosynostosis. **Methods:** We used data from craniosynostosis cases and control infants in the National Birth Defects Prevention Study (NBDPS) with estimated delivery dates from 1997 to 2002. Industrial hygienists reviewed occupational data from the computer-assisted telephone interview and assigned a yes/no rating of probable occupational PAH exposure for each job from 1 month before conception through delivery. We used logistic regression to assess the association between occupational exposure to PAHs and craniosynostosis. **Results:** The prevalence of exposure was 5.3% in case mothers (16/300) and 3.7% in control mothers (107/2,886). We observed a positive association between exposure to PAHs during the 1 month before conception through the third month of pregnancy and craniosynostosis (odds ratio [OR] = 1.75; 95% confidence interval [CI], 1.01–3.05) after adjusting for maternal age and maternal education. The number of cases for each craniosynostosis subtype limited subtype analyses to sagittal craniosynostosis; the odds ratio remained similar (OR = 1.76, 95% CI, 0.82–3.75), but was not significant. **Conclusion:** Our findings support a moderate association between maternal occupational exposure to PAHs and craniosynostosis. Additional work is needed to better characterize susceptibility and the role PAHs may play on specific craniosynostosis subtypes.

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**Key words:** craniosynostosis; polycyclic aromatic hydrocarbon (PAH); birth defects; case-control

## Introduction

Polycyclic aromatic hydrocarbons (PAHs) are a group of toxic chemicals that are ubiquitous in certain occupational settings, including the oil and gas industry, coal-fired and other power plants, and restaurants (Sjaastad & Svendsen, 2009). These toxicants have been linked to adverse birth outcomes such as intrauterine growth retardation (Choi et al., 2008), preterm birth (Singh et al., 2008), decreased infant growth (Choi et al., 2006; Langlois et al., 2014), as well as certain birth defects (e.g., gastroschisis [Lupo, Langlois, et al., 2012], oral clefts [Langlois et al., 2013], and neural tube defects [Ren et al., 2011]). However, no studies have examined the relationship between PAHs and craniosynostosis, a condition characterized by the premature closure of one or more of the sutures in the infant skull (Nagaraja et al., 2013). This relationship is of particular interest as previous assessments suggest craniosynostosis is associated with maternal smoking (Hackshaw et al., 2011), a major source of environmental PAHs.

Given the growing evidence of the teratogenic potential of PAHs, and the need to better understand modifiable risk factors for craniosynostosis—especially with well-designed, large-scale population-based studies—we investigated associations between maternal occupational exposure to PAHs and risk of craniosynostosis among offspring using data from the National Birth Defects Prevention Study (NBDPS).

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## Materials and Methods

The study population included craniosynostosis case and control infants from the NBDPS, with estimated delivery dates from October 1, 1997 through December 31, 2002. Details of the NBDPS have been published previously (Yoon et al., 2001). Briefly, the NBDPS is a multicenter, population-based, case–control study of major birth defects. During the period 1997 to 2002, case infants with one or more major birth defects were identified through eight birth defect surveillance systems in the United States (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, and Texas). The cases identified included live births, stillbirths, and induced pregnancy terminations. Clinical geneticists used standardized case definitions and confirmatory diagnostic procedures (Rasmussen et al., 2003) to classify case infants. Infants and fetuses with single gene disorders or chromosomal abnormalities were excluded, and each eligible case was classified as having an isolated defect (no additional major birth defect) or multiple defects (one or more additional unrelated major birth defects). The sutures involved were also identified (i.e., sagittal, coronal, metopic, lambdoid, multiple sutures, or unknown). Control infants (live born infants without major birth defects) were randomly selected from birth certificates or birth hospital records from the same geographic populations that gave rise to the cases.

Case and control mothers completed a 1-hr computer-assisted telephone interview (CATI) between 6 weeks and 2 years after the estimated date of delivery. The interview included sections on maternal health, lifestyle and behavioral characteristics, and occupational history. For each job, mothers were asked to describe: job title, typical job tasks, employer, what their employer made or did, any specific equipment or chemicals used, typical hours per week worked, and starting and stopping dates. Jobs were classified according to the Standard Occupational Classification (SOC) System (United States Department of Labor Bureau of Labor Statistics, 2000) and the North American Industry Classification System (United States Department of Labor Bureau of Labor Statistics, 1997). Two trained industrial hygienists, working independently and blinded to case-control status, reviewed job descriptions from the CATI and assigned a dichotomous (yes/no) rating of probable occupational PAH exposure for each job. Any discrepancies were resolved in a consensus meeting, which included a third hygienist. The approach used to estimate PAH exposure has been described previously (Rocheleau et al., 2011) and is described in detail in other NBDPS studies (Langlois et al., 2012, 2013; Lupo, Langlois, et al., 2012; Lupo, Symanski, et al., 2012; Langlois, 2014).

Before the interview, all mothers provided verbal consent for study participation. The Centers for Disease Control and Prevention Institutional Review Board (IRB), along with the IRBs for each participating center, approved the NBDPS.

Our analysis was limited to case infants with a diagnosis of craniosynostosis and all control infants with exposure information. Specifically, case and control mothers were eligible if they worked in part-time or full-time jobs (paid or volunteer) for at least 1 month from the 3 months before conception through the end month of pregnancy. Of the 4,584 eligible mothers with estimated delivery dates between 1997 and 2002, 1,275 (28%) were excluded from the analysis because they did not work during this time period. For our primary analysis, a mother was classified as exposed if she had one or more jobs rated as exposed during the critical period defined as 1 month before conception through the third month of pregnancy, and was classified as unexposed if all of her jobs during this time period were rated as unexposed. Although the critical period for exposure is likely in early pregnancy, we conducted a secondary analysis where the exposure window was defined as 1 month before conception through delivery, because suture closure is not completed until after birth.

Information about maternal demographic and infant characteristics was obtained from the CATI, and included maternal age at delivery ($<$20, 20–24, 25–29, 30–34, $\geq$35 years), prepregnancy body mass index (BMI, kg/m$^2$) ($<$18.5, 18.5–24.9, 25–29.9, $\geq$30), parity (0, $\geq$1), maternal race or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), maternal education ($<$12, 12, $>$12 years), gestational diabetes (yes/no), alcohol use 1 month before pregnancy through the third month of pregnancy (yes/no), smoking history 1 month before pregnancy through the third month of pregnancy (nonsmoker, light moderate, heavy), secondhand smoke at home (yes/no), secondhand smoke at work (yes/no), and infant sex (male/female). We calculated frequency distributions of these maternal demographics for cases and controls, and the crude odds ratios and 95% confidence intervals (CIs) for the associations between each maternal factor and craniosynostosis.

To examine the association between exposure to PAHs in the workplace and craniosynostosis, we used unconditional logistic regression models to calculate crude and multivariable adjusted odds ratios (ORs) and 95% CIs. The variables considered for our final model were determined a priori based on a review of the craniosynostosis literature, and all variables were established or suspected risk factors for craniosynostosis (maternal age, maternal education, race/ethnicity, smoking history, exposure to secondhand smoke at home, and body mass index) (Boulet et al., 2008; Carmichael et al., 2008; Lee et al., 2012). Variables were incorporated as confounders in the final model if inclusion resulted in $\geq$10% change in the estimate of the effect between PAHs and craniosynostosis. Due to the numbers of cases for each craniosynostosis subtype, we were only able to estimate a separate multiple logistic regression model for sagittal craniosynostosis.

**TABLE 1.** *Distribution of Maternal Factors among Employed[a] Mothers of Craniosynostosis Case Infants and Control Infants, National Birth Defects Prevention Study, 1997 to 2002 [n (%)]*

| Characteristic | Cases (*n*=316) *n* (%) | Controls (*n*=2,993) *n* (%) | OR (95% CI) |
|---|---|---|---|
| *Infant* | | | |
| Sex | | | |
| Male | 223 (71) | 1,495 (50) | 2.40 (1.86, 3.09) |
| Female | 93 (29) | 1,496 (50) | 1.00 (Ref) |
| *Maternal* | | | |
| Age (years) | | | |
| <20 | 14 (4) | 240 (8) | 1.00 (Ref) |
| 20–24 | 56 (18) | 645 (22) | 1.49 (0.81, 2.72) |
| 25–29 | 67 (21) | 801 (27) | 1.43 (0.79, 2.60) |
| 30–34 | 104 (33) | 858 (29) | 2.08 (1.17, 3.70) |
| ≥35 | 75 (24) | 449 (15) | 2.86 (1.58, 5.17) |
| Prepregnancy BMI (kg/m$^2$) | | | |
| Underweight (<18.5) | 16 (5) | 153 (5) | 1.02 (0.59, 1.75) |
| Normal weight (18.5–24.9) | 172 (55) | 1,676 (57) | 1.00 (Ref) |
| Overweight (25–29.9) | 73 (23) | 664 (23) | 1.07 (0.80, 1.43) |
| Obese (≥30) | 53 (17) | 439 (15) | 1.18 (0.85, 1.63) |
| Parity | | | |
| 0 | 139 (44) | 1,331 (44) | 1.00 (Ref) |
| ≥1 | 177 (56) | 1,661 (56) | 1.02 (0.81, 1.29) |
| Race/ethnicity | | | |
| Non-Hispanic white | 242 (77) | 1,940 (65) | 1.00 (Ref) |
| Non-Hispanic black | 14 (4) | 377 (13) | 0.30 (0.17, 0.52) |
| Hispanic | 45 (14) | 528 (18) | 0.68 (0.49, 0.95) |
| Other | 15 (5) | 141 (5) | 0.85 (0.49, 1.48) |
| Education (years) | | | |
| <12 | 21 (7) | 296 (10) | 1.00 (Ref) |
| 12 | 73 (23) | 741 (25) | 1.39 (0.84, 2.30) |
| >12 | 221 (70) | 1,951 (65) | 1.60 (1.00, 2.54) |
| Gestational diabetes | | | |
| No | 288 (95) | 2,804 (96) | 1.00 (Ref) |
| Yes | 16 (5) | 118 (4) | 1.32 (0.77, 2.26) |
| Smoking[b] | | | |
| Nonsmoker | 243 (77) | 2,378 (79) | 1.00 (Ref) |
| Light (15–24 cigarettes/day) | 50 (16) | 423 (14) | 1.15 (0.84, 1.60) |
| Moderate (15–24 cigarettes/day) | 21 (7) | 159 (5) | 1.29 (0.80, 2.08) |
| Heavy (≥25 cigarettes/day) | 2 (0.6) | 33 (1) | 0.59 (0.14, 2.29) |
| Secondhand smoke at home[b] | | | |
| No | 245 (78) | 2,456 (82) | 1.00 (Ref) |
| Yes | 71 (22) | 535 (18) | 1.33 (1.01, 1.76) |

**TABLE 1.** *Continued*

| Characteristic | Cases ($n$=316) $n$ (%) | Controls ($n$=2,993) $n$ (%) | OR (95% CI) |
|---|---|---|---|
| Secondhand smoke at work[b] | | | |
| No | 262 (83) | 2,412 (81) | 1.00 (Ref) |
| Yes | 54 (17) | 572 (19) | 0.87 (0.64, 1.18) |

[a]Employed for at least one month from the three months before conception through the end of pregnancy.

[b]One month before conception through the third month of pregnancy.

BMI, body mass index; CI, confidence interval; OR, odds ratio.

## Results

The study population included 316 craniosynostosis cases and 2,993 control infants, with delivery dates from October 1, 1997, through December 31, 2002. Maternal occupational exposure to PAHs was 5.3% among case mothers and 3.7% among control mothers during the month before conception through the third month of pregnancy. Mothers of case infants were older (mean age case mothers = 30.0 years; mean age control mothers = 28.2 years) and more likely to be exposed to secondhand smoke at home (Table 1). Case infants were more likely to be males.

In the unadjusted analysis (Table 2), maternal occupational exposure to PAHs during the 1 month before conception through the third month of pregnancy was positively, but not significantly, associated with craniosynostosis (OR = 1.44; 95% CI, 0.84–2.47). However, in the final model, adjusted for maternal age and education, mothers of cases were 75% (95% CI, 1.01–3.05) more likely to be exposed to occupational PAHs when compared with control mothers. In the fully adjusted model where exposure was defined as 1 month before conception through delivery, the effect was attenuated (OR = 1.55; 95% CI, 0.91–2.70).

Our analyses of specific craniosynostosis subtypes were limited by sample size (sagittal: 163 cases [52%]; metopic: 50 cases [16%]; coronal: 57 cases [18%]; lambdoid: 15 cases [5%]; multiple types: 28 cases [9%]; unspecified: 3 cases [1%])] Therefore, we only analyzed the largest subtype (i.e., sagittal). Specifically, the OR from the multivariable-adjusted model for sagittal craniosynostosis suggested increased risk, but it was not statistically significant (OR = 1.76; 95% CI, 0.82–3.75).

## Discussion

Using data from the largest population-based case-control study of birth defects in the United States, we observed a modest association between maternal occupational exposure to PAHs during the early months of pregnancy and risk of craniosynostosis among offspring. Our findings are in keeping with a growing body of literature suggesting the teratogenic potential of PAHs (Ren et al., 2011).

While there have been no previous assessments of maternal occupational exposure to PAHs and craniosynostosis, these toxicants have been linked to birth defects in other epidemiologic research. For example, studies have reported associations between PAHs and gastroschisis (Lupo, Langlois, et al., 2012), small for gestational age (Langlois et al., 2014), and neural tube defects (Ren et al., 2011). There is also biological evidence that PAHs may be teratogenic. PAHs are lipophilic and readily absorbed by human tissue, including the placenta (Agency for Toxic Substances and Disease Registry, 1995). Once inhaled or

**TABLE 2.** *Associations between Maternal Occupational Exposure to Polycyclic Aromatic Hydrocarbons and Craniosynostosis in Offspring, National Birth Defects Prevention Study, 1997 to 2002*

| | | | Crude OR | | Adjusted OR[a] | |
|---|---|---|---|---|---|---|
| | Cases ($n$) | Controls ($n$) | OR | 95% CI | OR | 95% CI |
| Exposure status | | | | | | |
| No PAH exposure | 300 | 2,886 | 1.0 | (Reference) | 1.0 | (Reference) |
| PAH exposure | 16 | 107 | 1.44 | (0.84, 2.47) | 1.75 | (1.01, 3.05) |

[a]Adjusted for maternal age and maternal education.

CI, confidence interval; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon.

ingested, they are metabolized into compounds capable of binding to DNA. These PAH-DNA adducts can trigger cellular mutations that are teratogenic (Wells et al., 2010). Furthermore, PAH-DNA adducts have been detected in fetal organs, umbilical cord blood, and amniotic fluid (Agency for Toxic Substances and Disease Registry, 1995). Finally, birth defects and other adverse fetal outcomes have been reported in animal models after maternal exposure to PAHs (Lambert & Nebert, 1977; Barbieri et al., 1986; Incardona et al., 2004).

Our findings must be considered in light of certain limitations. There is the potential for exposure misclassification when using expert assessments of job descriptions, although this method is generally considered superior to self-reported exposures that depend on participant awareness of PAH exposures and accurate recall. Furthermore, assessing occupational exposure to PAHs, even if captured without any exposure misclassification, is not a complete assessment of exposure, given how ubiquitous PAHs are in the environment, and we lacked additional information on other potential environmental sources. That said, occupational exposure to PAHs often exceeds the level of exposure in the environment (Brandt & Watson, 2003). We did not have information on the intensity and frequency of exposure, which prevented an analysis of between- and within-job exposure variability, as well as an exposure-response analysis.

Because this is an observational study, uncontrolled or residual confounding could explain the relation between exposure to PAHs and craniosynostosis. However, detailed information on the health and lifestyle of the participants permitted evaluation of many potential confounders. We did not observe any change to our conclusions when smoking (or exposure to secondhand smoke) was considered in our models. The sample size limited this and other stratified and subtype analyses. For example, we were only able to evaluate associations among sagittal craniosynostosis. Larger sample sizes are needed to examine the effects of PAHs on other craniosynostosis subtypes.

Strengths of our study include the use of data from the NBDPS, the largest population-based case-control study of birth defects, which has extensive occupational PAH exposure information from 1997 to 2002, as well as detailed information on potential confounders. Furthermore, the thorough case classification process in the NBDPS by clinical geneticists excluded cases due to single gene disorders or chromosomal abnormalities, resulting in a more homogeneous craniosynostosis case group.

## Conclusions

To our knowledge, this is the first study to assess maternal occupational exposure to PAHs and craniosynostosis in offspring. Our analysis suggests that PAH exposure during early pregnancy is associated with a moderately increased risk of craniosynostosis in offspring. Because PAHs are ubiquitous in our environment, it is important to consider their effects on human health, and increase awareness of potential harm so that those at greatest risk may use measures to minimize exposure, especially during pregnancy. Future investigations could be improved by incorporating additional measures of exposure and the inclusion of additional cases for a closer examination of PAHs and craniosynostosis subtype.

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