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# Association between Maternal Occupational Exposure to Polycyclic Aromatic Hydrocarbons and Rare Birth Defects of the Face and Central Nervous System

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## Abstract

**Background:** Previous studies suggested associations between maternal smoking, a source of exposure to polycyclic aromatic hydrocarbons (PAHs) and other chemicals, and central nervous system and face birth defects; however no previous studies have evaluated maternal occupational PAH exposure itself.

**Methods:** Jobs held in the periconceptional period were retrospectively assigned for occupational PAH exposures. Associations between maternal occupational PAH exposure and selected rare defects of the face (cataracts, microphthalmia, glaucoma, microtia, and choanal atresia) and central nervous system (holoprosencephaly, hydrocephaly, cerebellar hypoplasia, and Dandy-Walker malformation) were evaluated using data from the National Birth Defects Prevention Study, a population-based case-control study in the United States. Crude and adjusted odds ratios (ORs) with 95% confidence intervals were calculated to estimate associations between each evaluated defect and PAH exposure using multivariable logistic regression.

**Results:** Food and beverage serving, as well as cooks and food preparation occupations were among the most frequent jobs held by exposed mothers. Cataracts, microtia, microphthalmia, and holoprosencephaly were significantly associated with PAH exposure with evidence of dose-response (p-values for trend ≤0.05). Hydrocephaly was associated with any PAH exposure, but not significant for trend. Sensitivity analyses that reduced possible sources of exposure misclassification tended to strengthen associations.

**Conclusions:** This is the first population-based case-control study to evaluate associations between maternal occupational PAH exposures and these rare birth defects of the central nervous system and face.

**Keywords**

National Birth Defects Prevention Study; polycyclic aromatic hydrocarbons; birth defects; occupation; exposure assessment

## Background

Several studies from the National Birth Defects Prevention Study (NBDPS) have reported an association between occupational exposures to polycyclic aromatic hydrocarbons (PAHs) and adverse birth outcomes, such as birth defects and small for gestational age offspring (Langlois et al., 2014; Langlois et al., 2013; Langlois et al., 2012; Lupo et al., 2012; O'Brien et al., 2016).

PAHs are a group of chemicals formed during the incomplete combustion of organic substances. Several PAHs and/or their metabolites have been classified as known or suspected mutagens and carcinogens in animals and/or humans (Agency for Toxic Substances and Disease Registry, 1995; U.S. Environmental Protection Agency, 2008). Additionally, PAHs can form DNA adducts in many tissues of the human body and cross the placenta (Jedrychowski et al., 2013; Pratt et al., 2011). Important sources of exposure include cigarette smoke through either active smoking or second-hand smoke, as well as inhalation of the compounds in a variety of settings (such as at home, outdoors, or the workplace) and/or ingestion of PAH-containing foods (i.e. charbroiled meats) (Agency for Toxic Substances and Disease Registry, 1995). Cigarette smoking has been identified as a risk factor for several birth defects affecting the face and central nervous system (e.g. holoprosencephaly, choanal atresia, neural tube defects, cerebellar hypoplasia, and primary congenital glaucoma) (Croen, Shaw, & Lammer, 2000; Johnson & Rasmussen, 2010; Kancherla et al., 2014; Miller, Rasmussen, Siega-Riz, Frias, & Honein, 2010; National Institute of Neurological Disorders and Stroke; Sanbe et al., 2009; Vogt, Horvath-Puho, & Czeizel, 2006). A meta-analysis showed a 19% increase in odds ratios for non-chromosomal facial defects (cleft lip or cleft palate) and a 25% increase in odds ratios for eye defects (anophthalmia/microphthalmia, esotropia, exotropia, and optic hypoplasia) in offspring of women who smoked during pregnancy compared to women who did not smoke while pregnant (Hackshaw, Rodeck, & Boniface, 2011).

The workplace can be a major source of PAH exposure, depending on the type and duration of an occupation (Agency for Toxic Substances and Disease Registry, 1995; Brandt & Watson, 2003). Occupational groups such as artists, public servants, cleaning service providers, hairdressers, farm workers, landscapers, chemical/semiconductor workers, metal workers, textile workers, manufacturing and transportation workers—among others—have increased odds ratios for offspring with ear, eye, and orofacial defects (Herdt-Losavio et al., 2010). Several of these occupations have the potential for exposure to PAHs, and considering the rarity of many of these defects, it can be a challenge to evaluate potential associations between these defects and occupational exposures.

This study uses data from the National Birth Defects Prevention Study (NBDPS) to evaluate a group of rare birth defects of the central nervous system (cerebellar hypoplasia, Dandy-

Walker malformation, holoprosencephaly, and hydrocephaly) and face (cataracts, glaucoma/anterior chamber eye defects (ACD), microphthalmia, microtia/anotia, and choanal atresia). Due to their rarity, there have been no prior studies of occupational PAHs exposure and these defects. However, given evidence of the mechanisms by which PAHs might influence birth defects (and indirect evidence that suggests PAH exposure might at least be a plausible explanation for observed associations between certain occupations and increased rates of certain defects, as well as between smoking and these defects), data available from NBDPS that is suitable to explore this relationship presents a unique research opportunity. Although direct measurements of occupational exposures was not available—as often occurs in retrospective studies— participants in the NBDPS provided detailed narrative descriptions of their jobs before and during pregnancy. Industrial hygienists were able to review of these descriptions to assess likely PAH exposure, an approach that has generally been found to have greater validity than self-reported occupational exposure (Bauer, Romitti, & Reynolds, 1999; Kromhout, Oostendorp, Heederik, & Boleij, 1987; Rocheleau et al., 2011) and is able to take into account individual-level variation in job tasks, unlike a job-exposure matrix.

## Methods

### Study Population

This analysis used data from the NBDPS, the largest population-based case-control study of birth defects conducted in the United States (US). Full study details have been published elsewhere (Centers for Disease Control and Prevention; Reefhuis et al., 2015; Yoon et al., 2001). To summarize, mothers of infants with selected structural birth defects born from 1997–2011 (cases) were continuously identified from active birth defects surveillance systems and confirmed by clinicians based on medical record review. Controls were live-born infants, with no major birth defects or chromosomal disorders, and delivered within the same year as cases. Control were randomly selected from vital records or from birth hospital records from the same study region as the cases (Cogswell et al., 2009). Cataracts and glaucoma/ACD were first included in the NBDPS for births on or after January 1, 2000; the control groups for those two defects are therefore also restricted to this time period. Study regions included Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. Study centers in all regions included live births as cases; most also included stillbirths and therapeutic abortions with prenatally diagnosed birth defects.

Participating mothers completed a computer-assisted telephone interview (CATI) in English or Spanish within two years of the study child’s birth. The interview covered many demographic, maternal health, and lifestyle questions, including detailed descriptions of jobs held during the index pregnancy and three months prior to conception. Institutional review boards (IRB) at the Centers for Disease Control and Prevention and each participating study center approved the study protocols, and all participants provided informed consent.

Birth defects included in the current analysis are cataracts, cerebellar hypoplasia, choanal atresia, Dandy-Walker malformation, glaucoma/ACD, holoprosencephaly, hydrocephaly, microphthalmia, and microtia. These defects were selected because they were included in at least some previous studies of smoking or environmental tobacco smoke exposure, but had

not been studied with regard to parental occupational PAH exposure. ACD includes absence of the lens, spherical lens, lens coloboma, aniridia, Peters anomaly, Axenfeld anomaly, and Rieger anomaly. Cases were further categorized as isolated (no other major defects or multiple major defects only within the same organ system), multiple (two or more major defects in different organ systems), or complex (an embryologically related pattern of major defects) (Reefhuis et al., 2015). Cases with birth defects caused by known chromosomal or genetic abnormalities were excluded. Because cataracts and glaucoma/ACD were not included in 1997–1999, controls from 1997–1999 are not included in comparisons for these defects. Mothers who were outside of the labor market (defined as having no job lasting at least 1 month in the period 3 months before conception through the end of the index pregnancy) were also excluded to limit confounding related to exiting the workforce. Mothers who did not report employment were also excluded.

During the NBDPS interview, employed mothers (n = 30, 483) were asked a series of open-ended questions for each job they held for one month or more during the period 3 months before conception through the end of pregnancy. These questions were: the employer/ company name (“What were the names of the companies or organizations you worked for between [dates]?”), the mother’s job title (“What was your job title there?”), what the company made/did, (“What did your company make or do?”/ [if conglomerate] “What did your division make or do?”), job duties (“Describe what you did and how you did it. What were your main activities or duties? [probe] Anything else?”), any equipment or chemicals used (“Describe any chemicals or substances you handled, or machines that you used or worked in the same room with. [probe] Anything else?”), the typical number of hours she worked at that job on a work day, the typical number of days she worked that job per week, the month and year she started the job, and the month and year she stopped the job.

## Exposure Assessment

From the narrative job description, job coders used this job description to assign Standard Occupational Codes (SOC) and North American Industry Classification System (NAICS) codes. Exposure raters used NAICS and SOC during exposure assessment to rate similar jobs in a group and to perform quality control checks.

Exposure assessment took place at two different points in time: births from 1997–2002 were reviewed in an exposure assessment that began in 2006 (Rocheleau et al., 2011); births occurring from 2003–2011 were reviewed in an exposure assessment that began in 2015. Both exposure assessments were coordinated by collaborators at the National Institute for Occupational Safety and Health. Before beginning each exposure assessment, the raters—all industrial hygienists—together reviewed available data from previous studies of PAH exposure (including hazard evaluations and exposure studies in different workplaces) and compiled tables of job tasks and the range of exposure previous studies had identified. Raters also rated a set of sample jobs and then met to discuss their assignments, in order to calibrate their ratings and assure that they were using consistent definitions.

During exposure assessment, each job reported by a participant was rated independently by two raters (as described for the first exposure assessment in Rocheleau et al., 2011)

with any discrepancies between the raters' assignments resolved by consensus with a third rater. Raters assigned a PAH inhalation exposure category (none, direct exposure only, indirect exposure only, both direct and indirect exposure) for occupational exposure to PAHs, excluding second-hand smoke. Exposure to second-hand smoke at work and home, as well as direct smoking by the mother, was taken from mothers' self-reported exposure.

For jobs with potential occupational PAH exposure, raters further assigned: intensity (very low, low, moderate, high) of direct and of indirect exposure; percent of work time of exposed direct and indirect exposure; whether exposure was continuous or intermittent; and the rater's confidence in the assignment (very low/best guess, low, moderate, high). Direct exposure refers to exposure occurring when the worker is directly engaged in a task that involves PAH exposure. Indirect exposure refers to exposure occurring due to PAH exposure occurring in the work environment that is not related to the tasks the worker is doing. Categorical intensity scores were quantitatively mapped for calculations: very low = 0.1 $\mu g/m^3$, low = 1.0 $\mu g/m^3$, moderate = 8.0 $\mu g/m^3$, high = 10.0 $\mu g/m^3$. Weighted intensity ($I_W$) was calculated from intensity (I)$_)$ and frequncy of exposure ($f)_{\text{direct/indirect exposure}}$) as for direct exposure and indirect exposure:

$$I_W = \left(I_{\text{direct exposure}} \times f_{\text{direct exposure}}\right) + \left(I_{\text{indirect exposure}} \times f_{\text{indirect exposure}}\right)$$

For this analysis, we examined PAH exposure in the month before conception through three months after conception (B1-P3). This corresponds to biological periods of risk for the occurrence of the facial and central nervous system defects evaluated by this study. Cumulative exposure ($C_{\text{exposure}}$) during the B1-P3 exposure window was estimated for each job using a calculation incorporating weighted intensity ($I_W$), hours worked ($F_{\text{self-reported work}}$) and number of days worked during the critical period of exposure ($D_{\text{B1-P3 work}}$).

$$C_{\text{exposure}}\left(\mu g/m^3\text{-hours}\right) = I_W\left(\mu g/m^3\right) \times F_{\text{selt-reported work}}\left(\frac{hours/week}{7\ days/week}\right) \times D_{\text{B1-P3 work}}$$

For mothers with more than one job during the B1-P3 exposure window, the estimate of total PAH exposure was the sum of $C_{\text{exposure}}$ from each job. Any PAH exposure occurring outside the B1-P3 window was considered not biologically relevant and therefore not considered for the purposes of this analysis.

Women who reported employment but did not provide a job description, or provided insufficient detail for raters to estimate PAH exposure, were excluded (n = 14 cases and 14 controls) from analysis.

## Covariates

Several covariates were evaluated as potential confounders or effect modifiers based on previously described associations with the birth defects of interest or PAHs in the literature (Anderson et al., 2005; Bhatti et al., 2003; Canfield, Langlois, Nguyen, & Scheuerle, 2009; Croen et al., 2000; Forrester & Merz, 2006; Hackshaw et al., 2011; Johnson & Rasmussen,

2010; Kalyvas et al., 2016; Kancherla et al., 2014; Mastroiacovo et al., 1995; Miller et al., 2010; Prakalapakorn, Rasmussen, Lambert, & Honein, 2010; Reeder et al., 2015; Shaw, Carmichael, Kaidarova, & Harris, 2003, 2004; Stothard, Tennant, Bell, & Rankin, 2009; Zhang, Zhang, Yu, & Shen, 2009): maternal age at delivery; maternal race/ethnicity; maternal pre-pregnancy body mass index (BMI); maternal diabetes; maternal smoking; maternal alcohol consumption; maternal exposure to second-hand smoke at home or work; infant sex; gestational age of infant at birth; and infant birthweight. Study center was also considered.

## Statistical analysis

Chi-square tests were conducted to test for the association between each maternal and infant characteristic and each defect considered. Chi-square tests were also used to test for association between each maternal and infant characteristic and PAH exposure. Crude odds ratios (cORs) and 95% confidence intervals were calculated to measure associations between each defect and dichotomous PAH exposure. PAH exposure was considered as both dichotomous (any/none) and a categorical variable (none, below the median, equal or above the median; based on the median of estimated exposure in controls). The distributions of SOC groups, and the frequency of jobs within each group being rated as exposed/unexposed, were also described.

Multivariable logistic regression was used to calculate adjusted odds ratios (aORs) and confidence intervals for the association of maternal PAH exposure and infant defects using forward selection. Covariates were added to the model if they had met these criteria for confounding: 1) were identified as a possible confounder in a directed acyclic graph, 2) in a bivariate comparison was associated with the outcome with a p-value $\leq 0.05$, and 2) in a bivariate comparison was associated with the exposure among controls with a p-value $\leq 0.05$. To be retained in the final multivariable model, inclusion of the covariate had to result in a 10% change or more in the odds ratio for the main effect (PAH exposure and the birth defect). Models were restricted to individuals with complete data for all covariates in the model. The final model included maternal smoking, secondhand-smoke exposure at home or work during the first trimester of pregnancy, and study center. Maternal age and maternal race also met the criteria for retention in models of choanal atresia. Effect modification was evaluated by calculating stratified odds ratios and 95% confidence intervals by levels of the variables identified as potential effect modifiers. The Breslow-Day statistic for homogeneity of odds ratios was calculated for stratified odds ratios. Variables evaluated as potential effect modifiers were identified on the basis of both prior literature and possible mechanistic pathways of PAHs effects. These variables were maternal BMI, maternal age, and infant sex.

Subanalyses consisted of restricting to mothers not exposed to non-occupational sources of PAH, such as active smoking or second-hand smoke, and excluding mothers with jobs classified with low confidence for the exposure assessment. An additional subanalysis restricted cases to those with an isolated phenotype to reduce heterogeneity. All analyses were conducted in SAS version 9.4 (Copyright (c) 2002–2012 by SAS Institute Inc., Cary, NC, USA.). Data are not presented if based on fewer than 3 observations in any cell.

## Results

The final study population per defect consisted of 6,849 control mothers for cataracts and glaucoma and 8,140 control mothers for cerebellar hypoplasia, choanal atresia, Dandy-Walker malformation, holoprosencephaly, hydrocephaly, microphthalmia, and microtia. The number of case mothers ranged from 48 to 418, and the percentage of mothers exposed to PAHs varied by case group, from 8.3 to 21.8.

The distribution of covariates among case and control mother-infant pairs was evaluated for all defects (Table 1). Overall, a higher proportion of mothers of infants with microtia (46.4% of cases vs. 18.6% of controls) and holoprosencephaly (30.7% of cases vs. 18.6% of controls) were Hispanic, while mothers with infants with Dandy-Walker malformation were more likely to report being non-Hispanic blacks (32.3%) than controls (11.7%). Additionally, a higher proportion of infants with cataracts (56%), choanal atresia (65%), and holoprosencephaly (60%) were females compared to controls (48.5%, 48.9%, and 48.9%, respectively).

The distribution of maternal and infant covariates among all PAH exposed vs. unexposed mothers eligible for this analysis are shown in Table 1. Approximately 11% of the study population was considered to have had an occupational exposure to PAHs. Compared to non-exposed mothers, exposed mothers tended to be younger, less educated, less likely to be non-Hispanic white, have lower incomes, and more likely to smoke or be exposed to secondhand-smoke.

While most mothers reported having only one job throughout the 4-month study window (86.2%), some mothers held multiple jobs (up to eight) during this period. Among jobs rated as PAH-exposed, the most common were food and beverage serving related occupations (n = 2041 jobs, 33% of all exposed jobs); cooks and food preparation occupations (n = 771 jobs, 12% of all exposed jobs); and other production occupations (n = 557 jobs, 9% of all exposed jobs). Within each of these job groups, however, there was considerable variation in PAH exposure. Overall, 64% of food and beverage serving related occupations were considered exposed to PAHs; 77% of all cooks and food preparation occupations; and 16% of all production occupations.

The crude and adjusted ORs for the association between maternal occupational exposure to PAHs and the risk of each defect are presented in Table 2. Because crude analyses were generally similar to adjusted analyses, only the latter are discussed. Cataracts (aOR: 1.49, 95% CI: 1.04–2.13), microtia (aOR: 1.35, 95% CI: 1.00–1.83), holoprosencephaly (aOR: 2.25, 95% CI: 1.37–3.72), and hydrocephaly (aOR: 1.66, 95% CI: 1.22–2.26) showed statistically significant increased ORs.

For exposure-response analyses, estimated PAH exposure categories included no PAH exposure, below (low) and above (high) the median of the cumulative exposure of PAHs among controls for the defect group. At the high exposure level, PAH exposure was significantly associated with cataracts (aOR = 1.66, 95% CI: 1.05–2.64), microphthalmia (aOR = 1.88, 95% CI: 1.10–3.22), microtia (aOR = 1.73, 95% CI: 1.19–2.51), and holoprosencephaly (aOR = 2.38, 95% CI: 1.24–4.56). At the low exposure level, PAH

was significantly associated with holoprosencephaly (aOR = 2.14, 95% CI: 1.09–4.20) and hydrocephaly (aOR = 2.22, 95% CI: 1.54–3.21). The trend test showed significant crude and adjusted p-values for trend ($p \leq 0.05$) for cataracts, microphthalmia, microtia, and holoprosencephaly (Table 3).

To remove other sources of PAH exposure from tobacco smoke, we conducted a subanalysis restricted to mothers not exposed to other sources of PAH exposure (i.e. active smoking and secondhand-smoke at home or work during the first trimester of pregnancy; n = 19,541; Table 4). Overall, ORs strengthened for microtia (aOR = 2.47, 95% CI: 1.58–3.87) at the high exposure level, and for Dandy-Walker malformation (cOR = 2.38, 95% CI: 1.02–5.55; only crude OR) and holoprosencephaly (aOR = 2.59, 95% CI: 1.10–6.13) at the low exposure level. For hydrocephaly, ORs were attenuated but still significant at the low exposure level (aOR = 1.80, 95% CI: 1.01–3.23). The trend test showed significant p-values for trend ($p \leq 0.05$) for microtia (crude and adjusted) and Dandy-Walker malformation (crude only).

To reduce heterogeneity in the birth defect phenotypes, we also conducted a subanalysis restricted to cases with isolated phenotype (i.e. no other major structural birth defects). Odds ratios were generally similar to the main analysis, with these exceptions: isolated Dandy-walker malformation was significantly associated with high PAH exposure (aOR = 2.09, 95% CI: 1.02–4.29); and point estimates for cerebellar hypoplasia and choanal atresia increased—however, this finding was based on very sparse data and non-significant, so this result should be treated with caution (Table S1).

To evaluate the potential impact of exposure misclassification, a subanalysis was conducted by excluding jobs with low confidence scores in the exposure assessment (n= 668 mothers and n = 764 jobs), as well as mothers whose overall exposure status changed from exposed to unexposed due to the exclusion of these jobs (n = 80 mothers; Table S2). A low confidence score indicated that the exposure rating was based on the expert's best educated guess, rather than being informed by measurement from similar jobs or direct report of tasks known to generate PAHs. Compared to the main exposure-response analysis, odds ratios strengthened for cataracts, Dandy-Walker malformation, holoprosencephaly, and hydrocephaly. The trend test showed significant crude and adjusted p-values for trend ($p \leq 0.05$) for cataracts, microphthalmia, microtia, and holoprosencephaly.

To evaluate for potential effect modification, PAH exposure was analyzed as a dichotomous variable (yes/no as in Table 2) stratified by maternal BMI, maternal age, and infant sex. After stratifying by BMI, we observed significant ORs for the association between PAH exposure and cataracts (aOR = 2.09, 95% CI: 1.32–3.30), cerebellar hypoplasia (aOR = 2.73, 95% CI: 1.03–7.20), and hydrocephaly (aOR = 1.88, 95% CI: 1.23–2.88) among mothers who have normal weight or are underweight (Table S3). In contrast, stronger associations were observed between PAH exposure and holoprosencephaly among mothers who were overweight or obese (aOR = 2.87, 95% CI: 1.41–5.88) than among those who have normal weight or are underweight (aOR = 1.87, 95% CI: 0.88–3.96). However, none of the Breslow-Day tests indicated that the difference in odds ratios was statistically significant.

Maternal age was dichotomized into mothers under 30/30 years or older. Overall, stronger associations were found between PAH exposure and most defects among mothers 30 years or older versus younger mothers, except for cataracts and Dandy-Walker malformation (Table S4). The association between PAH exposure and increased risk of birth defects was statistically significant for cataracts only among mothersunder 30 years old, and for holoprosencephaly and hydrocephaly among mothers both under and over 30 years old.

After stratifying by infant sex, results showed an increased risk for cataracts (aOR = 1.71, 95% CI: 1.04–2.80), holoprosencephaly (aOR = 3.12, 95% CI: 1.66–5.87) and hydrocephaly (aOR = 1.84, 95% CI: 1.17–2.87) in female infants of exposed mothers (Table S5). We did not observe significant associations in male infants.

## Conclusions

This is the first study evaluating the potential association between maternal occupational exposure to PAHs and selected rare birth defects of the face and central nervous system. Crude and adjusted results suggest an increased risk of cataracts, microtia, and holoprosencephaly in mothers exposed to any PAHs, as well as an exposure-response relationship. Hydrocephaly was associated with any PAH exposure, but in an exposure-response analysis an increased risk was only observed for PAH levels below the median. While it did not reach statistical significance in a dichotomous analysis, microphthalmia was significantly associated with higher (i.e. above the median) PAH exposure but not lower exposure.

When evaluating exposure-response in isolated cases, results showed an increased risk of microtia and Dandy-Walker malformation, while there was an increased risk of hydrocephaly at PAH levels below the median. For holoprosencephaly, we observed increased odds ratios at PAH levels above and below the median. After removing non-occupational sources of PAHs (i.e. smoking and secondhand smoke), exposure-response results showed an increased risk of microtia, holoprosencephaly, and hydrocephaly. Excluding jobs with a low confidence for the exposure assessment strengthened the association between PAH exposure and several defects (cataracts, microphthalmia, microtia, holoprosencephaly, and hydrocephaly). However, lack of an exposure-response trend for hydrocephaly suggests caution in interpreting those results.

The association between PAH exposure and cataracts, hydrocephaly, and holoprosencephaly was stronger among mothers of female infants than among mothers of male infants. Only a few of studies have previously examined variations in prevalence or risk factors for these defects based on infant sex. A previous population-based case-control study in Hungary found that isolated congenital cataracts were more prevalent among male infants versus female infants, but the difference was not statistically significant. (Vogt, Puho, & Czeizel, 2005). However, another study from Atlanta, Georgia, US, found no difference in the rate of total or isolated cataracts by infant sex (Bhatti et al., 2003). A previous study in Denmark found an association between male infant sex and congenital hydrocephaly (Munch, Rasmussen, Wohlfahrt, Juhler, & Melbye, 2014). Our study population had about 10% more female infants with holoprosencephaly compared to controls. This is a similar

finding to previous studies, although there are inconsistencies regarding the association between female infant sex and an increased risk for holoprosencephaly (Croen, Shaw, & Lammer, 1996; Croen et al., 2000; Miller et al., 2010; Olsen, Hughes, Youngblood, & Sharpe-Stimac, 1997; Rasmussen, Moore, Khoury, & Cordero, 1996).

This analysis found a statistically significant increased risk of cataracts, cerebellar hypoplasia, and hydrocephaly in underweight or normal weight women exposed to PAHs. Being overweight or obese increased the risk of holoprosencephaly in exposed mothers. There is no consensus in the literature on how BMI affects the risk of delivering children with hydrocephaly. One study found a statistically significant increased risk of hydrocephaly in underweight mothers (Block et al., 2013), while a meta-analysis showed an increased risk in obese mothers (Stothard et al., 2009). Other studies have not found an association between maternal obesity and hydrocephaly (Waller et al., 2007; Watkins, Rasmussen, Honein, Botto, & Moore, 2003). In holoprosencephaly, maternal BMI has not been identified as a risk factor. PAHs are highly lipophilic (Mansour, 2016) and tend to accumulate in organs with abundant fat tissue. It is possible that in mothers who are overweight or obese, PAHs accumulate in in fat tissues of the body, resulting in a lower exposure to the fetus.

There are several strengths in this study. As the largest population-based case-control study of birth defects, the NBDPS provides a unique opportunity to examine potential associations between occupational exposures and rare birth defects that otherwise could not be evaluated. Detailed case classifications and exposure assessments were provided by clinical geneticists and subject matter expert industrial hygienists, respectively. Our approach also allowed us to account for the actual working experience a mother might have held over the index period—including multiple jobs—rather than relying on a report of main job or typical occupation. Overall participation rates were relatively high compared to similar population-based surveys (67% of the mothers of cases and 65% of the mothers of controls who were invited to participate in the NBDPS took part in the study (Reefhuis et al., 2015)). Although we cannot rule out that non-participation might have biased results, a previous evaluation of NBDPS data comparing demographics of the control participants with the eligible population they were drawn from found that participants were generally representative (Cogswell et al., 2009).

Another strength of this study is that mothers in this study population held diverse jobs that represent various sources of PAHs, not only those for which permissible exposure limits have been established (i.e., coal tar pitch volatiles). PAH exposure is ubiquitous and occurs over an extremely wide range of exposures; from 0.02–1.2 $\mu g/m^3$ in rural ambient air to 0–383 $\mu g/m^3$ in coke oven operations (Agency for Toxic Substances and Disease Registry, 1995). Studies that only consider exposure close to or exceeding the permissible exposure limits (200 $\mu g/m^3$) might miss important health impacts at lower exposures that are more common in the population (Occupational Safety and Health Administration (OSHA), 2019). We found that estimated intensity and frequency of PAH exposure varied between individuals with the same occupation and industry, based on variation within the reported job tasks that workers performed. This supports the rationale using expert raters versus using

a job-exposure matrix (JEM), since the latter assumes constant exposure between workers with the same occupation.

This study is not without limitations. Even though NBDPS is a large study, sample size for these rare defects was fairly small. While many states included stillbirths and therapeutic abortions as cases for some or all of the study period (Reefhuis et al., 2015)—a major strength compared to many birth defect studies—it is still possible that some cases of birth defects were missed in the NBDPS study population because of miscarriages, early pregnancy terminations, or stillbirths and therapeutic abortions not ascertained by the participating states. Therefore, these associations should be interpreted with caution until confirmed by other studies. Exposure misclassification is possible since neither direct measurement nor biomarkers were available; however, we sought to evaluate the potential influence of misclassification by conducting a subanalysis excluding jobs with a low confidence. This evaluation suggests that exposure misclassification likely results in underestimation of the odds ratio. Because PAHs were evaluated as a group, it is not possible to determine which specific PAHs or mixture of PAHs could be driving these results. Additionally, the only route of exposure to PAHs evaluated was inhalation at workplace settings; it was not possible to account for other settings where PAH exposure occurs through inhalation. This study did not include estimates of potential exposure through dermal contact or ingestion. We were not able to study the associations between PAH exposure and the risk of selected birth defects in diabetic mothers due to sample size constraints.

This study provides initial evidence suggesting a potential association between maternal occupational exposure to PAHs and some facial defects (i.e. cataracts and microtia), as well as certain central nervous system defects (i.e. holoprosencephaly and hydrocephaly) that warrant additional investigation. Additionally, findings suggest a potential exposure-response relationship between PAH exposure and several face and central nervous system defects; the trend test was consistently significant for microtia and holoprosencephaly throughout exposure-response subanalyses. Future studies could evaluate deeper the characteristics of jobs where a high number of each of these defects occur, as well as potential specific PAHs that might be involved.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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## References:

Agency for Toxic Substances and Disease Registry. (1995). Toxicological profile for polycyclic aromatic hydrocarbons (PAHs). In (pp. 22–23). Atlanta, GA: US Department of Health and Human Services, Public Health Service.

Anderson JL, Waller DK, Canfield MA, Shaw GM, Watkins ML, & Werler MM (2005). Maternal obesity, gestational diabetes, and central nervous system birth defects. Epidemiology, 16(1), 87–92. [PubMed: 15613950]

Bauer EP, Romitti PA, & Reynolds SJ (1999). Evaluation of reports of periconceptual occupational exposure: maternal-assessed versus industrial hygienist-assessed exposure. Am J Ind Med, 36(5), 573–578. doi:10.1002/(sici)1097-0274(199911)36:5<573::aid-ajim9>3.0.co;2-l [PubMed: 10506739]

Bhatti TR, Dott M, Yoon PW, Moore CA, Gambrell D, & Rasmussen SA (2003). Descriptive epidemiology of infantile cataracts in metropolitan Atlanta, GA, 1968–1998. Arch Pediatr Adolesc Med, 157(4), 341–347. doi:10.1001/archpedi.157.4.341 [PubMed: 12695229]

Block SR, Watkins SM, Salemi JL, Rutkowski R, Tanner JP, Correia JA, & Kirby RS (2013). Maternal pre-pregnancy body mass index and risk of selected birth defects: evidence of a dose-response relationship. Paediatr Perinat Epidemiol, 27(6), 521–531. doi:10.1111/ppe.12084 [PubMed: 24117964]

Brandt HC, & Watson WP (2003). Monitoring human occupational and environmental exposures to polycyclic aromatic compounds. Ann Occup Hyg, 47(5), 349–378. [PubMed: 12855487]

Canfield MA, Langlois PH, Nguyen LM, & Scheuerle AE (2009). Epidemiologic features and clinical subgroups of anotia/microtia in Texas. Birth Defects Res A Clin Mol Teratol, 85(11), 905–913. doi:10.1002/bdra.20626 [PubMed: 19760683]

Centers for Disease Control and Prevention, N., Division of Birth Defects and Developmental Disabilities,. NBDPS Public Access Procedures. Retrieved from https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html

Cogswell ME, Bitsko RH, Anderka M, Caton AR, Feldkamp ML, Hockett Sherlock SM, … Reefhuis J (2009). Control selection and participation in an ongoing, population-based, case-control study of birth defects: the National Birth Defects Prevention Study. Am J Epidemiol, 170(8), 975–985. doi:10.1093/aje/kwp226 [PubMed: 19736223]

Croen LA, Shaw GM, & Lammer EJ (1996). Holoprosencephaly: epidemiologic and clinical characteristics of a California population. Am J Med Genet, 64(3), 465–472. doi:10.1002/(sici)1096-8628(19960823)64:3<465::aid-ajmg4>3.0.co;2-o [PubMed: 8862623]

Croen LA, Shaw GM, & Lammer EJ (2000). Risk factors for cytogenetically normal holoprosencephaly in California: a population-based case-control study. Am J Med Genet, 90(4), 320–325. [PubMed: 10710231]

Forrester MB, & Merz RD (2006). Descriptive epidemiology of anophthalmia and microphthalmia, Hawaii, 1986–2001. Birth Defects Res A Clin Mol Teratol, 76(3), 187–192. doi:10.1002/bdra.20237 [PubMed: 16498668]

Hackshaw A, Rodeck C, & Boniface S (2011). Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. Hum Reprod Update, 17(5), 589–604. doi:10.1093/humupd/dmr022 [PubMed: 21747128]

Herdt-Losavio ML, Lin S, Chapman BR, Hooiveld M, Olshan A, Liu X, … Druschel CM (2010). Maternal occupation and the risk of birth defects: an overview from the National Birth Defects Prevention Study. Occup Environ Med, 67(1), 58–66. doi:10.1136/oem.2009.048256 [PubMed: 20029025]

Jedrychowski WA, Perera FP, Tang D, Rauh V, Majewska R, Mroz E, … Jacek R (2013). The relationship between prenatal exposure to airborne polycyclic aromatic hydrocarbons (PAHs) and PAH-DNA adducts in cord blood. J Expo Sci Environ Epidemiol, 23(4), 371–377. doi:10.1038/jes.2012.117 [PubMed: 23299301]

Johnson CY, & Rasmussen SA (2010). Non-genetic risk factors for holoprosencephaly. Am J Med Genet C Semin Med Genet, 154c(1), 73–85. doi:10.1002/ajmg.c.30242 [PubMed: 20104598]

Kalyvas AV, Kalamatianos T, Pantazi M, Lianos GD, Stranjalis G, & Alexiou GA (2016). Maternal environmental risk factors for congenital hydrocephalus: a systematic review. Neurosurg Focus, 41(5), E3. doi:10.3171/2016.8.focus16280

Kancherla V, Romitti PA, Sun L, Carey JC, Burns TL, Siega-Riz AM, … Olney RS (2014). Descriptive and risk factor analysis for choanal atresia: The National Birth Defects Prevention Study, 1997–2007. Eur J Med Genet, 57(5), 220–229. doi:10.1016/j.ejmg.2014.02.010 [PubMed: 24576610]

Kromhout H, Oostendorp Y, Heederik D, & Boleij JSM (1987). Agreement between qualitative exposure estimates and quantitative exposure measurements. 12(5), 551–562. doi:10.1002/ajim.4700120509

Langlois PH, Hoyt AT, Desrosiers TA, Lupo PJ, Lawson CC, Waters MA, … National Birth Defects Prevention, S. (2014). Maternal Occupational exposure to polycyclic aromatic hydrocarbons and small for gestational age offspring. Occup Environ Med, 71, 529–535. doi:10.1136/oemed2013-101833 10.1136/oemed-2013-101833 [PubMed: 24893704]

Langlois PH, Hoyt AT, Lupo PJ, Lawson CC, Waters MA, Desrosiers TA, … Lammer EJ (2013). Maternal occupational exposure to polycyclic aromatic hydrocarbons and risk of oral cleft-affected pregnancies. Cleft Palate Craniofac J, 50(3), 337–346. doi:10.1597/12-104 [PubMed: 23136939]

Langlois PH, Hoyt AT, Lupo PJ, Lawson CC, Waters MA, Desrosiers TA, … National Birth Defects Prevention, S. (2012). Maternal occupational exposure to polycyclic aromatic hydrocarbons and risk of neural tube defect-affected pregnancies. Birth Defects Res A Clin Mol Teratol, 94(9), 693–700. doi:10.1002/bdra.23045 [PubMed: 22807044]

Lupo PJ, Langlois PH, Reefhuis J, Lawson CC, Symanski E, Desrosiers TA, … National Birth Defects Prevention, S. (2012). Maternal occupational exposure to polycyclic aromatic hydrocarbons: effects on gastroschisis among offspring in the National Birth Defects Prevention Study. Environ Health Perspect, 120(6), 910–915. doi:10.1289/ehp.1104305 [PubMed: 22330681]

Mansour MSM A.-S. HI (2016). A review on polycyclic aromatic hydrocarbons:Source, environmental impact, effect on humanhealth and remediation. Egyptian Journal of Petroleum, 25(1), 107–123. doi:10.1016/j.ejpe.2015.03.011

Mastroiacovo P, Corchia C, Botto LD, Lanni R, Zampino G, & Fusco D (1995). Epidemiology and genetics of microtia-anotia: a registry based study on over one million births. J Med Genet, 32(6), 453–457. [PubMed: 7666397]

Miller EA, Rasmussen SA, Siega-Riz AM, Frias JL, & Honein MA (2010). Risk factors for non-syndromic holoprosencephaly in the National Birth Defects Prevention Study. Am J Med Genet C Semin Med Genet, 154c(1), 62–72. doi:10.1002/ajmg.c.30244 [PubMed: 20104597]

Munch TN, Rasmussen ML, Wohlfahrt J, Juhler M, & Melbye M (2014). Risk factors for congenital hydrocephalus: a nationwide, register-based, cohort study. J Neurol Neurosurg Psychiatry, 85(11), 1253–1259. doi:10.1136/jnnp-2013-306941 [PubMed: 24667207]

National Institute of Neurological Disorders and Stroke. Cerebellar Hypoplasia Information Page. Retrieved from https://www.ninds.nih.gov/Disorders/All-Disorders/Cerebellar-Hypoplasia-Information-Page

O'Brien JL, Langlois PH, Lawson CC, Scheuerle A, Rocheleau CM, Waters MA, … Lupo PJ (2016). Maternal occupational exposure to polycyclic aromatic hydrocarbons and craniosynostosis among offspring in the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol, 106(1), 55–60. doi:10.1002/bdra.23389 [PubMed: 26033890]

Occupational Safety and Health Administration (OSHA). (2019). OSHA Annotated PELs Table Z-1. Retrieved from https://www.osha.gov/dsg/annotated-pels/tablez-1.html#annotated_table_Z-1

Olsen CL, Hughes JP, Youngblood LG, & Sharpe-Stimac M (1997). Epidemiology of holoprosencephaly and phenotypic characteristics of affected children: New York State, 1984–1989. Am J Med Genet, 73(2), 217–226. [PubMed: 9409876]

Prakalapakorn SG, Rasmussen SA, Lambert SR, & Honein MA (2010). Assessment of risk factors for infantile cataracts using a case-control study: National Birth Defects Prevention Study, 2000–2004. Ophthalmology, 117(8), 1500–1505. doi:10.1016/j.ophtha.2009.12.026 [PubMed: 20363508]

Pratt MM, John K, MacLean AB, Afework S, Phillips DH, & Poirier MC (2011). Polycyclic aromatic hydrocarbon (PAH) exposure and DNA adduct semi-quantitation in archived human tissues. Int J Environ Res Public Health, 8(7), 2675–2691. doi:10.3390/ijerph8072675 [PubMed: 21845152]

Rasmussen SA, Moore CA, Khoury MJ, & Cordero JF (1996). Descriptive epidemiology of holoprosencephaly and arhinencephaly in metropolitan Atlanta, 1968–1992. Am J Med Genet, 66(3), 320–333. doi:10.1002/(sici)1096-8628(19961218)66:3<320::aid-ajmg16>3.0.co;2-o [PubMed: 8985495]

Reeder MR, Botto LD, Keppler-Noreuil KM, Carey JC, Byrne JL, & Feldkamp ML (2015). Risk factors for Dandy-Walker malformation: a population-based assessment. Am J Med Genet A, 167a(9), 2009–2016. doi:10.1002/ajmg.a.37124 [PubMed: 25941000]

Reefhuis J, Gilboa SM, Anderka M, Browne ML, Feldkamp ML, Hobbs CA, … Honein MA (2015). The national birth defects prevention study: A review of the methods. Birth Defects Res A Clin Mol Teratol, 103(8), 656–669. doi:10.1002/bdra.23384 [PubMed: 26033852]

Rocheleau CM, Lawson CC, Waters MA, Hein MJ, Stewart PA, Correa A, … Reefhuis J (2011). Inter-rater reliability of assessed prenatal maternal occupational exposures to solvents, polycyclic aromatic hydrocarbons, and heavy metals. J Occup Environ Hyg, 8(12), 718–728. doi:10.1080/15459624.2011.627293 [PubMed: 22074298]

Sanbe A, Mizutani R, Miyauchi N, Yamauchi J, Nagase T, Yamamura K, & Tanoue A (2009). Inhibitory effects of cigarette smoke extract on neural crest migration occur through suppression of R-spondin1 expression via aryl hydrocarbon receptor. Naunyn Schmiedebergs Arch Pharmacol, 380(6), 569–576. doi:10.1007/s00210-009-0455-3 [PubMed: 19768455]

Shaw GM, Carmichael SL, Kaidarova Z, & Harris JA (2003). Differential risks to males and females for congenital malformations among 2.5 million California births, 1989–1997. Birth Defects Res A Clin Mol Teratol, 67(12), 953–958. doi:10.1002/bdra.10129 [PubMed: 14745913]

Shaw GM, Carmichael SL, Kaidarova Z, & Harris JA (2004). Epidemiologic characteristics of anotia and microtia in California, 1989–1997. Birth Defects Res A Clin Mol Teratol, 70(7), 472–475. doi:10.1002/bdra.20042 [PubMed: 15259037]

Stothard KJ, Tennant PW, Bell R, & Rankin J (2009). Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA, 301(6), 636–650. doi:10.1001/jama.2009.113 [PubMed: 19211471]

U.S. Environmental Protection Agency. (2008). Polycyclic Aromatic Hydrocarbons (PAHs).

Vogt G, Horvath-Puho E, & Czeizel AE (2006). A population-based case-control study of isolated primary congenital glaucoma. Am J Med Genet A, 140(11), 1148–1155. doi:10.1002/ajmg.a.31276 [PubMed: 16652361]

Vogt G, Puho E, & Czeizel AE (2005). Population-based case-control study of isolated congenital cataract. Birth Defects Res A Clin Mol Teratol, 73(12), 997–1005. doi:10.1002/bdra.20188 [PubMed: 16323161]

Waller DK, Shaw GM, Rasmussen SA, Hobbs CA, Canfield MA, Siega-Riz AM, … Correa A (2007). Prepregnancy obesity as a risk factor for structural birth defects. Arch Pediatr Adolesc Med, 161(8), 745–750. doi:10.1001/archpedi.161.8.745 [PubMed: 17679655]

Watkins ML, Rasmussen SA, Honein MA, Botto LD, & Moore CA (2003). Maternal obesity and risk for birth defects. Pediatrics, 111(5 Pt 2), 1152–1158. [PubMed: 12728129]

Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, … Edmonds LD (2001). The National Birth Defects Prevention Study. Public Health Rep, 116 Suppl 1, 32–40.

Zhang QG, Zhang J, Yu P, & Shen H (2009). Environmental and genetic factors associated with congenital microtia: a case-control study in Jiangsu, China, 2004 to 2007. Plast Reconstr Surg, 124(4), 1157–1164. doi:10.1097/PRS.0b013e3181b454d8 [PubMed: 19935299]

**Table 1.**

Characteristics of PAH exposed and unexposed employed mothers in the National Birth Defects Prevention Study, 1997–2011

| Characteristic | No PAHs | | PAHs | |
|---|---|---|---|---|
| | Control N (%) | Case N (%) | Control N (%) | Case N (%) |
| **Maternal age at delivery** * | | | | |
| < 20 years old | 428 (5.8%) | 81 (5.8%) | 136 (16.6%) | 41 (18.2%) |
| 20–24 years old | 1549 (21.2%) | 305 (22.0%) | 305 (37.2%) | 78 (34.7%) |
| 25–29 years old | 2113 (28.9%) | 419 (30.2%) | 189 (23.1%) | 51 (22.7%) |
| 30–34 years old | 2091 (28.6%) | 374 (26.9%) | 120 (14.7%) | 36 (16.0%) |
| 35 years old or older | 1140 (15.6%) | 209 (15.1%) | 69 (8.4%) | 19 (8.4%) |
| **Maternal race** [a] | | | | |
| NH White | 4732 (64.6%) | 809 (58.3%) | 429 (52.4%) | 98 (43.6%) |
| NH Black | 847 (11.6%) | 169 (12.2%) | 102 (12.5%) | 37 (16.4%) |
| Hispanic/Other | 1742 (23.8%) | 408 (29.4%) | 288 (35.2%) | 90 (40.0%) |
| **Maternal education** * | | | | |
| 0–12 years | 2179 (29.8%) | 491 (35.4%) | 504 (61.5%) | 162 (72.0%) |
| >12 years | 5130 (70.1%) | 895 (64.5%) | 313 (38.2%) | 63 (28.0%) |
| **Total Annual Household Income** * | | | | |
| < $20,000 | 1632 (22.3%) | 377 (27.2%) | 407 (49.7%) | 117 (52.0%) |
| $20,000–49,999 | 2225 (30.4%) | 456 (32.9%) | 244 (29.8%) | 66 (29.3%) |
| ≥ $50,000 | 3018 (41.2%) | 481 (34.7%) | 116 (14.2%) | 21 (9.3%) |
| Missing | 446 (6.1%) | 74 (5.3%) | 52 (6.3%) | 21 (9.3%) |
| **Singleton pregnancy** | | | | |
| Yes | 7075 (96.6%) | 1303 (93.9%) | 800 (97.7%) | 216 (96.0%) |
| No | 238 (3.3%) | 85 (6.1%) | 18 (2.2%) | 9 (4.0%) |
| **Use of folic acid supplement B1 – P1** * | | | | |
| Any | 4198 (57.3%) | 773 (55.7%) | 352 (43.0%) | 84 (37.3%) |
| None | 3123 (42.7%) | 615 (44.3%) | 466 (56.9%) | 141 (62.7%) |
| **Maternal smoking B1 – P3** * | | | | |
| Any | 1274 (17.4%) | 226 (16.3%) | 262 (32.0%) | 64 (28.4%) |
| None | 6047 (82.6%) | 1162 (83.7%) | 555 (67.8%) | 161 (71.6%) |
| **Maternal alcohol consumption B1 – P3** | | | | |
| Any | 3105 (42.4%) | 521 (37.5%) | 335 (40.9%) | 79 (35.1%) |
| None | 4192 (57.3%) | 867 (62.5%) | 481 (58.7%) | 145 (64.4%) |
| **Any SHS home or work B1-P3** * | | | | |
| Yes | 1667 (22.8%) | 346 (24.9%) | 357 (43.6%) | 92 (40.9%) |
| No | 5636 (77.0%) | 1036 (74.6%) | 460 (56.2%) | 129 (57.3%) |
| **Prepregnancy BMI** * | | | | |
| Underweight | 327 (4.5%) | 59 (4.3%) | 45 (5.5%) | 13 (5.8%) |

| Characteristic | No PAHs | | PAHs | |
|---|---|---|---|---|
| | Control | Case | Control | Case |
| | N (%) | N (%) | N (%) | N (%) |
| Normal weight | 3903 (53.3%) | 671 (48.3%) | 394 (48.1%) | 105 (46.7%) |
| Overweight | 1657 (22.6%) | 314 (22.6%) | 180 (22.0%) | 50 (22.2%) |
| Obese | 1287 (17.6%) | 291 (21.0%) | 166 (20.3%) | 41 (18.2%) |
| Missing | 147 (2.0%) | 53 (3.8%) | 34 (4.2%) | 16 (7.1%) |
| **Maternal diabetes** | | | | |
| Not diagnosed ever | 6781 (92.6%) | 1243 (89.6%) | 748 (91.3%) | 194 (86.2%) |
| Diagnosed during index pregnancy | 328 (4.5%) | 81 (5.8%) | 42 (5.1%) | 9 (4.0%) |
| Diagnosed before index pregnancy | 152 (2.1%) | 50 (3.6%) | 18 (2.2%) | 17 (7.6%) |
| Diagnosed after index pregnancy | 51 (0.7%) | 13 (0.9%) | 10 (1.2%) | 4 (1.8%) |
| **Study center** * | | | | |
| Arkansas | 909 (12.4%) | 164 (11.8%) | 135 (16.5%) | 38 (16.9%) |
| California | 669 (9.1%) | 154 (11.1%) | 75 (9.2%) | 23 (10.2%) |
| Georgia | 834 (11.4%) | 151 (10.9%) | 75 (9.2%) | 24 (10.7%) |
| Iowa | 960 (13.1%) | 177 (12.8%) | 102 (12.5%) | 29 (12.9%) |
| Massachusetts | 1008 (13.8%) | 178 (12.8%) | 77 (9.4%) | 10 (4.4%) |
| New Jersey | 396 (5.4%) | 90 (6.5%) | 11 (1.3%) | 4 (1.8%) |
| New York | 676 (9.2%) | 104 (7.5%) | 53 (6.5%) | 17 (7.6%) |
| North Carolina | 584 (8.0%) | 92 (6.6%) | 106 (12.9%) | 29 (12.9%) |
| Texas | 642 (8.8%) | 131 (9.4%) | 95 (11.6%) | 26 (11.6%) |
| Utah | 643 (8.8%) | 147 (10.6%) | 90 (11.0%) | 25 (11.1%) |
| **Infant gender** * | | | | |
| Male | 3707 (50.6%) | 711 (51.2%) | 450 (54.9%) | 117 (52.0%) |
| Female | 3610 (49.3%) | 674 (48.6%) | 369 (45.1%) | 108 (48.0%) |
| **Infant gestational age** | | | | |
| Very preterm (<32 wks) | 103 (1.4%) | 115 (8.3%) | 14 (1.7%) | 21 (9.3%) |
| Preterm (32–36 wks) | 568 (7.8%) | 266 (19.2%) | 74 (9.0%) | 40 (17.8%) |
| Term (37–45 wks) | 6650 (90.8%) | 1007 (72.6%) | 731 (89.3%) | 164 (72.9%) |
| **Infant birthweight** | | | | |
| Very low birthweight (<1500g) | 73 (1.0%) | 100 (7.2%) | 11 (1.3%) | 20 (8.9%) |
| Low birthweight (1500–2499g) | 368 (5.0%) | 229 (16.5%) | 48 (5.9%) | 26 (11.5%) |
| Normal birthweight (2500–3999g) | 6018 (82.2%) | 928 (66.9%) | 681 (83.2%) | 163 (72.4%) |
| Macrosomic (≥4000g) | 765 (10.4%) | 118 (8.5%) | 66 (8.1%) | 11 (4.9%) |
| Missing | 97 (1.3%) | 13 (0.9%) | 13 (1.6%) | 5 (2.2%) |

PAH = polycyclic aromatic hydrocarbon; B1 = one month prior to conception; P1 = one month after conception; P3 = three months after conception; NH = non-Hispanic; SHS = secondhand smoke; BMI = body mass index.

*Variable was associated with PAH exposure (any/none) among controls ($p \leq 0.05$)

†Diabetes diagnosis includes Type 1, Type 2, gestational, and unknown type diabetes.

[‡]Sums and percentages may not add up to total due to missing values (maternal race [n=2], maternal education [n=16], singleton pregnancy [n=9], use of folic acid supplement [n=1], maternal smoking [n=2], maternal alcohol consumption [n=28], diabetes diagnosis [n=12], any SHS at home or work [n=30], and infant gender [n=7])

**Table 2.**

Crude and adjusted odds ratios (ORs) for the association between PAHs and selected birth defects, National Birth Defects Prevention Study 1997–2011

| Birth Defect | Control | | Cases | | Crude OR (95% CI) | Adjusted OR (95% CI)[§] |
|---|---|---|---|---|---|---|
| | Unexposed | Exposed | Unexposed | Exposed | | |
| Cataract[†] | 6063 | 767 | 215 | 39 | **1.43 (1.01–2.03)** | **1.49 (1.04–2.13)** [a] |
| Glaucoma/ACD[†] | 6063 | 767 | 121 | 13 | 0.85 (0.48–1.51) | 0.85 (0.47–1.53) [a] |
| Microphthalmia[†] | 7303 | 816 | 139 | 20 | 1.29 (0.80–2.07) | 1.18 (0.73–1.92) [a] |
| Microtia[†] | 7303 | 816 | 360 | 53 | 1.32 (0.98–1.77) | **1.35 (1.00–1.83)** [a] |
| Choanal atresia[‡] | 7303 | 816 | 108 | 10 | 0.83 (0.43–1.59) | 1.25 (0.64–2.46) [b] |
| Cerebellar hypoplasia[†] | 7303 | 816 | 40 | 8 | 1.79 (0.84–3.84) | 1.56 (0.71–3.41) [a] |
| Dandy Walker[†] | 7303 | 816 | 109 | 18 | 1.48 (0.89–2.45) | 1.30 (0.78–2.19) [a] |
| Holoprosencephaly[†] | 7303 | 816 | 79 | 21 | **2.38 (1.46–3.87)** | **2.25 (1.37–3.72)** [a] |
| Hydrocephaly[†] | 7303 | 816 | 280 | 54 | **1.73 (1.28–2.33)** | **1.66 (1.22–2.26)** [a] |

PAH = polycyclic aromatic hydrocarbon; B1 = one month prior to conception; P3 = three months after conception; SHS = secondhand-smoke;

[†]Adjusted for maternal smoking B1-P3, any SHS exposure B1-P3, and study center

[‡]Adjusted for maternal age, maternal race, maternal smoking B1-P3, any SHS exposure B1-P3, and study center

[§]Adjusted estimates restricted to individuals with complete data for all covariates; this excluded a total of 21 controls and 12 cases

**Table 3.**

PAH exposure-response analysis for all jobs of case and control mothers of infants with selected birth defects of the central nervous system and face, National Birth Defects Prevention Study 1997–2011

| Birth Defect | Exposure Level | Control n | Cases n | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|---|
| Cataract *†§ | None | 6064 | 215 | 1.0 (reference) | 1.0 (reference) |
| | Low | 383 | 17 | 1.25 (0.76–2.07) | 1.32 (0.79–2.20) |
| | High | 383 | 22 | **1.62 (1.03–2.54)** | **1.66 (1.05–2.64)** |
| Glaucoma/ACD †§ | None | 6064 | 121 | 1.0 (reference) | 1.0 (reference) |
| | Low | 383 | 8 | 1.05 (0.51–2.16) | 1.05 (0.51–2.19) |
| | High | 383 | 5 | 0.65 (0.27–1.61) | 0.66 (0.26–1.63) |
| Microphthalmia *‡§ | None | 7304 | 139 | 1.0 (reference) | 1.0 (reference) |
| | Low | 408 | 4 | 0.52 (0.19–1.40) | 0.48 (0.18–1.31) |
| | High | 407 | 16 | **2.07 (1.22–3.50)** | **1.88 (1.10–3.22)** |
| Microtia *‡§ | None | 7304 | 360 | 1.0 (reference) | 1.0 (reference) |
| | Low | 408 | 19 | 0.95 (0.59–1.52) | 0.97 (0.60–1.57) |
| | High | 407 | 34 | **1.70 (1.18–2.44)** | **1.73 (1.19–2.51)** |
| Choanal atresia ‡¶ | None | 7304 | 108 | 1.0 (reference) | 1.0 (reference) |
| | Low | 408 | 6 | 1.00 (0.43–2.28) | 1.34 (0.58–3.11) |
| | High | 407 | 4 | 0.67 (0.24–1.81) | 1.14 (0.41–3.20) |
| Cerebellar hypoplasia ‡§ | None | 7304 | 40 | 1.0 (reference) | 1.0 (reference) |
| | Low | 408 | 4 | 1.79 (0.64–5.03) | 1.57 (0.55–4.47) |
| | High | 407 | 4 | 1.80 (0.64–5.04) | 1.55 (0.54–4.44) |
| Dandy Walker ‡§ | None | 7304 | 109 | 1.0 (reference) | 1.0 (reference) |
| | Low | 408 | 7 | 1.15 (0.53–2.49) | 1.03 (0.47–2.25) |
| | High | 407 | 11 | 1.81 (0.97–3.39) | 1.58 (0.83–2.99) |
| Holoprosencephaly *‡§ | None | 7304 | 79 | 1.0 (reference) | 1.0 (reference) |
| | Low | 408 | 10 | **2.27 (1.17–4.41)** | **2.14 (1.09–4.20)** |

| Birth Defect | Exposure Level | Control n | Cases n | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|---|
| | High | 407 | 11 | **2.50 (1.32–4.73)** | **2.38 (1.24–4.56)** |
| Hydrocephaly[≠§] | None | 7304 | 280 | 1.0 (reference) | 1.0 (reference) |
| | Low | 408 | 36 | **2.30 (1.60–3.30)** | **2.22 (1.54–3.21)** |
| | High | 407 | 18 | 1.15 (0.71–1.88) | 1.10 (0.67–1.80) |

PAH = polycyclic aromatic hydrocarbon; B1 = one month prior to conception; P3 = three months after conception; SHS = secondhand-smoke

[*] Trend analysis p-value ≤ 0.05

[†] Exposure levels correspond to none (0 μg/m3-hours), low (0<exp ≤45.26 μg/m3-hours), and high (>45.26μg/m3-hours)

[≠] Exposure levels correspond to none (0 μg/m3-hours), low (0<exp ≤51.43 μg/m3-hours), and high (exp >51.43 μg/m3-hours)

[§] Adjusted for study center, maternal smoking, and SHS at home or work during B1-P3

[¶] Adjusted for maternal age, maternal race, study center, maternal smoking, and any SHS at home or work during B1-P3

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**Table 4.**

PAH exposure-response analysis for all jobs of case and control mothers of selected birth defects of the central nervous system and face, excluding mothers who smoked or had any secondhand-smoke exposure at home or work during B1-P3, National Birth Defects Prevention Study 1997–2011

| Birth Defect | Exposure Level | Control n | Cases n | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|---|
| Cataract †§ | None | 4338 | 157 | 1.0 (reference) | 1.0 (reference) |
| | Low | 187 | 6 | 0.89 (0.39–2.03) | 0.93 (0.40–2.13) |
| | High | 179 | 9 | 1.39 (0.70–2.77) | 1.52 (0.76–3.05) |
| Glaucoma/ACD †§ | None | 4338 | 86 | 1.0 (reference) | 1.0 (reference) |
| | Low | 187 | 3 | 0.81 (0.25–2.58) | 0.83 (0.26–2.67) |
| | High | 179 | 3 | 0.85 (0.27–2.70) | 0.90 (0.28–2.90) |
| Microphthalmia ‡§ | None | 5093 | 86 | 1.0 (reference) | 1.0 (reference) |
| | Low | 196 | 1 | n/a | n/a |
| | High | 189 | 6 | 1.88 (0.81–4.36) | 2.00 (0.86–4.65) |
| Microtia *‡§ | None | 5093 | 240 | 1.0 (reference) | 1.0 (reference) |
| | Low | 196 | 9 | 0.97 (0.49–1.93) | 0.93 (0.47–1.85) |
| | High | 189 | 25 | **2.81 (1.81–4.34)** | **2.47 (1.58–3.87)** |
| Choanal atresia ‡¶ | None | 5093 | 83 | 1.0 (reference) | 1.0 (reference) |
| | Low | 196 | 5 | 1.57 (0.63–3.90) | 2.03 (0.80–5.13) |
| | High | 189 | 2 | n/a | n/a |
| Dandy Walker ‡§ | None | 5093 | 68 | 1.0 (reference) | 1.0 (reference) |
| | Low | 196 | 4 | 1.53 (0.55–4.23) | 1.49 (0.54–4.14) |
| | High | 189 | 6 | **2.38 (1.02–5.55)** | 2.17 (0.92–5.09) |
| Holoprosencephaly ‡§ | None | 5093 | 56 | 1.0 (reference) | 1.0 (reference) |
| | Low | 196 | 6 | **2.78 (1.19–6.54)** | **2.59 (1.10–6.13)** |
| | High | 189 | 3 | 1.44 (0.45–4.65) | 1.36 (0.42–4.42) |
| Hydrocephaly ‡§ | None | 5093 | 185 | 1.0 (reference) | 1.0 (reference) |
| | Low | 196 | 13 | **1.83 (1.02–3.26)** | **1.80 (1.01–3.23)** |

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| Birth Defect | Exposure Level | Control n | Cases n | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|---|
| | High | 189 | 9 | 1.31 (0.66–2.60) | 1.29 (0.65–2.56) |

PAH = polycyclic aromatic hydrocarbon; B1 = one month prior to conception; P3 = three months after conception; n/a = not available, the number of exposed cases was too low for meaningful analysis (n<3).

Not enough sample size to run the analysis for cerebellar hypoplasia.

[*] Trend analysis p-value ≤ 0.05

[†] Exposure levels correspond to none (0 μg/m3-hours), low (0<exp ≤45.26 μg/m3-hours), and high (>45.26μg/m3-hours)

[‡] Exposure levels correspond to none (0 μg/m3-hours), low (0<exp ≤51.43 μg/m3-hours), and high (exp >51.43 μg/m3-hours)

[§] Adjusted for study center

[¶] Adjusted for study center, maternal age and maternal race