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

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Abstract

BACKGROUND—There is evidence in experimental model systems that exposure to polycyclic aromatic hydrocarbons (PAHs) results in congenital heart defects (CHDs); however, to our knowledge, this relationship has not been examined in humans. Therefore, we conducted a case-control study assessing the association between estimated maternal occupational exposure to PAHs and CHDs in offspring.

METHODS—Data on CHD cases and control infants were obtained from the National Birth Defects Prevention Study for the period of 1997 to 2002. Exposure to PAHs was assigned by industrial hygienist consensus, based on self-reported maternal occupational histories from 1 month before conception through the third month of pregnancy. Logistic regression was used to

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evaluate the association between maternal occupational PAH exposure and specific CHD phenotypic subtypes among offspring.

RESULTS—The prevalence of occupational PAH exposure was 4.0% in CHD case mothers (76/1907) and 3.6% in control mothers (104/2853). After adjusting for maternal age, race or ethnicity, education, smoking, folic acid supplementation, and study center, exposure was not associated with conotruncal defects (adjusted odds ratio [AOR], 0.98; 95% confidence interval [CI], 0.58–1.67), septal defects (AOR, 1.28; 95% CI, 0.86–1.90), or with any isolated CHD subtype.

CONCLUSIONS—Our findings do not support an association between potential maternal occupational exposure to PAHs and various CHDs in a large, population-based study. For CHD phenotypic subtypes in which modest nonsignificant associations were observed, future investigations could be improved by studying populations with a higher prevalence of PAH exposure and by incorporating information on maternal and fetal genotypes related to PAH metabolism.

Keywords

birth defects; congenital heart defects; epidemiology; maternal occupation; polycyclic aromatic hydrocarbons

INTRODUCTION

Congenital heart defects (CHDs) are the most common group of structural defects, occurring in approximately 1 of every 100 births (Botto et al., 2007). In addition to being the most prevalent group of birth defects, CHDs are the leading cause of birth defect–related mortality (Jenkins et al., 2007). Although some CHDs occur in association with known genetic disorders (e.g., 22q11 deletion syndrome) and teratogenic exposures (e.g., maternal pregestational diabetes), the majority (approximately 80%) are of unknown etiology (Harper, 2004). Suspected risk factors for CHDs include maternal obesity (indexed by body mass index [BMI]) and maternal folate status (Jenkins et al., 2007). In addition, occupational exposures have been suggested as potential risk factors for CHDs (Herdt-Losavio et al., 2010).

There is evidence in experimental model systems that prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) is associated with CHDs (Farwell et al., 2006; Incardona et al., 2004). Additionally, studies in humans suggest maternal occupational and environmental exposure to PAHs is associated with structural birth defects including neural tube defects (Naufal et al., 2010; Ren et al., 2011; Langlois et al., 2012) and gastroschisis (Lupo et al., 2012). Despite this evidence, to our knowledge there have been no studies evaluating the potential association between maternal occupational exposure to PAHs and CHDs among offspring.

The identification of risk factors for CHDs is complicated by the vast range of cardiac defect phenotypes (e.g., tetralogy of Fallot, hypoplastic left heart syndrome), which may differ in their underlying etiology. It is therefore important to study specific phenotypic subtypes of CHDs and evaluate associations among those cases that have been properly classified (Botto

et al., 2007). To this end, we used data from the National Birth Defects Prevention Study (NBDPS), the largest population-based case-control study of birth defects in the United States; it offers a unique opportunity to explore the association between maternal occupational exposure to PAHs and specific phenotypic subtypes of CHDs among offspring because of its detailed review and refined classification of CHD cases and the industrial hygienist–estimated maternal occupational exposure information for PAHs among study participants who delivered from 1997 through 2002.

MATERIALS AND METHODS

Study Participants

The study population included CHD case and unaffected control infants from the NBDPS, with estimated dates of delivery from October 1, 1997, through December 31, 2002. NBDPS cases were identified from eight birth defects surveillance systems throughout the United States: Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, and Texas (Yoon et al., 2001). Case infants were live born, stillborn, or electively terminated. Control infants (live born infants without major birth defects) were selected randomly from birth certificates or birth hospital records from the same geographic populations that gave rise to the cases. Mothers of cases and controls completed a 1-hour computer-assisted telephone interview (CATI) in either English or Spanish from 6 weeks to 2 years after the estimated date of delivery. Interviewers obtained information on maternal demographic characteristics, exposures (e.g., nutritional and occupational) and medication use both before and during pregnancy. The Centers for Disease Control and Prevention (CDC) Institutional Review Board (IRB), along with the IRBs for each participating state, have approved the NBDPS. In addition, this analysis was approved by the IRB of The University of Texas Health Science Center at Houston.

Classification of CHDs

The systematic review of all NBDPS case records by clinical geneticists resulted in the exclusion of those with recognized or strongly suspected single-gene conditions or chromosome abnormalities. All CHD cases were confirmed by echocardiography, cardiac catheterization, surgery, or autopsy (Rasmussen et al., 2003; Botto et al., 2007), and their diagnostic information was reviewed by a team of clinicians with expertise in pediatric cardiology and clinical genetics for classification on two axes. The first axis of classification focused on the heart itself. *Simple cardiac defects* were defined as anatomically discrete or a well-recognized single entity (e.g., hypoplastic left heart syndrome, tetralogy of Fallot). *Associations* were defined as common combinations of (typically two) cardiac defects (e.g., ventricular septal defect, pulmonary valve stenosis). Cases that included three or more distinct CHDs were considered *complex* (Botto et al., 2007). The second axis of classification considered whether the infant had defects outside the heart. Infants with no major extracardiac defects were classified as isolated CHD cases, whereas those with extracardiac defects were classified as multiple CHD cases (Rasmussen et al., 2003; Botto et al., 2007). Clinical reviewers also determined the specific CHD phenotypic subtypes of every case according to rigorous guidelines (Botto et al., 2007).

Inclusion and Exclusion Criteria

To assess associations in relatively homogeneous case groups, we included only case infants with simple and isolated CHDs based on the NBDPS classification strategy described above (Botto et al., 2007). Because maternal pregestational diabetes, multiple gestations, and first-degree family history of CHDs are strong and well-established risk factors for CHDs (Jenkins et al., 2007), we excluded all cases and controls with these characteristics. CHDs were analyzed by specific subtype when at least 50 cases were available for analysis.

PAH Exposure Assessment

The NBDPS CATI includes occupation-related questions for jobs held for at least 1 month during the period from the 3 months before conception through the end of pregnancy. Information collected includes job title, name of company or organization, service provided or product made by the company, main activities or duties, and machines used. Mothers reported month and year for start and stop date of each job, as well as days per week and hours per day worked. Each job was coded for occupation and industry using the Standard Occupational Classification System (SOC; 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).

Expert industrial hygienists reviewed all jobs of mothers who reported any employment to estimate potential exposure to PAHs. This expert review strategy was based on an approach previously developed and used in the Baltimore-Washington Infant Study (Jackson et al., 2004) and described previously (Langlois et al., 2012). Specifically, as part of the NBDPS occupational exposure assessment, industrial hygienists involved in the project participated in a training session before reviewing the job histories. During training, the industrial hygienists were given definitions of the exposure variables (e.g., exposure to any PAH in each job) and a sample set of 100 jobs. Each industrial hygienist independently rated the 100 jobs, then all industrial hygienists worked together to examine the rationale and assumptions behind their rating decisions, including discussing mechanisms of exposure and modifying factors. This process was intended to help the industrial hygienists calibrate their ratings. After training was complete, two industrial hygienists, working independently and blinded to case-control status, reviewed occupational data reported during the CATI (both job title and work-related activities) to determine a dichotomous (yes or no) rating of potential occupational exposure to PAHs for each job. Discrepancies between the two industrial hygienists were resolved by a consensus conference that involved the original two industrial hygienists plus a third (Rocheleau et al., 2011). During the consensus conference, industrial hygienists discussed each discrepant rating until all three agreed. If they could not come to agreement through discussion, they reviewed the literature to inform further discussion until agreement was reached (Rocheleau et al., 2011).

For this analysis, we focused on potential exposures during the critical time window for the development of CHDs (i.e., the month before conception through the third month of pregnancy; Selevan et al., 2000). Therefore, a woman was classified as exposed if she had one or more jobs that were rated as exposed during this critical window, and she was classified as unexposed if all of her jobs were rated as unexposed during this same window.

Covariates

Data for maternal characteristics that are generally accepted or suspected to be associated with CHD risk were obtained from the CATI and included: infant sex (male or female), maternal age at delivery (<20, 20–34, ≥35 years); maternal race or ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or other); maternal education (<12, 12, 13–15, ≥16 years); parity (0 or ≥1 previous births); gestational diabetes (yes or no); maternal use of supplements containing folic acid in the month before conception through the third month of pregnancy (yes or no); maternal alcohol use in the month before conception through the third month of pregnancy (yes or no); maternal smoking in the month before conception through the third month of pregnancy (nonsmoker, light [<15 cigarettes per day], moderate [15–24 cigarettes per day] or heavy [≥25 cigarettes per day]); secondhand smoke at home in the month before conception through the third month of pregnancy (yes or no); secondhand smoke at work in the month before conception through the third month of pregnancy (yes or no); and maternal pre-pregnancy BMI. Maternal pre-pregnancy BMI (kg/m^2) was categorized according to the National Heart, Lung and Blood Institute cutoff points as follows: underweight (<18.5 kg/m^2), average weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (≥30.0 kg/m^2). To account for potential dietary sources of PAHs (Boers et al., 2005), data on meat consumption (none or less than once a month, one to three times a month, four times a month, or more than four times a month) during the year preceding the pregnancy of interest was obtained from a modified Willett Food Frequency Questionnaire (58 food items) administered during the NBDPS CATI (Willett et al., 1987). For meat consumption, women were asked whether they ate beef, pork, lamb, or cabrito as a main dish and how often they ate these items on average during the year before they became pregnant.

Statistical Analysis

Frequency distributions of maternal demographic and behavioral factors were tabulated for case and control infants. Chi-square tests were used to identify factors that were significantly different ($p < 0.05$) between case and control infants. Frequency distributions of the SOC major job groups (n = 23) were tabulated for mothers of cases and controls, stratified by occupational PAH exposure status. In addition, we used the Student's *t* test to assess differences in mean time to interview for case and control mothers, as well as exposed and unexposed mothers, because the time lapse between estimated date of delivery and interview ranged from 6 weeks to 2 years. This was done to evaluate the potential of recall bias owing to differences in time to interview.

Unconditional logistic regression was used to calculate crude and adjusted odds ratios (AORs) and 95% confidence intervals (CIs) to estimate the association between maternal occupational exposure to PAHs and the odds of CHDs (as a group and by phenotypic subtype) in offspring. Based on previous studies, we included maternal age, race or ethnicity, education, smoking, folic acid supplementation, and study center in all models (Correa et al., 2008; Gilboa et al., 2010; Lupo et al., 2012). In addition, we incorporated variables as confounders in the final models if inclusion resulted in a 10% or greater change in the estimate of effect between maternal occupational exposure to PAHs and each of the

CHD subtypes assessed. All analyses were conducted using Intercooled Stata, version 10.1 (StataCorp LP, College Station, TX).

RESULTS

Participation in the NBDPS was 71% among mothers of cases and 69% among control mothers. Of the 4693 CHD case mothers and 4116 control mothers included in the NBDPS for the period 1997 to 2002, 72% (n = 3339 CHD case mothers; n = 2993 control mothers) were employed for at least 1 month during the critical window of exposure (the remaining 28% reported no job during the critical window and were not included in this analysis as to limit our inferences to women who were specifically employed during the critical period of development). CHD cases with defects designated as “associations” (n = 589) or complex (n = 224) were not included. In addition, CHD cases with extracardiac defects (n = 561) were not included. Finally, exclusions for CHD case and control infants were based on maternal pregestational diabetes (n = 104 CHD cases; n = 15 controls), multiple gestations (n = 237 CHD cases; n = 95 controls), and first-degree family history of CHDs (n = 121 CHD cases; n = 31 controls). After exclusions, there were 1907 CHD case infants and 2853 control infants eligible.

Selected maternal characteristics are summarized by case-control status in Table 1. The distribution among the smoking categories and BMI categories were different among CHD case and control mothers. In addition, CHD case mothers were more likely to have gestational diabetes compared to control mothers. There was no significant difference in the average time to interview between case and control mothers (11.3 vs. 10.3 months; $p = 0.32$) or between PAH-exposed and unexposed mothers (11.3 vs. 11.4 months; $p = 0.67$).

Table 2 displays the number of jobs linked to the 23 SOC major job groups for mothers of cases and controls stratified by exposure status. Jobs in the SOC job group “Food Preparation and Serving Related” were the most frequent jobs among exposed case mothers (n = 32 of 74 individual jobs held by exposed case mothers during the critical window), followed by “Sales and Related Occupations” (n = 25). Similarly, the most common jobs among exposed control mothers were in “Food Preparation and Serving Related Occupations” (n = 47 of 101 individual jobs), followed by “Sales and Related Occupations” (n = 28). Some jobs could not be linked to the SOC major job groups and are not represented in Table 2.

Overall, the prevalence of occupational PAH exposure was 4.0% in CHD case mothers (76/1907) and 3.6% in control mothers (104/2853). In adjusted analyses (Table 3), there were nonsignificant positive associations between estimated maternal occupational PAH exposure and various CHD phenotypic subtypes ranging from an AOR of 1.19 (95% CI, 0.68–2.10) for perimembranous ventricular septal defects to an AOR of 1.84 (95% CI, 0.72–4.68) for muscular ventricular septal defects. Also, nonsignificant negative associations were seen for right ventricular outflow tract defects (AOR, 0.54; 95% CI,: 0.23–1.24) and pulmonary valve stenosis (AOR, 0.51; 95% CI, 0.19–1.42).

DISCUSSION

Our analyses did not indicate that estimated maternal occupational exposures to PAHs were associated with risk of phenotypic subgroupings of CHDs. There were suggestions of slight positive and negative associations with some CHD phenotypic subtypes; however, these associations were imprecise and not statistically significant ($p > 0.05$ for all associations).

Our previous research in the NBDPS indicated that estimated maternal occupational exposure to PAHs was associated with gastroschisis (AOR, 1.75; 95% CI, 1.05–2.92; Lupo et al., 2012). In addition, there have been two studies in China reporting an association between PAHs and neural tube defects (Naufal et al., 2010; Ren et al., 2011). Because PAHs are lipophilic, they readily penetrate cellular membranes (including the placenta; Agency for Toxic Substances and Disease Registry, 1995). During PAH metabolism, enzymatic activity can result in the formation of reactive intermediates that covalently bind to DNA, forming adducts. DNA adducts have been shown to result in a spectrum of cellular mutations that may be teratogenic (Wells et al., 2010). Although exposure to PAHs in developing fish results in CHDs (Clark et al., 2010; Farwell et al., 2006; Incardona et al., 2004; Wassenberg and Di Giulio, 2004; Wassenberg et al., 2005), our results did not support this association in humans. If PAHs do contribute to the risk of human malformations, it is possible that their effects may be specific to certain organ systems; associations may be stronger for certain types of birth defects (e.g., gastroschisis, neural tube defects) compared to CHDs. In addition, timing, dose, and route may be critical in relation to disease etiology.

Our findings must be considered in the light of certain limitations. The main limitation is related to the occupational exposure assessment. Although our approach relied on expert industrial hygienist consensus, there is still a potential for misclassification when assigning exposure based on questionnaire responses about jobs. However, our approach is superior to a strategy that relies solely on maternal self-report of PAH exposure, because knowledge of PAH exposure is likely to be limited (Olsson et al., 2010). Although the use of personal monitoring or biomarkers of exposure would be preferred, these data are typically unavailable in population-based studies of birth defects (Yoon et al., 2001). In addition, as PAHs are lipophilic, exposure that occurred before the 3 months preceding conception may be important; however, this information is not collected as part of the NDBPS. The absence of information on environmental sources of PAHs is also a potential limitation, but occupational exposures are generally higher than those found in the environment (Brandt and Watson, 2003). We also evaluated and took into account potential confounding by direct and secondhand smoke and meat consumption, which are important sources of environmental PAHs (Boers et al., 2005; Hansen et al., 2008). However, given that such assessment was based on interview data subject to misclassification error, residual confounding remains a potential source of bias for possible associations.

Strengths of this study include the use of data from the NBDPS, the largest population-based case-control study exploring risk factors for birth defects; it has an extensive occupational PAH exposure assessment available for study participants from 1997 to 2002. As part of the NBDPS, we also had information on potentially important confounding factors such as maternal nutrition, pre-pregnancy BMI, and smoking. In addition, the case classification

undertaken by NBDPS pediatric cardiologists and clinical geneticists to exclude cases owing to single gene disorders or chromosomal abnormalities resulted in more homogeneous CHD case groups compared with studies that do not use similar criteria.

To our knowledge, this is the first study evaluating the association between maternal occupational exposure to PAHs and CHDs. We observed small positive associations with some CHD phenotypic subtypes, although effect measure estimates were generally imprecise. Future investigations could be improved by working with larger sample sizes in populations with higher potential for PAH exposure and by incorporating information on maternal and fetal genotypes related to PAH metabolism, because ongoing research suggests that genetic susceptibility in combination with environmental exposures predisposes individuals to the greatest risk (Whyatt et al., 1998; Wassenberg and Di Giulio, 2004; Wassenberg et al., 2005; Shimada, 2006; Sanyal and Li, 2007).

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Table 1

Maternal Demographic and Behavioral Factors among Congenital Heart Defect Cases and Controls, National Birth Defects Prevention Study, 1997–2002[a]

	CHD cases (n = 1907)		Controls (n = 2853)	
	n	%	n	%
Infant sex[b]				
Male	1036	54.4	1422	49.9
Female	868	45.6	1429	50.1
Maternal age (years)				
<20	147	7.7	235	8.2
20–34	1455	76.3	2208	77.4
≥35	305	16.0	410	14.4
Race/ethnicity				
Non-Hispanic White	1246	65.4	1838	64.6
Non-Hispanic Black	256	13.4	357	12.5
Hispanic	319	16.7	513	18.0
Other	85	4.5	138	4.9
Education (years)				
<12	213	11.2	290	10.2
12	521	27.4	714	25.1
13–15	550	28.9	858	30.1
≥16	620	32.5	986	34.6
Body mass index (kg/m^2)[b]				
Underweight (<18.5)	94	5.0	149	5.3
Normal weight (18.5–24.9)	995	53.3	1594	57.1
Overweight (25–29.9)	435	23.3	638	22.8
Obese (≥30)	343	18.4	413	14.8
Parity				
0	845	44.4	1261	44.2
≥1	1060	55.6	1591	55.8
Gestational diabetes[b]				
No	1754	94.0	2691	96.1
Yes	113	6.0	110	3.9
Folic acid supplement use[c]				
No	927	48.6	1352	47.4
Yes	980	51.4	1501	52.6
Alcohol use[c]				
No	1100	58.1	1586	55.8
Yes	792	41.9	1256	44.2
Smoking[b,c]				
Nonsmoker	1474	77.3	2260	79.2

	CHD cases (n = 1907)		Controls (n = 2853)	
	n	%	n	%
Light (<15 cigarettes per day)	297	15.6	408	14.3
Moderate (15–24 cigarettes per day)	97	5.1	152	5.3
Heavy (≥25 cigarettes per day)	39	2.0	33	1.2
Secondhand smoke at home[C]				
No	1543	81.0	2338	82.0
Yes	363	19.0	513	18.0
Secondhand smoke at work[C]				
No	1515	79.5	2297	80.78
Yes	390	20.5	547	19.2
Meat consumption				
None or less than once per month	270	14.2	391	13.7
One to three times per month	523	27.4	714	25.1
Four times per month	550	28.9	843	29.6
More than four times per month	563	29.5	899	31.6

[a] Excluded nonworking mothers, associated and complex CHDs, infants with extracardiac defects (i.e., multiple defects), maternal pregestational diabetes, multiple gestations, and first-degree family history of CHDs.

[b] Chi-square test: $p < 0.05$.

[c] One month before pregnancy through the third month of pregnancy.

CHD, congenital heart defect.

Table 2

Maternal Jobs Linked to Standard Occupation Code Major Job Groups (n = 23) for Mothers[a] of Congenital Heart Defect Cases and Controls by Polycyclic Aromatic Hydrocarbon Exposure Status, National Birth Defects Prevention Study, 1997–2002

	Cases		Controls	
	Exposed	Unexposed	Exposed	Unexposed
Standard occupation code major group	**n**	**n**	**n**	**n**
Management	0	180	3	286
Business and financial operations	0	76	0	132
Computer and mathematical	0	28	1	45
Architecture and engineering	0	17	1	11
Life, physical, and social science	0	15	0	34
Community and social services	0	35	1	61
Legal	0	31	0	29
Education, training, and library	0	144	1	250
Arts, design, entertainment, sports and media	1	37	0	37
Health care practitioners and technical	0	129	0	220
Health care support	3	98	2	137
Protective service	0	13	0	24
Food preparation and serving related	32	116	47	186
Building and grounds cleaning and maintenance	0	48	1	64
Personal care and service	3	66	7	118
Sales and related	25	223	28	322
Office and administrative support	1	420	0	553
Farming, fishing, and forestry	0	13	1	43
Construction and extraction	1	3	0	4
Installation, maintenance, and repair	1	3	1	4
Production	5	89	5	117
Transportation and material moving	2	37	2	52
Military specific	0	0	0	3

[a]Individuals may be represented twice if multiple jobs were held during the critical window of exposure (i.e., 1 month before pregnancy through the third month of pregnancy). Some jobs were not linked to the standard occupation code major job groups.

Table 3

Crude and Adjusted Associations between Maternal Occupational Exposure to Industrial Polycyclic Aromatic Hydrocarbons and the Risk of Congential Heart Defects in Offspring, National Birth Defects Prevention Study, 1997–2002

CHD subgroup	Total n	Exposed n	Crude OR	95% CI	Adjusted OR[a]	95% CI
Controls	2853	104				
Conotruncal defects	450	17	1.04	0.62–1.75	0.98	0.58–1.67
Tetralogy of Fallot	231	13	1.59	0.87–2.85	1.56	0.85–2.86
Left ventricular outflow tract defects	318	15	1.31	0.75–2.28	1.31	0.74–2.30
Hypoplastic left heart syndrome	136	7	1.43	0.65–3.15	1.30	0.58–2.90
Coarctation of the aorta	116	6	1.44	0.62–3.36	1.66	0.70–3.93
Right ventricular outflow tract defects	315	6	0.52	0.23–1.19	0.54	0.23–1.24
Pulmonary valve stenosis[b]	220	4	0.49	0.18–1.34	0.51	0.19–1.42
Septal defects	725	35	1.34	0.91–1.98	1.28	0.86–1.90
Ventricular septal defect, perimembranous	327	15	1.27	0.73–2.21	1.19	0.68–2.10
Ventricular septal defect, muscular[b]	104	7	1.95	0.79–4.79	1.84	0.72–4.68
Atrial septal defect, secundum	205	11	1.50	0.79–2.84	1.39	0.72–2.66

[a] Adjusted for maternal age, race or ethnicity, education, smoking, folic acid supplementation, and study center (no other variables met the criteria to be included as confounders).

[b] Total controls for these subgroups are different because of differences in ascertainment across study centers. CHD, congenital heart defect; OR, odds ratio; CI, confidence interval.