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Maternal occupational exposure to polycyclic aromatic hydrocarbons and the risk of isolated congenital heart defects among offspring

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ABSTRACT

Background: Although there is evidence in experimental model systems that exposure to polycyclic aromatic hydrocarbons (PAHs) is linked with congenital heart defects (CHDs), few studies have examined the association in humans. We conducted a case-control study to examine the association between maternal exposure to PAHs and CHDs in offspring using data from the National Birth Defects Prevention Study (NBDPS) (1997–2011).
Methods: We obtained detailed information on maternal occupation during the month before to three months after conception. Expert raters, masked to case-control status, assessed job descriptions to assign categorical levels of exposure. Categories were quantitatively mapped to estimate cumulative exposure to PAHs, incorporating exposure intensity, frequency, work duration, and work hours. Quartiles were generated for cumulative maternal exposure to PAHs. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using unconditional logistic regression for quartiles of PAH exposure and six CHD groupings (e.g. conotruncal) and specific subtypes (e.g. tetralogy of Fallot [ToF]). Final models were adjusted for maternal age, race/ethnicity, education, smoking, anticonvulsant use, folic acid supplementation, and study center.
Results: There were 4,775 case and 7,734 control infants eligible for the study. The prevalence of occupational exposure to PAHs was 10.2% among both case and control mothers. In adjusted analysis, compared to mothers with no occupational PAH exposure, those in the highest quartile of exposure were more likely to have offspring in the conotruncal heart defects group (OR 1.41; 95% CI 1.00–2.00), and with ToF (OR 1.83; 95% CI 1.21–2.78).
Conclusions: Women in the highest quartile of estimated cumulative occupational PAH exposure during early pregnancy were more likely to have offspring with conotruncal heart defects, specifically ToF, compared to women with no occupational PAH exposure. Other comparisons between PAHs and other CHDs subgroups did not show any statistically precise associations.

1. Introduction

Congenital heart defects (CHDs) are a commonly occurring group of malformations with a birth prevalence of 1 per 100 live births in the United States (US), impacting pediatric morbidity and mortality (Botto et al., 2007; Moller et al., 1993; Christianson et al., 2006). Although some CHDs occur in association with certain genetic syndromes (e.g., trisomy 21, 22q11 deletion, Alagille syndrome, Noonan syndrome) and

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teratogenic exposures (e.g., anticonvulsants, maternal pregestational diabetes), approximately 80% are of unknown etiology (Christianson et al., 2006; Jenkins et al., 2007; Caton et al., 2009). While environmental and occupational factors have been suggested as potential risk factors for CHDs, the evidence is still incomplete (Jenkins et al., 2007).

One group of contaminants found in the environment and workplace that is hypothesized to be associated with adverse birth outcomes is polycyclic aromatic hydrocarbons (PAHs) (Perera et al., 1998). The primary sources of exposure to PAHs for most of the US population include tobacco smoke, wood smoke, ambient air pollution (e.g. vehicle exhaust, coal combustion), as well as consumption of charbroiled foods (Mumtaz and George, 1995). PAHs are suspected teratogens because of their ability to readily penetrate cellular membranes, including the embryonic and fetal blood-brain barrier, resulting in increased oxidative stress and DNA damage (Huang et al., 2013; Hanzalova et al., 2010; Patri et al., 2010; Anwer and Mehrotra, 1988). A variety of birth outcomes and anomalies, including CHDs, have been reported following PAH exposure in experimental animal model systems (Anwer and Mehrotra, 1988; Barbieri et al., 1986; Farwell et al., 2006; Incardona et al., 2004; Sestak et al., 2018; Ng et al., 2009). Additionally, recent studies in humans suggest maternal occupational and environmental exposure to PAHs is associated with other structural birth defects such as neural tube defects and gastroschisis (Lupo et al., 2012a; Naufal et al., 2010; Ren et al., 2011). While there is evidence in a few human studies that PAHs are associated with CHDs, these studies have largely been limited by sample size, inability to evaluate specific subtypes, and non-specific PAH exposure assessment (Li et al., 2018; Lupo et al., 2012b).

The National Birth Defects Prevention Study (NBDPS) is the largest population-based case-control study of birth defects and provides a unique opportunity to examine the association between maternal PAH exposure and birth defects. With the goal to update a previous NBDPS study on PAH exposure and CHDs from 1997 to 2002 (Lupo et al., 2012b), we conducted an investigation of the overall association and potential dose-response relationship between PAH exposure and CHDs using NBDPS data from 1997 through 2011.

2. Materials and methods

2.1. Study participants

The study population included CHD case and non-malformed control infants born to working pregnant women from the NBDPS, with estimated dates of delivery from October 1, 1997 through December 31, 2011. NBDPS cases were identified from ten birth defects surveillance systems throughout the US: Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, Texas, North Carolina, and Utah (Reefhuis et al., 2015; 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 within each surveillance system that gave rise to the cases. All states included live-born infants as cases and controls; most states also included stillbirths and elective terminations (details described elsewhere) (Reefhuis et al., 2015). Mothers of cases and controls completed an approximately 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, approved the NBDPS; all participants provided informed consent.

2.2. Classification of CHDs

Following detailed NBDPS case record review by clinical geneticists, those with recognized or strongly suspected single-gene conditions or chromosome abnormalities were excluded. All CHD cases were confirmed by echocardiography, cardiac catheterization, surgery, or autopsy (Botto et al., 2007; Rasmussen et al., 2003), and their diagnostic information was reviewed by a team of clinicians with expertise in pediatric cardiology and clinical genetics for classification on two axes. In addition to assigning a diagnostic code for each cardiac defect present, the pattern of heart defects was also classified as: 1) simple cardiac defects (anatomically discrete or a well-recognized single entity e.g. hypoplastic left heart syndrome, tetralogy of Fallot); 2) associations (common combinations of two cardiac defects e.g. ventricular septal defect, pulmonary valve stenosis); and 3) complex (cases that included three or more distinct CHDs) (Botto et al., 2007). The infant was also classified as having isolated CHD (no major extracardiac defects) or multiple CHD (infants with both a cardiac defect and one or more structural defects outside the heart) (Botto et al., 2007; Rasmussen et al., 2003). Clinical reviewers determined the specific CHD subtypes of every case according to rigorous guidelines (Botto et al., 2007).

2.3. Inclusion and exclusion criteria

To assess associations in relatively homogeneous case groups, we included only case infants with simple and isolated CHDs (a single congenital heart defect without presence of any other structural defects) (Botto et al., 2007). Because maternal pregestational diabetes, multi-fetal gestations, and first-degree family history of CHDs are strong and well-established risk factors for CHDs, and to be consistent with the previous assessment (Jenkins et al., 2007), we excluded all cases and controls with these characteristics. CHDs were analyzed by specific subtype when at least 100 cases were available for analysis. The analysis was restricted to the critical time window for the development of CHDs (i.e., the month before conception through the third month of pregnancy).

2.4. PAH exposure assessment

Case and control mothers completed a 1-hour CATI that included occupation-related questions for jobs held for at least one month during the period from the 3 months before conception through the end of pregnancy. Information collected included a narrative description of the job title, name of company or organization, service provided or product made by the company, the job's main activities or duties, and machines/equipment/chemicals used. Mothers reported month and year for start and stop dates of each job, as well as days per week and hours per day worked. All jobs were classified based on the Standard Occupational Classification System (SOC) and North American Industry Classification System (NAICS). (United States Department, 2000).

The PAH exposure assessment strategy has been previously described (Rocheleau et al., 2011). Expert industrial hygienists reviewed each narrative job description to estimate potential exposure to PAHs. This expert review strategy was based on an approach described previously (Lupo et al., 2012a, 2012b; Jackson et al., 2004). The expert raters conducting the exposure assessment were all industrial hygienists who first reviewed the published and grey literature, including Occupational Safety and Health Administration (OSHA) and National Institute for Occupational Safety and Health (NIOSH) data from measurements taken in workplaces. A series of tables summarizing exposure measurements for specific tasks and jobs were created to help guide raters in their assignments. Each job was independently assigned PAH exposure metrics by two raters who were masked to case-control status, and any discrepancies were resolved by a consensus conference with a third industrial hygienist. Exposure assessment was conducted in two batches many years apart (1997–2002 and 2003–2011), but both

assessments followed the same process; to assure comparability between the ratings, in the second exposure assessment training also included re-rating and discussing 200 jobs from the first exposure assessment (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 time window, and she was classified as unexposed if all of her jobs were rated as unexposed during this same window.

Data for characteristics that are generally accepted or suspected to be associated with CHDs were obtained from the CATI and included: infant sex (male or female), maternal age at delivery (< 20, 20–34, ≥35 years); maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other); maternal education (< 12, 12, 13–15, ≥16 years); parity (0 or ≥1 previous births); maternal 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 cigarette 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); use of anticonvulsants (yes or no); and maternal pre-pregnancy body mass index (BMI). Maternal pre-pregnancy BMI 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 were 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 (adult goat meat)as a main dish and how often they ate these items on average during the year before they became pregnant.

2.5. 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. Quartiles were generated for cumulative PAH exposure levels among exposed controls.

PAH intensity scores were also quantitatively mapped to an estimated intensity level by the experts. Cumulative exposure, as unit-hours, was estimated by: (weighted intensity in mg/hr) × ((self-reported work frequency in hours per week)/(7 days/week)) × (job duration (days employed in the job) during the one month before through three months after conception), where weighted typical intensity levels was calculated as: (fraction of time direct × intensity level direct) + (fraction of time indirect × intensity level indirect) (Rocheleau et al., 2011). Detailed information on the calculation of cumulative PAHs is mentioned elsewhere (Rocheleau et al., 2011). Unconditional logistic regression was used to calculate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) to estimate the association between each quartile of maternal occupational exposure to PAHs and the odds of CHDs (as a group and by subtype) in offspring, with no exposure as the reference group. Based on previous studies, we included maternal age, race and ethnicity, education, maternal cigarette smoking, anticonvulsant use, folic acid supplementation, and study center as final covariates in all models (Lupo et al., 2012a, 2012b; Correa et al., 2008; Gilboa et al., 2010). We evaluated additional covariates for inclusion in the final model with the criteria that inclusion must have resulted in a 10% or greater change in the OR between PAH exposure and the CHD subtype. Finally, we conducted log linear likelihood ratio test for trend in the multivariable models to assess the linear trends between cumulative exposure categories and each CHD subtype.

Since the initial published study on NBDPS used data from 1997 to 2002, we also conducted a secondary analysis to compare the exposure to PAHs (coded as dichotomous yes/no variable for job exposed to PAHs) and risk of CHDs groups and subtype across different time periods (1997–2002, 2003–2011 and 1997–2011). Furthermore, an analysis to assess interaction for relevant covariates in the primary association such as BMI was also conducted. All analyses were conducted using STATA 15 (Stata Statistical Software, 2019).

3. Results

Of the 12,584 CHD case mothers and 11,829 control mothers included in the NBDPS for the period 1997 through 2011, 69% (8,644 case mothers; 8,140 control mothers) were employed for at least 1 month during the critical window of exposure (the remaining 31% mothers 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).

Exclusions for CHD case and control infants were based on maternal pregestational diabetes (n = 298), multi-fetal gestations (n = 834), and first-degree family history of CHDs (n = 410). Furthermore, CHD cases with extracardiac defects (multiple or complex) (n = 1,204); CHD cases with defects designated as “association” (n = 1,281); and “complex” CHDs (n = 1,204) were not included because of smaller sample sizes and to maintain homogenous case groups. After exclusions, there were 4,775 CHD case infants and 7,734 control infants eligible for analyses.

Table 1 displays selected characteristics summarized by case-control status. There were significant differences in the distributions of infant sex (45% females in cases and 49% females in controls), maternal education (38.9% case mothers vs. 41.3% controls had ≥16 years education), BMI (20.3% case mothers vs. 18.1% control mothers were ≥30 kg/m^2 [obese]), and alcohol use (40.2% case mothers vs. 42.4% control mothers). CHD case mothers were also more likely to have gestational diabetes and report exposure to secondhand smoke at home and work than control mothers. The overall prevalence of PAHs exposure was 10.2% among case mothers and 10.2% among control mothers.

Table 2 displays the number of jobs linked to the 23 SOC major job groups for mothers of cases and controls by exposure status. The most frequent jobs in which case mothers were exposed during the critical window of development were reported in “Food Preparation and Serving Related” (n = 299 cases; n = 517 controls) and “Sales and Related Occupations” (n = 65 cases; n = 83 controls). Some jobs could not be coded to a single SOC major job group and are not represented in Table 2 (n = 3).

Tables 3 and 4 show crude and adjusted associations between quartiles of cumulative PAH exposure and risk of CHDs among case and control mothers respectively. The quartiles were classified as Q1 (0.04–7.2 $\mu g/m^3$-hr), Q2 (7.54–51.43 $\mu g/m^3$-hr), Q3 (52.11–218.06 $\mu g/m^3$-hr), and Q4 (≥219.43 $\mu g/m^3$-hrs). In unadjusted analysis (Table 3), exposure to cumulative PAHs in fourth quartile (Q4) was positively associated with conotruncal heart defects as group (OR 1.43; 95% CI 1.02–2.00), tetralogy of Fallot (ToF) (OR 1.81; 95% CI 1.21–2.72), and

Table 1
Maternal demographic and behavioral factors among congenital heart defect cases and unaffected controls, national birth defects prevention study, 1997–2011[a,b].

		CHD Cases		Controls		*Chi-Square p-value*
		n = 4775		*n = 7734*		
		n	*%*	*n*	*%*	
Infant Sex	Male	2620	54.94	3940	50.96	< 0.001
	Female	2149	45.06	3791	49.04	
Maternal Age	< 20	313	6.55	545	7.05	0.13
	20–34	3719	77.88	6077	78.58	
	≥35	743	15.56	1112	14.38	
Maternal Race/Ethnicity	Non-Hispanic White	3047	63.81	4878	63.07	0.34
	Non-Hispanic Black	582	12.19	899	11.62	
	Hispanic	845	17.7	1461	18.89	
	Other	301	6.3	496	6.41	
Maternal Education (years)	< 12 years	527	11.04	776	10.04	0.04
	12 years	1161	24.32	1799	23.27	
	13–15 years	1224	25.64	1956	25.3	
	≥16 years	1856	38.93	3190	41.32	
Maternal Body Mass Index (kg/m2)	Underweight (< 18.5)	208	4.46	360	4.76	< 0.001
	Normal (18.5–24.9)	2389	51.23	4088	54.05	
	Overweight (25–29.9)	1120	24.02	1748	23.11	
	Obese (≥30)	946	20.29	1368	18.09	
Parity	0	2135	44.71	3498	45.23	0.57
	≥1	2640	55.29	4236	54.77	
Gestational Diabetes	No	4336	93.93	7206	95.49	< 0.001
	Yes	280	6.07	340	4.51	
Periconceptional Folic Acid Supplement Use	No	2142	44.86	3450	44.61	0.79
	Yes	2633	55.14	4283	55.39	
Periconceptional Maternal Alcohol Use	No	2841	59.77	4438	57.56	0.02
	Yes	1912	40.23	3272	42.44	
Maternal Prenatal Anticonvulsant Use	No	4720	98.89	7666	99.13	0.17
	Yes	53	1.11	67	0.87	
Maternal Prenatal Cigarette Smoking	Non Smoker	3809	79.85	6268	81.15	0.06
	Light (< 15 cigs/day)	695	14.57	1049	13.58	
	Moderate(15–24 cigs/day)	211	4.42	347	4.49	
	Heavy (≥25 cigs/day)	55	1.15	60	0.78	
Secondhand Smoke at Home	No	4069	85.27	6711	86.83	0.01
	Yes	703	14.73	1018	13.17	
Secondhand Smoke at Work	No	3901	81.85	6463	83.77	0.01
	Yes	865	18.15	1252	16.23	
Maternal Meat Consumption	None or less than once per month	939	19.91	1559	20.58	0.07
	One to three times per month	1318	27.95	2205	29.11	
	Four times per month	1072	22.73	1749	23.09	
	More than four times per month	1387	29.41	2062	27.22	
Maternal Exposure to PAHs	No	4287	89.78	6944	89.79	0.99
	Yes	488	10.22	790	10.21	

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

atrial septal defects (secundum) (OR 1.56; 95% CI 1.03–2.37). After adjusting for potential confounders (Table 4), the associations remained significant for conotruncal heart defects as a group (OR 1.41; 95% CI 1.00–2.00) and ToF specifically (OR 1.83; 95% CI 1.21–2.78). While not statistically significant, there was a decreasing pattern of risk of right ventricular outflow tract obstruction defects (RVOTO) with increasing exposure (OR 1.19; 95% CI 0.78–1.81 in Q1 vs. OR 0.64: 95% CI 0.37–1.12 in Q4). We did not observe significant linear trends for any of the CHDs subgroups or subtypes.

Supplemental Table S1 shows comparison of adjusted odds ratio for associations between maternal occupational exposure to PAHs (yes/no) and CHDs by three time-periods (1997–2002, 2003–2011, 1997–2011). While there were some effect estimates that changed direction or magnitude, overall these differences did not represent a consistent trend.

4. Discussion

We found little evidence that PAHs were strongly associated with CHDs overall or with selected subtypes in this study, which is one of the largest population studies conducted to date. However, our findings suggest that higher estimated exposure levels (≥219.43 μg/m^3-hr) were positively associated with conotruncal heart defects, largely driven by the association with ToF. Overall, these conclusions are consistent with an earlier and smaller subset of data from the NBDPS (Lupo et al., 2012b).

While we observed a positive association with one group of CHDs, results from our current study and the previous NBDPS assessment are partially consistent to other studies published in literature. For instance, a recent study by Li and colleagues from China that explored the association of maternal exposure to PAHs and CHDs among 627 infants found significant positive associations between maternal exposure to PAHs and some CHD subtypes including septal defects (OR 2.37, 95% CI: 1.38–4.09), right-sided obstructive malformations (OR 2.42, 95% CI: 1.19–4.93), and left-sided obstructive malformations (OR 2.66, 95% CI: 1.08–6.52), along with conotruncal heart defects (OR 2.35, 95% CI: 1.25–4.42) (Li et al., 2018). The study, however, used a different cut-off point for assessing PAHs exposure in form of a PAH metabolite, 1-Hydroxypyrene-glucuronide, using Youden's Index. This might account for differences in observed risk across in the current study, in addition to

Table 2
Maternal jobs linked to standard occupation code (SOC) major job groups (n = 23) for mothers of congenital heart defect cases and unaffected controls by estimated polycyclic aromatic hydrocarbons exposure status, national birth defects prevention study, 1997–2011[a].

SOC Groups	CHD Cases		Controls	
	n = 5519		*n = 9121*	
	Exposed	Unexposed	Exposed	Unexposed
11-0000 Management Occupations	7	309	18	500
13-0000 Business and Financial Operations Occupations	1	226	1	341
15-0000 Computer and Mathematical Occupations	1	69	0	127
17-0000 Architecture and Engineering Occupations	1	29	6	32
19-0000 Life, Physical, and Social Science Occupations	1	47	2	133
21-0000 Community and Social Service Occupations	0	112	0	209
23-0000 Legal Occupations	0	70	0	90
25-0000 Educational Instruction and Library Occupations	1	460	1	878
27-0000 Arts, Design, Entertainment, Sports, and Media Occupations	1	107	2	193
29-0000 Healthcare Practitioners and Technical Occupations	0	431	1	749
31-0000 Healthcare Support Occupations	1	284	1	434
33-0000 Protective Service Occupations	3	38	6	71
35-0000 Food Preparation and Serving Related Occupations	299	228	517	385
37-0000 Building and Grounds Cleaning and Maintenance Occupations	15	181	14	248
39-0000 Personal Care and Service Occupations	10	343	11	565
41-0000 Sales and Related Occupations	65	616	83	1045
43-0000 Office and Administrative Support Occupations	20	1078	26	1691
45-0000 Farming, Fishing, and Forestry Occupations	5	63	18	112
47-0000 Construction and Extraction Occupations	4	10	3	25
49-0000 Installation, Maintenance, and Repair Occupations	7	14	4	10
51-0000 Production Occupations	35	209	55	314
53-0000 Transportation and Material Moving Occupations	21	92	51	142
55-0000 Military Specific Occupations	0	3	1	5

[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 (n = 3) were not linked to standard occupation code major job groups.

Table 3
Crude association between cumulative maternal occupational exposure to polycyclic aromatic hydrocarbons and risk of congenital heart defects in offspring, national birth defects prevention study, 1997–2011 - dose-response analysis by Quartiles(Q1-Q4)[a].

CHD Subgroup	Total	Exposed	Crude OR (95%CI)			
			Q1	Q2	Q3	Q4
	N	N	0.04–7.53 μg/m^3-hr OR (95%CI)	7.54–52.10 μg/m^3-hr OR (95%CI)	52.11–219.42 μg/m^3-hr OR (95%CI)	219.43–8861.1 μg/m^3-hr OR (95%CI)
Controls	*6944*	*790*				
Conotruncal	1153	115	0.88 (0.58–1.33)	0.74 (0.47–1.15)	0.86 (0.57–1.31)	**1.43 (1.02–2.00)**[e]
Tetralogy of Fallot	615	70	0.97 (0.57–1.64)	0.70 (0.38–1.29)	1.05 (0.63–1.76)	**1.81 (1.21–2.72)**[e]
d-Transposition of great arteries	380	30	0.90 (0.46–1.77)	0.79 (0.39–1.62)	0.41 (0.15–1.11)	0.91 (0.46–1.78)
Atrioventricular Septal Defects	121	7	0.62 (0.15–2.51)	0.30 (0.04–2.19)	0.63 (0.15–2.56)	0.62 (0.15–2.52)
Anomalous Pulmonary Venous Return	173	22	0.70 (0.22–2.20)	1.15 (0.47–2.83)	1.90 (0.92–3.92)	1.40 (0.61–3.21)
TAPVR[b]	154	20	0.79 (0.25–2.49)	1.30 (0.52–3.20)	1.87 (0.86–4.05)	1.32 (0.53–3.25)
LVOTO[c]	839	95	1.05 (0.69–1.59)	0.79 (0.49–1.27)	1.02 (0.67–1.57)	1.13 (0.75–1.71)
Hypoplastic Left Heart Syndrome	358	34	0.65 (0.29–1.47)	0.75 (0.35–1.61)	1.22 (0.66–2.25)	1.09 (0.57–2.07)
Coarctation of Aorta	343	36	1.03 (0.52–2.03)	0.79 (0.37–1.70)	1.05 (0.53–2.07)	1.26 (0.68–2.34)
Aortic Stenosis	222	24	1.77 (0.92–3.40)	0.88 (0.36–2.15)	0.72 (0.27–1.97)	0.89 (0.36–2.19)
RVOTO[d]	860	91	1.19 (0.78–1.80)	1.13 (0.74–1.72)	1.21 (0.80–1.83)	0.64 (0.37–1.11)
RVOTO (Restricted)	858	91	1.19 (0.78–1.80)	1.13 (0.74–1.73)	1.21 (0.80–1.84)	0.64 (0.37–1.11)
RVOTO (No Ebstein)	795	87	1.24 (0.81–1.89)	1.13 (0.73–1.75)	1.26 (0.83–1.93)	0.70 (0.40–1.21)
Pulmonary Valve Stenosis	639	70	1.30 (0.83–2.04)	0.95 (0.57–1.59)	1.43 (0.92–2.22)	0.54 (0.28–1.07)
Pulmonary Atresia	105	10	1.11 (0.35–3.53)	1.10 (0.34–3.49)	0.75 (0.18–3.08)	0.74 (0.18–3.03)
Septal	1533	158	0.71 (0.48–1.07)	1.11 (0.80–1.55)	0.89 (0..61–1.28)	1.33 (0.98–1.82)
Perimembranous Ventricular Septal Defect	567	56	0.62 (0.31–1.21)	1.02 (0.60–1.74)	0.91 (0.52–1.61)	1.31 (0.81–2.12)
Atrial Septal Defect - Secundum	664	76	0.84 (0.48–1.45)	1.30 (0.83–2.03)	0.85 (0.49–1.48)	**1.56 (1.03–2.37)**[e]
Atrial Septal Defect - Not Otherwise Specified	178	19	1.10 (0.45–2.72)	1.31 (0.57–3.00)	0.90 (0.33–2.45)	0.89 (0.33–2.42)[e]
Atrial Septal Defect - Secundum or Not Otherwise Specified	842	95	0.89 (0.55–1.44)	1.30 (0.87–1.95)	0.86 (0.53–1.41)	1.42 (0.96–2.09)

[a] Total controls for these subgroups are different because of differences in ascertainment across study centers. CHDs, congenital heart defects; OR, odds ratio; [CI], confidence interval.
[b] Total Anomalous Pulmonary Venous Return.
[c] Left Ventricular Outflow Tract Obstructive Defects.
[d] Right Ventricular Outflow Tract Obstructive Defects.
[e] $p < 0.05$.

Table 4
Adjusted association between cumulative maternal occupational exposure to polycyclic aromatic hydrocarbons and risk of congenital heart defects in offspring, national birth defects prevention study, 1997–2011 - dose-response analysis by quartile[a,b].

CHDs Subgroup	Total	Exposed	Adjusted OR (95%CI)			
			Q1	Q2	Q3	Q4
	N	N	0.04–7.53 μg/m^3-hr OR (95%CI)	7.54–52.10 μg/m^3-hr OR (95%CI)	52.11–219.42 μg/m^3-hr OR (95%CI)	219.43–8861.1 μg/m^3-hr OR (95%CI)
Controls	*6944*	*790*				
Conotruncal	1153	115	0.90 (0.60–1.37)	0.68 (0.43–1.09)	0.87 (0.57–1.33)	**1.41 (1.00–2.00)***
Tetralogy of Fallot	70		1.01 (0.59–1.73)	0.66 (0.35–1.26)	1.10 (0.65–1.85)	**1.83 (1.21–2.78)***
d-Transposition of great arteries	380	30	0.91 (0.46–1.79)	0.71 (0.33–1.52)	0.41 (0.15–1.11)	0.92 (0.46–1.84)
Atrioventricular Septal Defects	121	7	0.58 (0.14–2.38)	0.29 (0.04–2.14)	0.61 (0.15–2.53)	0.64 (0.15–2.64)
Anomalous Pulmonary Venous Return	173	22	0.67 (0.21–2.14)	1.08 (0.43–2.69)	1.72 (0.83–3.60)	1.22 (0.53–2.85)
TAPVR[c]	154	20	0.77 (0.24–2.46)	1.23 (0.50–3.08)	1.72 (0.78–3.76)	1.16 (0.46–2.90)
LVOTO[d]	839	95	1.05 (0.69–1.60)	0.85 (0.52–1.37)	1.09 (0.70–1.68)	1.25 (0.83–1.90)
Hypoplastic Left Heart Syndrome	358	34	0.64 (0.28–1.45)	0.77 (0.36–1.67)	1.20 (0.64–2.23)	1.09 (0.57–2.11)
Coarctation of Aorta	343	36	1.06 (0.54–2.10)	0.90 (0.42–1.94)	1.17 (0.59–2.33)	1.49 (0.79–2.81)
Aortic Stenosis	222	24	1.71 (0.88–3.30)	0.95 (0.38–2.36)	0.79 (0.29–2.16)	1.05 (0.42–2.63)
RVOTO[e]	860	91	1.19 (0.78–1.81)	1.14 (0.74–1.74)	1.20 (0.79–1.83)	0.64 (0.37–1.12)
RVOTO (Restricted)	858	91	1.19 (0.79–1.81)	1.14 (0.74–1.74)	1.21 (0.79–1.84)	0.64 (0.37–1.12)
RVOTO (No Ebstein)	795	87	1.25 (0.82–1.92)	1.14 (0.73–1.78)	1.27 (0.83–1.94)	0.71 (0.41–1.23)
Pulmonary Valve Stenosis	639	70	1.33 (0.85–2.09)	0.96 (0.57–1.62)	1.41 (0.91–2.21)	0.54 (0.28–1.07)
Pulmonary Atresia	105	10	1.15 (0.36–3.69)	1.16 (0.36–3.73)	0.81 (0.20–3.33)	0.81 (0.20–3.38)
Septal	1533	158	0.68 (0.45–1.01)	1.01 (0.72–1.41)	0.81 (0.56–1.18)	1.14 (0.83–1.57)
Perimembranous Ventricular Septal Defect	567	56	0.59 (0.30–1.16)	0.94 (0.55–1.61)	0.85 (0.48–1.51)	1.15 (0.70–1.87)
Atrial Septal Defect - Secundum	664	76	0.80 (0.46–1.39)	1.16 (0.74–1.83)	0.77 (0.44–1.34)	1.32 (0.86–2.03)
Atrial Septal Defect - Not Otherwise Specified	178	19	0.98 (0.40–2.43)	1.06 (0.46–2.46)	0.79 (0.29–2.17)	0.66 (0.24–1.82)
Atrial Septal Defect - Secundum or Not Otherwise Specified	842	95	0.84 (0.52–1.36)	1.14 (0.76–1.72)	0.78 (0.47–1.27)	1.18 (0.79–1.75)

*$p < 0.05$.
[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. CHDs, congenital heart defect; OR, odds ratio; CI, confidence interval.
[c] Total Anomalous Pulmonary Venous Return.
[d] Left Ventricular Outflow Tract Obstructive Defects.
[e] Right Ventricular Outflow Tract Obstructive Defects.

differences in populations. Moreover, two studies reported an association between maternal exposure to particulate matter (both PM2.5 and PM10, which contain significant amount of PAHs variably) (Murillo et al., 2017) and some CHD subtypes, namely atrial septal defects and pulmonary valve stenosis (Padula et al., 2013; Gilboa et al., 2005). Furthermore, another recent study from China reported that CHDs were associated with an interaction between PAHs and a specific genetic polymorphism in the *EPHX1* gene (Tao et al., 2019).

To more fully explore the relationship between PAHs and CHDs, a unique aspect of this study was the assessment of increasing level of PAH exposure on the risk of CHDs. In fact, we did not observe a linear trend between increasing quartile of exposure and any CHD subtype. While this could be indicative of a threshold effect, it is not clear from this assessment. We also explored differences by time period, to see if magnitudes of associations varied over the past two decades. Overall, results were not consistent, with some associations being stronger during the earlier time period (1997–2002) and some being stronger in the more recent time period (2003–2011).

The strongest finding in our assessment was between maternal occupational exposure to PAHs and conotruncal heart defects in offspring. The potential mechanisms underlying this association are unclear. However, as PAHs are lipophilic, it has been demonstrated that they freely penetrate cellular membranes, including the placenta (Mumtaz and George, 1995). As a result, we also conducted a secondary analysis to observe interaction effects of BMI and PAHs exposure, but we did not observe any statistically significant interaction. Also, during PAH metabolism, enzymatic activity can result in the formation of reactive intermediates that covalently bind to DNA, forming adducts that may be teratogenic (Wells et al., 2010). Additionally, there is evidence from animal models that maternal exposure to PAHs can lead to CHDs in offspring. Specifically, studies have demonstrated PAH exposure can lead to cardiac dysfunction in embryos of various fish model systems, including zebrafish and Atlantic killifish (Farwell et al., 2006; Incardona et al., 2004; Clark et al., 2010; Wassenberg and Di Giulio, 2004; Wassenberg et al., 2005). The teratogenic potential of PAHs has also been shown recently in other fish model systems including the widow tetra, Mandeli and Pelagic (Clifton and Pandian, 2016; Dhananjayan and Muralidharan, 2012; Romero et al., 2018). While these assessments were not specific to conotruncal heart defects, it does provide some support for the observed association.

Our study should be considered in the light of certain limitations. First, we had 20 unique comparisons of CHD groups and subtypes that might create an issue of multiple comparisons. Based on 20 hypotheses, we had 64% chance of observing at least one significant result, even if all of the tests were actually not significant. Although the probability for getting the positive association is higher, our study findings depend on consistency and biological plausibility based on previous literature. As a result, we did not adjust for multiple comparisons to avoid diminishing the p-value threshold for statistical significance. Second, since exposure was based on estimates calculated by industrial hygienists, there is the potential for exposure (random with respect to case status) misclassification. However, this approach has been used

extensively in estimates of occupational exposure to PAHs and is likely to be superior to self-report alone (Olsson et al., 2010). A third limitation is the potential for recall bias (as in any case-control study), and that this might vary in strength between women interviewed closer to delivery compared to those interviewed two years after delivery. However, we suspect that recall bias may have been relatively low in this study overall because the NBDPS has shown little evidence of this bias (Reefhuis et al., 2015) and because most women are unlikely to be aware which occupations have the highest PAH exposure (Rocheleau et al., 2011). Additionally, while we did evaluate a range of CHDs, we were unable to evaluate the role of maternal occupational exposures to PAHs on complex cases (i.e., cases that included three or more distinct CHDs) due to the sample size. It is possible that these exposures could be associated with these more severe phenotypes. Another limitation is our inability to fully assess environmental sources of PAHs in the analysis. Because of this, we could not fully account for the totality of PAH exposure, but it should be noted that exposures to external environmental sources of PAHs are likely to be lower compared to occupational sources (Brandt and Watson, 2003). Additionally, consistent with previous NBDPS assessments on PAHs and birth defects, we were able to assess confounding due to secondhand smoke at home or work and meat consumption, the two major sources of environmental PAHs (Lupo et al., 2012a; Naufal et al., 2010; Ren et al., 2011; Boers et al., 2005; Hansen et al., 2008). The final limitation is unknown validity of the exposure ratings, since direct measurements or biomarkers were unavailable. Although the use of multiple raters, literature reviews, and other tactics were utilized to improve the quality of the exposure assessment—and prior research shows that expert raters can achieve relatively high validity in occupational exposure assessments using expert judgement—we ultimately do not know how much exposure misclassification might be present (Blair et al., 2007; Friesen et al., 2011; Stewart, 1999; Stewart et al., 2003; Wheeler et al., 2013).

Our study also has notable strengths. First, the NBDPS is one of the largest and most comprehensive case-control studies of birth defects in the US with extensive information on occupational history and other important covariates, including maternal nutrition, pre-pregnancy BMI, and smoking. The information on several of these covariates was not only around the time of delivery, but throughout the entire time window prior to conception to end of pregnancy. Additionally, through the NBDPS, there was extensive clinical review of all cases, which limits the inclusion of syndromic cases, resulting in a more homogenous CHD case groups. This also provides an added benefit of inclusion of stillbirths and terminations, unlike majority of the previous studies that only focus on livebirths.

In summary, we found little evidence that maternal occupational exposure increased the risk of most sub-phenotypes of CHDs in offspring. However, we report a moderate association with conotruncal heart defects, which is consistent with some other reports, as well as evidence from animal models. While our study adds to the growing body of evidence on the role of PAHs on the risk of structural birth defects, future studies must consider better estimates of exposure, as well as factors that could modify risk (e.g., genotypes).

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Human subjects

1) The Centers for Disease Control and Prevention (CDC) Institutional Review Board (IRB), along with the IRBs for each participating state, approved the NBDPS; all participants provided informed consent. 2) I have provided written assurance in the manuscript that the study has been reviewed and approved by an accredited committee. 3) I have identified the institution with which the committee is affiliated.

Author contribution

Jenil Patel, MBBS, MPH, PhD: Data curation, Formal analysis, Project administration, Investigation, Methodology, Writing (original draft), Wendy N. Nembhard MPH, PhD, FACE: Supervision, Funding acquisition, Resources, Writing (review and editing), Maria D. Politis MPH, DrPH: Validation, Writing (review and editing), Carissa M. Rocheleau, PhD: Methodology, Writing (review and editing), Peter H. Langlois, PhD: Writing (review and editing), Gary M. Shaw, DrPH: Writing (review and editing), Paul A. Romitti, PhD: Writing (review and editing), Suzanne M. Gilboa, PhD: Writing (review and editing), Tania A. Desrosiers, PhD: Writing (review and editing), Tabassum Insaf, PhD: Writing (review and editing), Philip J. Lupo, MPH, PhD: Senior supervision, Funding acquisition, Project administration, Investigation, Methodology, Resources, Writing (original draft, review, and editing)

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Replication of the study has been conducted by Maria D. Politis, also a collaborator on this project.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.109550.

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