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Hypospadias risk is increased with maternal residential exposure to hormonally active hazardous air pollutants

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Abstract

Background: With the increasing birth prevalence of hypospadias, there is growing concern for pollutant exposure interfering with normal penile development. We assess the association between hypospadias and hormonally active hazardous air pollutants (HAHAPs) through a nationwide database of hazardous air pollutants and the Texas Birth Defects Registry (TBDR).

Methods: Using the TBDR, we identified 8,981 nonsyndromic isolated hypospadias cases from 1999 to 2008. Birth certificate controls were matched for birth year at a 10:1 ratio to cases. Estimated HAHAP concentrations from the 2005 U.S. EPA National-Scale Air Toxics Assessment were used to assign exposure based on maternal residence at birth. Exposure levels were categorized as quintiles based on the distribution in controls. Logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for each increasing exposure category of selected HAHAPs.

Results: Of the 10 HAHAPs studied, seven were significantly associated with hypospadias risk. The HAHAP that was most strongly associated with hypospadias was phenol, which was associated with risk in all groups except the high exposure group. Cumulative HAHAP exposure

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

CONFLICTS OF INTEREST

There are no real or perceived conflicts of interest.

demonstrated a modest increase in hypospadias risk (OR 1.15, 95% CI: 1.07–1.24, $p < 0.001$) in the medium and medium–high quintiles.

Conclusions: While maternal exposure to some HAHAPs was significantly associated with the risk of hypospadias in male offspring, the effects were modest, and no dose–response effects were observed. Future work should employ biomarkers of exposure to better delineate the relationship.

Keywords

congenital malformation; genitalia; penis development; pollutant

1 | INTRODUCTION

As the most common external male genital malformation, hypospadias occurs in 0.4–0.6% of male births, and the birth prevalence continues to grow (Carmichael, Shaw, & Lammer, 2012). In patients with hypospadias, the urethral opening is ectopically located on the ventral aspect of the penis instead of the tip due to a failure in urethral closure, which normally occurs between the 8th and 14th week of gestation (Baskin, 2000). In the short term, hypospadias generally requires at least one if not more surgeries for initial correction, potential-staged approaches and further surgeries for complications, such as meatal stenosis and fistula. Furthermore, long-term psychosexual and psychosocial effects have been noted in males with a history of hypospadias, usually related to embarrassment and concern regarding penile appearance (Mureau, 1997; Stanasel et al., 2015). While the exact etiology of hypospadias is still unclear, alterations in genes or signaling pathways (e.g., the androgen signaling axis) important in the mesenchymal-to-epithelial transition (MET) of the genital tubercle have been associated with this birth defect (Bouty, Ayers, Pask, Heloury, & Sinclair, 2015). Further risk factors and causal relationships are still being evaluated, especially with the growing birth prevalence of hypospadias (de Graaf et al., 2017; Yamada et al., 2006).

Research of potential exogenous factors causing hypospadias has identified the early first trimester as the critical period for pollutant exposure. While the mechanism of action is not yet known for many pollutants, it has been hypothesized that disruption of the hormonal cascades or MET process during urethral development can lead to hypospadias after in utero exposure (Ren et al., 2018). As such, endocrine disrupting compounds such as bisphenol A, atrazine, organic solvents, and pesticides have been evaluated in relation to hypospadias risk and show a positive association. However, these studies have largely focused on occupational exposures (Bonde et al., 2016; Bouty et al., 2015; Carbone et al., 2007; Carmichael et al., 2012; Cordier et al., 2012; Fernandez et al., 2016; Fernandez et al., 2007; Garlantezec, Monfort, Rouget, & Cordier, 2009; Giordano et al., 2010; Kalfa et al., 2015; Lindbohm, 1995; Marrocco et al., 2015; Molina-Molina et al., 2013; Nassar, Abeywardana, Barker, & Bower, 2010; Ormond et al., 2009; Pierik, Burdorf, Deddens, Juttmann, & Weber, 2004; Sathyanarayana et al., 2016; Vaktskjold et al., 2006; Warembourg et al., 2018; Winston et al., 2016). Much less is known in terms of the relationship between residential maternal exposure to hazardous air pollutants (HAPs) and hypospadias risk.

The Clean Air Act specified approximately 180 HAPs or “air toxics,” which are defined as compounds associated with adverse health outcomes including congenital anomalies and

cancer (EPA-450/3-92-010, 1994). The NationalScale Air Toxics Assessment (NATA) is a nationwide database developed by the U.S. Environmental Protection Agency to gain a better understanding of risks associated with HAPs. This national-level risk assessment uses the emissions of air toxics to produce census-tract level estimates of ambient and exposure concentrations for 180 air toxics and diesel particulate matter. With the concentration estimates, NATA has estimated both cancer and noncancer hazard risk for 138 HAPs (Rosenbaum et al., 1999).

We aim to combine this data provided by NATA with the Texas Birth Defects Registry (TBDR) to assess the spatiotemporal relationships between hormonally active hazardous air pollutants (HAHAPs) and the presence of hypospadias. We hypothesize that prenatal exposure to HAHAPs positively correlates with hypospadias prevalence.

2 | METHODS

2.1 | Study populations

The TBDR is maintained by the Birth Defects Epidemiology and Surveillance Branch of the Texas Department of the State Health Services (Serv from the TBDR, we obtained data on cases of hypospadias delivered in Texas between January 1, 1999 and December 31, 2008. Details of the TBDR have been described previously (Chambers et al., 2018). Briefly, the TBDR uses an active surveillance system, which identifies pregnancies and infants with birth defects that are diagnosed prenatally and within 1 year of delivery. TBRD staff members make routine visits to all pediatric hospitals, maternity hospitals, midwife facilities, and birthing centers in Texas to identify children born with birth defects. They evaluate discharge lists and unit logs for birth defect diagnostic codes, text descriptions relevant to birth defects, preterm births, and still-births. The Centers for Disease Control and Prevention modification of the British Pediatric Association Classification of Disease and the World Health Organization's International Classification of the Disease, ninth revision, clinical modification (BPA code) is used to code all diagnosed cases. For this assessment, we evaluated the following BPA codes: 752.600–752.607, 752.620, and 752.625–752.627. To avoid phenotypic and etiologic heterogeneity, all syndromic cases were excluded based on co-occurring BPA codes, and only cases of isolated hypospadias were included in the analysis (Rasmussen et al., 2003).

The control group consisted of nonsyndromic live births without hypospadias in the same 10-year timeframe (January 1, 1999 to December 31, 2008) randomly chosen from Texas birth records. The controls were matched to the cases by birth year at a ratio of 10:1 controls to cases with a total of 8,981 hypospadias cases and 89,810 control cases in the study group. Ten controls per case was selected based on the assessment by Langlois et al., which demonstrated the effect estimates were similar to using an entire birth cohort in the state of Texas (Langlois, Canfield, & Swartz, 2013). The Texas Department of State Health Services and Baylor College of Medicine Institutional Review Board approved the study protocol.

2.2 | Environmental exposure assessment

We obtained data on estimated concentrations of HAHAPs from the 2005 NATA Hazardous Air Pollutant Exposure Model, version 5 (HAPEM5) (EPA U.S., 2015) as this year served as a good midpoint in the period of case ascertainment. Weighted-average exposure concentrations ($\mu\text{g}/\text{m}^3$) were generated by the NATA model for census tracts. These subdivisions allow for the presentation of a relatively uniform set of statistical demographic data for each census tract. The HAPEM5 model was the most recent assessment available for our study population timeframe and also serves as a midpoint in the study period, and therefore it was selected for our evaluation (Ozkaynak, Palma, Touma, & Thurman, 2008). For each individual, the census tract was selected based on maternal residence at the time of delivery. HAHAP exposure in the general population was expressed as quintiles based on the distribution of HAHAP exposure levels ($\mu\text{g}/\text{m}^3$) in controls (low, low-medium, medium, medium-high, and high). In our analysis, we included the 10 HAHAPs available from NATA: biphenyl, 4-nitrophenol, bis(2-ethylhexyl) phthalate, cresols, dibutylphthalate, naphthalene, pentachlorophenol, phenol, and polychlorinated biphenyls.

2.3 | Potential confounders

Data on the following potential confounders were gathered from birth certificates and fetal death certificates provided by the Texas Department of State Health Services: Maternal age (25 years, 26–30 years, 31–35 years, or > 35 years), plurality (1, 2, or 3), birth weight (2,500 g, 2,501–3,999 g, or > 3,999 g), number of previous live births (0, 1, 2–3, or > 3), maternal race/ethnicity (nonHispanic White, nonHispanic Black, Hispanic, or other), maternal education (<12, 12, >12 years), maternal diabetes (Yes or No), and maternal smoking (Yes or No).

To estimate gestational age (27, 38–42, >42 weeks), the difference in weeks between the date of delivery and the mother's last menstrual period was calculated (Wier, Pearl, & Kharrazi, 2007). The U.S. Census 2000 Summary File was used to obtain the percentage of residents below the poverty line in each census tract-level (Bureau USC, 2010). The census-tract control population percentage below the poverty line was used to define quartiles (low, Medium-low, Medium-high, and high) for clear representation of the poverty level in each census tract.

2.4 | Statistical analysis

Logistic regression models were calculated to determine the association between maternal HAHAP exposure and hypospadias in offspring while accounting for potential confounding variables. Odds ratios (OR) were presented with 95% confidence intervals (CI) for all potential confounders and the 10 HAHAPs using the low quintile as a reference point. Supporting Information Table 1 identifies patients that were excluded from individual analyses due to missing data for one of the confounding variables or HAHAP variables. In the final model, only the confounders that resulted in >10% change in the estimated effect between the maternal HAHAP exposure quintile and nonsyndromic isolated hypospadias were included. Birth year was included in each multivariable model as it was a matching factor. All models except for phenol were also adjusted for race/ethnicity. Furthermore, the models for bis(2-ethylhexyl)phthalate, cresols, naphthalene, and pentachlorophenol were

also adjusted for poverty in addition to birth year and race/ethnicity. In addition, p -values for trend (p_{trend}) were calculated for the adjusted logistic regression models. Furthermore, these p -values were subsequently adjusted using the false discovery rate (FDR) at 5% to correct for multiple comparisons.

In addition, a cumulative-weighted risk model was created for all 10 HAHAPs combined. To develop a weighted exposure risk score variable, the quintile exposure for each HAHAP was multiplied by its respective OR and then summed over the 10 HAHAPs. By doing this, we were able to account for the magnitude of the effect for each HAHAP in the exposure risk score. This is consistent with genetic risk score methodology (Machiela et al., 2016). Again, a logistic regression analysis was performed for this new cumulative risk variable and presented as OR and 95% CI for increasing cumulative HAHAP exposure. Finally, a p_{trend} was calculated for this model. All statistical analyses were performed with Stata version 14.0 (Stata Corporation, College Station, TX).

2.5 | Reporting guidelines

To present our results, we followed the STROBE reporting guidelines for case-control studies (von Elm et al., 2007).

3 | RESULTS

Basic demographic information for the hypospadias cases and controls are presented in Table 1. Plurality, maternal age, maternal education, and poverty density were all significantly associated with an increased risk of hypospadias. The number of previous live births, gestational age, and birth weight were all inversely associated with the risk of hypospadias. Hypospadias was more common in nonHispanic Whites compared to all other races and ethnicities. Finally, a significantly increased risk of hypospadias was noted in the presence of both maternal smoking and diabetes.

The levels of HAHAP exposure estimates were categorized into one of five groups based on levels in control patients divided into quintiles of low, medium-low, medium, medium-high, and high exposure groups. After adjusting for potential confounding variables, seven out of 10 HAHAPs studied (biphenyl, bis(2-ethylhexyl)phthalate, dibutyl phthalate, dimethyl phthalate, pentachlorophenol, phenol, and polychlorinated biphenyls) showed a modest but significant association with hypospadias birth prevalence (Table 2). For pentachlorophenol and dimethyl phthalate, the risk of hypospadias increased significantly in the high-medium and high exposure groups, but not in the lower exposure groups. However, the positive association between HAHAP exposure and hypospadias did not always increase with increasing exposure levels. For example, phenol, which showed the strongest association with hypospadias risk (OR 1.27, 95% CI: 1.19–1.37) for medium level exposure, did not reach significance for the high level of exposure (OR 1.04, 95% CI: 0.97–1.12, $p = 0.293$). Dibutyl phthalate was only associated with an increased hypospadias risk in the medium-high quintile of exposure, but not in the high quintile of exposure. Similarly, the polychlorinated biphenyls were associated with a significantly increased risk of hypospadias in the medium quintile of exposure. Biphenyl was only associated with an increased hypospadias risk in the medium-low and medium exposure groups, while no significant

association was seen for the higher exposure quintiles. Contrary to all the other HAHAPs, bis(2-ethylhexyl)phthalate exposure was inversely associated with hypospadias risk, significantly so at the medium–low level.

The cumulative effect of HAHAPs on hypospadias risk was evaluated with a weighted-risk model where quintile exposure of each metal was multiplied by its respective OR and then summed over the 10 HAHAPs (Table 3). A bell-shaped exposure-disease risk relationship was observed with highest and most significant associations with hypospadias seen in the medium and medium–high weighted exposure groups (OR for both groups 1.15, 95% CI: 1.07–1.24, $p < 0.001$).

4 | DISCUSSION

In our study, we evaluated the relationship between the development of hypospadias and maternal exposure to individual and cumulative HAHAPs during pregnancy for a large population. Overall, we did not have evidence of a strong association between HAHAPs and hypospadias, but modest associations were seen when compared to the lowest quintile of HAHAP exposure. Phenol demonstrated the strongest association with hypospadias birth prevalence with a 1.3–fold increase in risk in the medium exposure quintile when compared to the low exposure quintile. Combined HAHAP exposure showed a continued positive correlation with a modest 1.2–fold hypospadias risk increase in the medium and medium–high exposure group. Similar results have been seen in other population-based studies evaluating effects of residential environmental exposures on male genital anomalies (Agopian, Lupo, Canfield, & Langlois, 2013; Bonde et al., 2016). On the other hand, studies evaluating hypospadias risk after occupational exposures to HAHAPs have found stronger associations, but it is important to note that the level of exposure is much higher in the occupational setting (Gaspari et al., 2011; Giordano et al., 2010; Nassar et al., 2010).

The distribution of hypospadias risk by increasing quintiles of HAHAP exposure did not always follow the same pattern. Pentachlorophenol and dimethyl phthalate showed an increasing hypospadias risk for the higher quintiles of exposure. However, other HAHAPs, such as dibutyl phthalate, polychlorinated biphenyls, and phenol, showed strongest associations with hypospadias risk on the medium and medium–high quintiles, with no significant relationship seen for the highest quintile. Agopian et al. had similar findings in a population-based exposure study for residential atrazine exposure (Agopian et al., 2013). Such findings may be related to a more severe phenotype presenting in the highest risk group that consists of multiple congenital anomalies. Such patients are not present in our study as syndromic patients were excluded. Furthermore, high exposure levels could also lead to an embryonic lethal phenotype or elective abortions in the face of severe malformations noted prenatally, again removing such cases from our study population. While these scenarios may explain some of the discrepancy, it is also possible that the weak association found at higher exposure levels could be due to a misclassification or uncontrolled confounding variables despite our efforts (Danysh, Mitchell, Zhang, Scheurer, & Lupo, 2015).

The most unexpected finding was the inverse association noted between bis(2-ethylhexyl)phthalate (DEHP) and hypospadias. Perinatal exposure to DEHP in rat models has correlated with decreased birth weight, decreased testis weight, decreased anogenital distance, and development of femalelike areolas/nipples (Gray et al., 2000) with a mechanism of action being distinct from androgen receptor ligands (Wolf et al., 1999). The direct association with hypospadias and high urine and plasma DEHP levels have also been shown in humans (Choi, Kim, Im, Lee, & Kim, 2012), but studies have found a stronger association with hydroceles and cryptorchidism rather than with hypospadias (Sathyanarayana et al., 2016). All these studies have evaluated DEHP levels in patients, while our study looked at residential exposure, which may not be associated with higher plasma or urinary levels seen in patients with DEHP exposure and hypospadias.

In our assessment, phenol was the HAHAP most associated with hypospadias. Previous studies evaluating phenols, specifically bisphenol A (BPA), and hypospadias risk have shown significant positive associations between hypospadias and elevated BPA levels in the serum (Guida et al., 2015), urine (Choi et al., 2012), and placenta (Fernandez et al., 2016). In vitro studies have shown BPA congeners and derivatives to disrupt multiple nuclear receptors that can interfere with the endocrine system, pointing toward a mechanism disrupting sexual differentiation in males (Molina-Molina et al., 2013). While environmental exposure to BPA has been linked to fetal malformations, higher levels of conjugated BPA in control patients have supported the hypotheses that maternal ability to metabolize BPA may also play a role (Guida et al., 2015). Moreover, genetic variability among individuals could influence their susceptibility to the effects of endocrine disruptors making them more sensitive to the estrogen-like effect of low-dose of BPA and increasing their risk of hypospadias (Qin et al., 2012). Our work and that of others suggest a hormonal relationship between hypospadias development and phenol exposure that could also be genetically influenced, but further evaluation must be done to explain the modest association found in our cohort.

The current report is one of the largest population-based cohort studies to evaluate the relationship between isolated hypospadias and maternal residential exposure to both individual and cumulative HAHAP obtained from an actively surveyed population-based source. This study has not identified strong associations, but some modest ones have been noted that are supported by previous literature. The actual clinical meaningfulness of these weak, but significant associations, are questionable when such low ORs are identified. One of our study biases has been the inability to quantify maternal exposure duration and the specific amount of exposure during the first trimester of pregnancy that is critical for the development of the genitalia. Specifically, it assigned HAHAP exposure based on residence at birth; exposure misclassification is possible because roughly 30% of women in Texas move between conception (closer to the development of hypospadias) and birth (Canfield et al., 2006), although the small distances usually moved suggest that the impact may be small (Lupo et al., 2010). Future studies with additional demographic and pregnancy information will help to avoid misclassification of patients in exposure categories and eliminate any bias. Also, further understanding of these HAHAPs in the residential setting is needed to better guide recommendations and precautions for expecting mothers. Future studies will need to focus on biomarkers to quantify exposure levels and test etiologic mechanisms of action for

these individual HAHAPs. In conclusion, this study is the critical first step in identifying and confirming exposure-disease risk relationships between HAHAP exposure and hypospadias.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

EPA	Environmental Protection Agency
HAHAP	hormonally active hazardous air pollutant
HAP	hazardous air pollutant
MET	mesenchyme-to-epithelial transition
NATA	National-Scale Air Toxics Assessment
TBDR	Texas Birth Defects Registry

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TABLE 1

Demographics of hypospadias cases and birth-year-matched control patients in Texas

	Controls	Cases	OR (95% CI)
Plurality			
1	87,408	8,553	1.00 (ref)
2	2,304	409	1.81 (1.63–2.02)
3 +	94	19	2.07 (1.26–3.38)
Maternal age (years)			
<25	38,162	3,388	1.00 (ref)
25–34	42,036	4,435	1.19 (1.13–1.25)
35+	9,605	1,157	1.36 (1.26–1.46)
Previous live births			
0	34,291	4,099	1.00 (ref)
1	27,431	2,580	0.79 (0.75–0.83)
2–3	22,177	1,856	0.70 (0.66–0.74)
4+	3,788	227	0.50 (0.44–0.57)
Race			
NonHispanic White	32,624	4,815	1.00 (ref)
NonHispanic Black	10,076	1,200	0.81 (0.75–0.86)
Hispanic	43,403	2,624	0.41 (0.39–0.43)
Other	3,565	328	0.62 (0.55–0.70)
Gestational age (weeks)			
Full term (37–41)	71,948	6,859	1.00 (ref)
Early term (<37)	9,990	1,480	1.55 (1.46–1.65)
Postterm (42+)	7,569	608	0.84 (0.77–0.92)
Birth weight (g)			
Normal (2,500–3,999)	75,416	6,915	1.00 (ref)
Low (<2,500)	6,209	1,418	2.49 (2.34–2.65)
High (4,000+)	8,138	645	0.86 (0.79–0.94)
Maternal diabetes			
No	86,765	8,636	1.00 (ref)
Yes	3,045	345	1.14 (1.02–1.28)
Maternal smoking			
No	84,135	8,359	1.00 (ref)
Yes	5,280	576	1.10 (1.00–1.20)
Maternal education			
Less than 12 years	27,701	1,812	1.00 (ref)
12 years	26,116	2,611	1.53 (1.44–1.63)
Greater than 12 years	35,070	4,476	1.95 (1.84–2.07)
Poverty density			
Low	21,731	2,827	1.00 (ref)
Medium–low	20,484	2,092	0.79 (0.74–0.83)

	Controls	Cases	OR (95% CI)
Medium-high	24,842	2,350	0.73 (0.69–0.77)
High	22,753	1,712	0.58 (0.54–0.62)

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Adjusted ORs (95% CIs) for the associations between hormonally active hazardous air pollutants (HAHAPs) and hypospadias

TABLE 2

	Pollutant level ($\mu\text{g}/\text{m}^3$)	Cases/controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-trend	FDR adjusted p-value
Biphenyl						
Low	4.28×10^{-9} –0.000020	1,724/16,808	1.00 (ref)	1.00 (ref)		
Medium–low	>0.000020–0.000046	1,836/16,703	1.07 (1.00–1.15)	1.08 (1.01–1.16)	0.157	0.524
Medium	>0.000046–0.000087	1,780/16,804	1.03 (0.96–1.11)	1.08 (1.01–1.16)		
Medium–high	>0.000087–0.00023	1,661/16,789	0.96(0.90–1.04)	1.06 (0.99–1.14)		
High	>0.00023–0.010	1,457/16,729	0.85 (0.79–0.91)	0.95 (0.88–1.02)		
4-Nitrophenol						
Low	0.00–0.000017	1,754/16,775	1.00 (ref)	1.00 (ref)		
Medium–low	>0.000017–0.000039	1,787/16,741	1.02(0.95–1.09)	1.04 (0.97–1.12)	0.224	0.560
Medium	>0.000039–0.000065	1,748/16,807	0.99 (0.93–1.07)	1.04 (0.97–1.11)		
Medium–high	>0.000065–0.00011	1,658/16,744	0.95 (0.88–1.02)	1.07 (0.99–1.15)		
High	>0.00011–0.0015	1,511/16,766	0.86 (0.80–0.93)	1.04 (0.96–1.12)		
Bis(2-ethylhexyl)phthalate						
Low	0.0052–0.0053	1,287/16,763	1.00 (ref)	1.00 (ref)		
Medium–low	>0.0053–0.0055	1,711/16,761	1.33 (1.23–1.43)	0.90 (0.82–0.99)	0.996	0.996
Medium	>0.0055–0.0056	2,004/16,748	1.56 (1.45–1.68)	0.97 (0.88–1.06)		
Medium–high	>0.0056–0.0057	1,724/16,834	1.33 (1.24–1.44)	0.92 (0.83–1.01)		
High	>0.0057–0.073	1,732/16,727	1.35 (1.25–1.45)	0.95 (0.87–1.05)		
Cresols						
Low	0.000016–0.000086	1,571/16,773	1.00 (ref)	1.00 (ref)		
Medium–low	>0.000086–0.00025	1,632/16,772	1.04(0.97–1.12)	1.02 (0.95–1.10)	0.418	0.697
Medium	>0.00025–0.0044	1,688/16,747	1.08 (1.00–1.16)	0.97 (0.90–1.06)		
Medium–high	>0.0044–0.0070	1,954/16,766	1.24(1.16–1.33)	1.06 (0.98–1.14)		
High	>0.0070–0.034	1,613/16,775	1.03 (0.95–1.10)	1.01 (0.92–1.10)		
Dibutylphthalate						
Low	4.37×10^{-8} –0.00018	1,678/16,749	1.00 (ref)	1.00 (ref)		
Medium–low	>0.00018–0.00043	1,762/16,801	1.05 (0.98–1.12)	1.07 (0.99–1.14)	0.298	0.596
Medium	>0.00043–0.00074	1,795/16,760	1.07 (1.00–1.15)	1.07 (1.00–1.15)		

	Pollutant level (µg/m ³)	Cases/controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-trend	FDR adjusted p-value
Medium-high	>0.00074-0.0011	1,733/16,788	1.03 (0.96-1.11)	1.09 (1.01-1.17)		
High	>0.0011-0.025	1,490/16,735	0.89 (0.83-0.96)	1.03 (0.96-1.11)		
Dimethyl phthalate						
Low	4.00×10^{-9} - 6.06×10^{-6}	1,716/16,818	1.00 (ref)	1.00 (ref)		
Medium-low	$>6.06 \times 10^{-6}$ -0.000015	1,597/16,654	0.94(0.88-1.01)	1.01 (0.94-1.09)	<0.001	0.001
Medium	>0.000015-0.000064	1,622/16,843	0.94(0.88-1.01)	1.07 (1.00-1.15)		
Medium-high	>0.000064-0.00020	1,641/16,767	0.96(0.89-1.03)	1.09 (1.01-1.17)		
High	>0.00020-0.047	1,882/16,751	1.10(1.03-1.18)	1.15 (1.07-1.23)		
Naphthalene						
Low	0.00047-0.013	1,508/16,760	1.00 (ref)	1.00 (ref)		
Medium-low	>0.013-0.024	1,827/16,758	1.21 (1.13-1.30)	1.04 (0.96-1.12)	0.933	0.996
Medium	>0.024-0.037	1,967/16,784	1.30(1.21-1.40)	1.06 (0.98-1.15)		
Medium-high	>0.037-0.051	1,707/16,774	1.13 (1.05-1.22)	1.03 (0.95-1.12)		
High	>0.051-0.25	1,449/16,757	0.96(0.89-1.04)	0.99 (0.90-1.09)		
Pentachlorophenol						
Low	$0.00-2.67 \times 10^{-8}$	1,298/16,761	1.00 (ref)	1.00 (ref)		
Medium-low	$>2.67 \times 10^{-8}$ - 1.54×10^{-7}	1,651/16,810	1.27 (1.18-1.37)	1.04 (0.96-1.14)	0.051	0.255
Medium	$>1.54 \times 10^{-7}$ - 4.08×10^{-7}	1,631/16,757	1.26 (1.16-1.36)	0.99 (0.90-1.09)		
Medium-high	$>4.08 \times 10^{-7}$ - 6.34×10^{-6}	1,949/16,760	1.50 (1.40-1.62)	1.06 (0.98-1.15)		
High	$>6.34 \times 10^{-6}$ -0.0019	1,929/16,745	1.49 (1.38-1.60)	1.10 (1.01-1.20)		
Phenol						
Low	0.000013-0.00075	1,493/16,765	1.00 (ref)	1.00 (ref)		
Medium-low	>0.00075-0.0017	1,783/16,774	1.19 (1.11-1.28)	1.19 (1.11-1.28)	0.628	0.893
Medium	>0.0017-0.0039	1,900/16,757	1.27 (1.19-1.37)	1.27 (1.19-1.37)		
Medium-high	>0.0039-0.0074	1,726/16,750	1.16(1.08-1.24)	1.16 (1.08-1.24)		
High	>0.0074-0.20	1,556/16,787	1.04(0.97-1.12)	1.04 (0.97-1.12)		
Polychlorinated biphenyls						
Low	$0.00-9.42 \times 10^{-7}$	1,391/16,791	1.00 (ref)	1.00 (ref)		
Medium-low	$>9.42 \times 10^{-7}$ - 5.36×10^{-6}	1,792/16,761	1.29 (1.20-1.39)	1.07 (0.99-1.15)	0.714	0.893
Medium	$>5.36 \times 10^{-6}$ - 9.00×10^{-6}	1,749/16,736	1.26 (1.17-1.36)	1.11 (1.03-1.20)		

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	Pollutant level (µg/m ³)	Cases/controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-trend	FDR adjusted p-value
Medium-high	>9.00 × 10 ⁻⁶ -0.0000016	1,675/16,857	1.20 (1.11–1.29)	1.08 (1.00–1.16)		
High	>0.000016–0.00027	1,851/16,688	1.34 (1.24–1.44)	1.03 (0.95–1.11)		

Biphenyl, 4-nitrophenol, dibutylphthalate, dimethyl phthalate and polychlorinated biphenyls adjusted for race and birth year. Bis(2-ethylhexyl)phthalate, cresols, naphthalene and pentachlorophenol adjusted for race, birth year and poverty. Phenol adjusted for birth year.

TABLE 3

Adjusted ORs for the associations between HAHAP-weighted risks and hypospadias

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	<i>p</i>-trend
HAHAP-weighted risk			
Low	1.00 (ref)	1.00 (ref)	
Medium–low	1.16 (1.08–1.25)	1.05 (0.98–1.13)	0.050
Medium	1.33 (1.24–1.43)	1.15 (1.07–1.24)	
Medium–high	1.32 (1.23–1.42)	1.15 (1.07–1.24)	
High	0.99 (0.92–1.07)	1.03 (0.96–1.12)	

HAHAP-weighted risks adjusted for race and birth year.