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Is maternal employment site a source of exposure misclassification in studies of environmental exposures and birth outcomes? A simulation-based bias analysis of haloacetic acids in tap water and hypospadias

Ibrahim Zaganjor[a], Alexander P. Keil[a], Thomas J. Luben[a,b], Tania A. Desrosiers[a], Lawrence S. Engel[a], Jennita Reefhuis[c], Adrian M. Michalski[d], Peter H. Langlois[e], Andrew F. Olshan[a], and The National Birth Defects Prevention Study

Background: In population research, exposure to environmental contaminants is often indirectly assessed by linking residence to geocoded databases of environmental exposures. We explored the potential for misclassification of residence-based environmental exposure as a result of not accounting for the workplace environments of employed pregnant women using data from a National Birth Defects Prevention Study (NBDPS) analysis of drinking water haloacetic acids and hypospadias.

Methods: The original analysis used NBDPS data from women with haloacetic acid exposure information in eight states who delivered an infant with second- or third-degree hypospadias (cases) or a male infant without a birth defect (controls) between 2000 and 2005. In this bias analysis, we used a uniform distribution to randomly select 11%–14% of employed women that were assumed to change municipal water systems between home and work and imputed new contaminant exposures for tap water beverages consumed at work among the selected women using resampled values from the control population. Multivariable logistic regression was used to estimate the association between hypospadias and haloacetic acid ingestion with the same covariates and exposure cut-points as the original study. We repeated this process across 10,000 iterations and then completed a sensitivity analysis of an additional 10,000 iterations where we expanded the uniform distribution (i.e., 0%, 28%).

Results: In both simulations, the average results of the 10,000 iterations were nearly identical to those of the initial study.

Conclusions: Our results suggest that household estimates may be sufficient proxies for worksite exposures to haloacetic acids in tap water.

Keywords: Exposure misclassification; Bias analysis; Birth defects; Disinfection by-products; Haloacetic acids; Hypospadias

[a]*Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina;* [b]*Epidemiology Branch, Public Health and Environmental Systems Division, Center for Public Health and Environmental Assessment, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, North Carolina;* [c]*Division of Birth Defects and Infant Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia;* [d]*New York State Department of Health, Bureau of Environmental and Occupational Epidemiology, Albany, New York; and* [e]*Division of Epidemiology, Human Genetics, and Environmental Sciences, University of Texas School of Public Health, Austin, Texas*

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**Corresponding author: Address: Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599. E-mail: Ibrahim.zaganjor@gmail.com (I. Zaganjor).*

Introduction

In epidemiologic studies of environmental exposures and birth outcomes, maternal residence is commonly used to estimate exposure to potential hazards from geographic exposure sources. Different residence-based estimates of exposure, such as Euclidean distance to a point source exposure or linkage of residential geocodes to nearest air pollution monitor, often serve as surrogate measures of individual-level exposure.[1,2] However, these measures implicitly assume that a woman is geographically static during pregnancy. Although previous research has evaluated potential bias stemming from residential mobility during pregnancy,[3,4] epidemiologic studies of perinatal outcomes and environmental exposures

What this study adds

Although employed women may spend a considerable portion of the day at their workplace, where exposure levels may be different than those at home, maternal residence is commonly used exclusively to estimate exposure to potential geospatial hazards in epidemiologic studies of perinatal outcomes and environmental exposures. Although we do not know if our results would be consistent under different scenarios (e.g., different environmental contaminants, exposure window, reproductive outcome, continuous exposure variable, etc.), our quantitative bias analysis results suggest that household estimates may be sufficient proxies for worksite exposures to haloacetic acids in tap water.

tend to ignore the contribution of employment outside the home during pregnancy.[5,6] This is an important consideration because employed women may encounter environmental exposures (e.g., air quality, drinking water contaminants) at the workplace that may be quite different from those at home.

Probabilistic bias analysis methods can be leveraged to explore the potential impact of maternal employment outside the home in epidemiologic studies that use residence-based exposure assignment. We demonstrate our approach to this type of bias analysis using data from a recent study of maternal exposure to drinking water disinfection by-products (DBP) and hypospadias among male offspring.[7] In the original study, the exposure assessment methods considered only residence-based DBP concentrations for both trihalomethanes and haloacetic acids. In this bias analysis, we explored the potential magnitude of exposure misclassification resulting from not properly accounting for the workplace environments of employed women.

Methods

Original study

The original study was completed among a subset of women in the National Birth Defects Prevention Study (NBDPS),[7] a large, multi-site case-control study that included data on water consumption and water use behaviors during the years 2000–2005.[8,9] Participants were from eight study sites that gathered DBP data from public water systems (PWSs): Arkansas, Georgia, Iowa, Massachusetts, North Carolina, New York, Texas, and Utah. Males with second- or third-degree hypospadias delivered at one of the eight sites between 2000 and 2005 were included as cases. Controls were males without a major structural birth defect delivered during the same time period in the same catchment area.

During the NBDPS interview, women reported occupational information (e.g., job title, industry, hours per week) and details on water consumption behaviors at their respective worksites including the water source(s) used (unfiltered tap, filtered tap, drinking fountain [coded as unfiltered tap], bottled/cooler, brought from home, other) and the amount of water consumed per day from each source.[9] However, job addresses were not collected, so it was assumed that household and worksite DBP concentrations were equivalent. Thus, household DBP concentration estimates were integrated with household and worksite water consumption data to estimate a woman's average daily ingestion of DBPs using methods that have been previously described.[9] Of these DBPs, we evaluated only haloacetic acid ingestion due to the non-volatile nature of these contaminants, which reduces potential exposure measurement error from other sources (e.g., dermal absorption/inhalation from showering/bathing). Thus, this study reports the association between hypospadias and the following DBPs: monobromoacetic acid (MBAA), monochloroacetic acid (MCAA), dibromoacetic acid (DBAA), dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), and the sum of these five haloacetic acids (HAA5s). It is important to note that Massachusetts and Utah did not provide individual haloacetic acid species exposure estimates and that women from these sites are only represented in the HAA5 analyses.

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Effect-measure modification by employment status

To determine if the association between maternal ingestion of haloacetic acids and hypospadias varied by employment status during the periconceptional period (month before conception and the first three months of pregnancy; "B1–P3"), we re-fit the original models within strata of employment status (employed B1–P3; not employed B1–P3). We also used the original adjustment set of study site, maternal age at conception (<20, 20–25, 26–35, 36+ years), maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other), pre-pregnancy body mass index (BMI, kg/m^2) (underweight [<18.5]; normal weight [18.5–24.9]; overweight [25.0–29.9]; obese [≥30.0]), maternal education (<high school, high school, >high school), and parity (0, 1, ≥2).

Probabilistic bias analysis

We performed a bias analysis to determine the sensitivity of the original results to potential haloacetic acid exposure misclassification due to maternal employment sites under the assumption that some employed women may have utilized different PWSs at home and work. Because workplace address was not collected in the NBDPS, we relied on contemporaneous studies of drinking water contaminants and pregnancy outcomes that reported 11%–14% of employed women change water systems between home and work.[10–13] For our primary bias analysis, we encoded this estimate into a uniform (11%, 14%) distribution on the percent of employed women in our analytic sample who changed water systems while at work.

Our probabilistic bias analysis proceeded by creating new workplace exposures for imputations that were derived from bootstrap samples of the population and the underlying distribution of haloacetic acid exposures. For the distribution of haloacetic acid exposures, we resampled (with replacement) the measured household haloacetic acid values from PWSs among controls stratified by study site, assuming that the distribution of workplace exposures in a given area would roughly be the same as residential exposures.

To impute new exposures at a given iteration of the bias analysis, we first randomly selected 11%–14% of employed women who were then assumed to have different water systems at home and work. Among these women, we imputed the new concentration values for all tap water beverages consumed at work using the resampled values from controls at the same study site. Unemployed women and employed women that were not selected maintained their original exposure estimates. The new workplace ingestion estimates were combined with the home haloacetic acid ingestion estimates to calculate total exposure. We then used multivariable logistic regression to calculate the log-odds of hypospadias with the same covariates as the original models. Exposure levels were categorized using the same contaminant ingestion cut-points as the original study (reported in μg/day).[7] These cut-points were based on the existing distribution of haloacetic acid ingestion among the controls: Q1) <50% (referent), Q2) ≥ 50% to <75%, and Q3) ≥ 75%. However, in circumstances where more than one-half of the controls had no exposure, all unexposed women were included in the lowest quantile (Q1). To account for random error, we used bootstrap sampling to resample cases and controls at each iteration of the bias analysis.[14] We repeated this process across 10,000 iterations and then summarized the results of the simulations using the mean log-odds ratios for each contaminant and 95% confidence intervals (CIs), also referred to as "simulations intervals," based on quantiles of the distribution of the log-odds ratios. We performed a sensitivity analysis in which we expanded the distribution of different PWSs at home and work to a uniform (0%, 28%) distribution.

Results

The characteristics of the original sample are presented in Table 1. The most notable difference is that cases were more

Table 1.

Distribution of maternal characteristics among cases and controls in initial sample with complete haloacetic acid ingestion data, National Birth Defects Prevention Study, 2000–2005 (n = 928)

	Cases (n = 271)		Controls (n = 657)	
Maternal characteristic	**N**	**%**	**n**	**%**
Maternal age at conception				
<20 years	24	8.9%	86	13.1%
20–25 years	70	25.8%	189	28.8%
26–35 years	147	54.2%	324	49.3%
36+ years	30	11.1%	58	8.8%
Maternal race/ethnicity				
Non-Hispanic White	186	68.6%	367	55.9%
Non-Hispanic Black	47	17.3%	119	18.1%
Hispanic	18	6.6%	120	18.3%
Other	20	7.4%	51	7.8%
Pre-pregnancy body mass index*				
Underweight	16	6.1%	29	4.6%
Normal weight	133	50.4%	332	52.5%
Overweight	67	25.4%	149	23.6%
Obese	48	18.2%	122	19.3%
Missing	7		25	
Maternal education				
<High school	23	8.5%	111	16.9%
High school	50	18.5%	157	23.9%
>High school	198	73.1%	389	59.2%
Number of previous live births				
0	151	55.7%	271	41.3%
1	82	30.3%	218	33.2%
≥2	38	14.0%	168	25.6%
Family history of hypospadias (first-degree relative)				
No	262	96.7%	653	99.4%
Yes	9	3.3%	4	0.6%
Employment (B1–P3)[α]				
No	55	20.3%	209	31.8%
Yes	216	79.7%	448	68.2%
Study site				
Arkansas	61	22.5%	150	22.8%
Georgia	57	21.0%	136	20.7%
Iowa	21	7.8%	64	9.7%
Massachusetts	65	24.0%	89	13.6%
New York	5	1.9%	20	3.0%
North Carolina	43	15.9%	105	16.0%
Texas	4	1.5%	74	11.3%
Utah	15	5.5%	19	2.9%

*Underweight (<18.5); Normal weight (18.5–24.9); Overweight (25–29.9); Obese (≥30).

[α]B1–P3: Month before conception to third month of pregnancy (i.e., periconceptional period).

likely to hold a job during the periconceptional period than controls (cases: 80%; controls: 68%). The results of the effect-measure modification assessment are reported in Table 2. Some variation was found when comparing the point estimates by maternal employment status. For example, the stratum-specific adjusted odds ratios for the second quantile of HAA5 exposure were on opposite sides of the null (unemployed: [adjusted odds ratio (aOR): 1.2; 95% CI = 0.6, 2.5], employed [aOR: 0.8; 95% CI = 0.5, 1.2]). However, patterns were not consistent among all of the exposures evaluated and the CIs for the stratum-specific odds ratios were imprecise.

The overall ingestion cut-points for each exposure (μg/day), the original study's results, and the results from the probabilistic bias analysis are presented in Table 3. In the simulation that utilized the probability distribution drawn from previous studies (i.e., 11%–14% of employed women) the average results of the 10,000 simulations were nearly identical to those of the initial study. Results were generally consistent even after expanding the bounds of the distribution (i.e., imputing a new workplace exposure among 0%–28% of employed women).

Discussion

In this study, we assessed (1) potential effect-measure modification of the association between haloacetic acid ingestion and hypospadias by maternal employment status and (2) the potential for bias due to misattribution of workplace tap water exposures on this association. Our results did not provide strong evidence for effect-measure modification by maternal employment status. Due to the small sample sizes of many groups, the CIs for the stratum-specific odds ratios in this assessment were imprecise. Moreover, all of the CIs for the unemployed strata overlapped with the odds ratio of the employed strata suggesting a lack of heterogeneity between the two groups using an alpha level of 0.05. We also observed that our bias analysis results were similar to the original estimates using several sets of assumptions about potential exposure misclassification resulting from improperly accounting for the workplace environments of employed women. While a couple of the contaminants' concentration distributions lacked variability (e.g., MBAA), we hypothesize that the robustness of the original results is likely due to limited consumption of unfiltered tap water at the workplace among employed women in the sample. Thus, it is unclear if our findings can be bridged to other environmental exposures at or around the workplace (e.g., air pollution) or other outcomes.

Haloacetic acids have been evaluated in relation to several different reproductive and birth outcomes.[15–17] Because town-level averages from PWSs are frequently used as surrogates for individual exposures in epidemiologic assessments of haloacetic acids and other DBPs,[18] the impacts of factors such as spatial and temporal variability of these contaminants have been evaluated previously.[19–21] Two studies of DBP exposure have suggested that employment status may be a potential source of exposure misclassification.[22,23] Using an example of perfluorooctanoate (PFOA) exposure and preeclampsia, Avanasi et al. evaluated the potential exposure mischaracterization that can arise when home and workplaces cannot be geocoded to the street-level and contaminant concentration estimates associated with the population-weighted ZIP code centroid are used in their place.[24] Interestingly, in the simulation that assumed geocode uncertainty in both household and workplace addresses, a notable impact was observed on the association between PFOA exposure and preeclampsia highlighting the importance of such uncertainty analyses in circumstances where exact residential and/or worksite addresses are not available for all individuals in the study.[24] However, to our knowledge, no study has used quantitative methods to evaluate the potential impact of assuming home and workplace DBP exposures in drinking water are equivalent (i.e., both sites rely on the same PWS) in studies of pregnant women. Thus, our study addresses a critical gap in the literature and provides evidence that this common exposure assessment assumption is unlikely to substantially bias results for studies of haloacetic acids.

Our study did have limitations that need to be considered. First, due to the small sample sizes of several groups, our effect-measure modification analysis yielded imprecise effect estimates and could not rule out meaningful effect-measure modification. We also did not know which women utilized different PWSs at work, but we addressed this limitation by using prior data from a similar population and showed this result was robust to different assumptions. Moreover, our study utilized a surrogate exposure metric that may not properly reflect each woman's personal exposure to haloacetic acids in tap water.

Our study also had several strengths. We assessed an understudied source of potential exposure misclassification that is commonly overlooked in environmental epidemiology studies of birth outcomes. Also, we used two different probability distributions (i.e., 11%, 14% and 0%, 28%) to expansively evaluate the sensitivity of the initial study's results with respect to this potential source of exposure misclassification. Due to NBDPS'

Table 2.

Association between maternal ingestion of haloacetic acids and hypospadias by maternal employment (B1–P3)[β], The National Birth Defects Prevention Study (2000–2005)

	Unemployed			Employed		
Exposure quantile	**n**	**aOR[Φ]**	**95% CI**	**n**	**aOR[Φ]**	**95% CI**
	HAA5 (n = 928)					
Q1 (<50%)	153	1.0	REF	326	1.0	REF
Q2 (≥50%–<75%)	60	1.2	0.6, 2.5	170	0.8	0.5, 1.2
Q3 (≥75%)	51	0.5	0.2, 1.3	168	0.7	0.5, 1.1
	MBAA (n = 736)					
Q1 (No exposure)[α]	138	1.0	REF	356	1.0	REF
Q2 (<75%)	15	1.4	0.3, 5.9	51	0.6	0.3, 1.3
Q3 (≥75%)	51	1.0	0.4, 2.6	125	0.6	0.4, 1.1
	MCAA (n = 736)					
Q1 (No exposure)[α]	127	1.0	REF	287	1.0	REF
Q2 (<75%)	35	0.7	0.2, 2.2	106	0.4	0.2, 0.8
Q3 (≥75%)	42	0.5	0.2, 1.5	139	0.6	0.4, 1.1
	DBAA (n = 736)					
Q1 (No exposure)[α]	133	1.0	REF	316	1.0	REF
Q2 (<75%)	25	1.0	0.3, 3.3	84	0.6	0.3, 1.2
Q3 (≥75%)	46	1.1	0.4, 3.1	132	0.7	0.4, 1.3
	DCAA (n = 736)					
Q1 (<50%)	117	1.0	REF	246	1.0	REF
Q2 (≥50%–<75%)	44	1.0	0.4, 2.7	149	0.9	0.6, 1.5
Q3 (≥75%)	43	0.7	0.3, 2.1	137	0.7	0.4, 1.2
	TCAA (n = 736)					
Q1 (<50%)	118	1.0	REF	247	1.0	REF
Q2 (≥50%–<75%)	40	0.6	0.2, 1.9	149	0.9	0.5, 1.4
Q3 (≥75%)	46	0.6	0.2, 1.6	136	0.8	0.5, 1.3

[β]B1–P3: Month before conception to third month of pregnancy (i.e., periconceptional period).

[α]Due to low exposure estimates, referent includes all unexposed women (i.e., exposure = 0 µg/day).

[Φ]Stratum specific odds ratios adjusted for maternal age at conception, study site, parity, maternal education, pre-pregnancy body mass index, maternal race/ethnicity, and maternal employment.

aOR indicates adjusted odds ratio; CI, confidence interval; REF, Referent group; HAA5, Total Haloacetic Acids; MBAA, monobromoacetic acid; MCAA, monochloroacetic acid; DBAA, dibromoacetic acid; DCAA, dichloroacetic acid; TCAA, trichloroacetic acid.

Table 3.

Bias analysis of workplace exposure misattribution: association of haloacetic acid exposure with odds of hypospadias, The National Birth Defects Prevention Study (2000–2005)

	Original results[7]			Exposure imputed among 11%–14% of employed women*			Exposure imputed among 0%–28% of employed women*		
Haloacetic acid ingestion (µg/day)[α]	**n**	**aOR[Φ]**	**95% CI**	**n**	**aOR[Φ]**	**95% CI**	**n**	**aOR[Φ]**	**95% CI**
HAA5	928			928			928		
Q1 (<11.5)		1.00	REF		1.00	REF		1.00	REF
Q2 (≥11.5–<33.7)		0.86	0.59, 1.25		0.85	0.58, 1.23		0.85	0.59, 1.24
Q3 (≥33.7)		0.71	0.48, 1.06		0.71	0.48, 1.05		0.71	0.48, 1.05
MBAA	736			736			736		
Q1 (0)[α]		1.00	REF		1.00	REF		1.00	REF
Q2 (>0–<0.7)		0.72	0.37, 1.42		0.71	0.36, 1.42		0.72	0.36, 1.43
Q3 (≥0.7)		0.70	0.43, 1.14		0.69	0.42, 1.11		0.69	0.42, 1.12
MCAA	736			736			736		
Q1 (0)[α]		1.00	REF		1.00	REF		1.00	REF
Q2 (>0–<2.5)		0.50	0.29, 0.85		0.52	0.30, 0.91		0.52	0.30, 0.92
Q3 (≥2.5)		0.63	0.38, 1.04		0.63	0.38, 1.05		0.63	0.38, 1.06
DBAA	736			736			736		
Q1 (0)[α]		1.00	REF		1.00	REF		1.00	REF
Q2 (>0–<1.2)		0.68	0.39, 1.22		0.70	0.39, 1.26		0.71	0.40, 1.27
Q3 (≥1.2)		0.82	0.50, 1.34		0.82	0.51, 1.33		0.83	0.51, 1.34
DCAA	736			736			736		
Q1 (<6.5)		1.00	REF		1.00	REF		1.00	REF
Q2 (≥6.5–<17.8)		0.95	0.62, 1.45		0.94	0.61, 1.45		0.95	0.61, 1.46
Q3 (≥17.8)		0.75	0.47, 1.18		0.75	0.48, 1.18		0.75	0.48, 1.19
TCAA	736			736			736		
Q1 (<3.6)		1.00	REF		1.00	REF		1.00	REF
Q2 (≥3.6–<13.8)		0.84	0.54, 1.30		0.83	0.53, 1.29		0.83	0.53, 1.30
Q3 (≥13.8)		0.74	0.47, 1.17		0.75	0.47, 1.19		0.75	0.48, 1.20

*Simulation completed 10,000 times.

[α]Due to low exposure estimates, referent includes all unexposed women (i.e., exposure = 0 µg/day).

[Φ]Adjusted for: maternal age at conception, study site, parity, maternal education, pre-pregnancy body mass index, and maternal race/ethnicity.

aOR indicates adjusted odds ratio; CI, confidence interval; REF, Referent group; HAA5, Total Haloacetic Acids; MBAA, monobromoacetic acid; MCAA, monochloroacetic acid; DBAA, dibromoacetic acid; DCAA, dichloroacetic acid; TCAA, trichloroacetic acid.

detailed water module, we also were able to disentangle household and workplace water consumption patterns and strictly apply the probabilistic bias analysis to water consumed at work. Lastly, we incorporated data from several U.S. study sites which may enhance the generalizability of our results.

Exposure misclassification is a common concern in environmental epidemiology studies.[25] Although we do not know if our results would hold under different scenarios (e.g., different environmental contaminants, exposure window, reproductive outcome, continuous exposure variable, etc.), our quantitative bias assessment indicates that workplace exposure misclassification among employed women may not be a substantial source of potential bias in studies of haloacetic acids and birth defects. Because it is often difficult to measure both household and workplace exposure, our results suggest that household estimates may be sufficient proxies for worksite exposures to haloacetic acids in tap water.

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