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Nina Iszatt, Mark J. Nieuwenhuijsen, Paul Nelson, Paul Elliott and Mireille B. Toledano

*Pediatrics* 2011;127;e389-e397; originally published online Jan 10, 2011;
DOI: 10.1542/peds.2009-3356



# Water Consumption and Use, Trihalomethane Exposure, and the Risk of Hypospadias

**AUTHORS:** Nina Iszatt, MSc,[a,b] Mark J. Nieuwenhuijsen, PhD,[a,c,d,e] Paul Nelson, PhD,[f] Paul Elliott, MBBS, PhD, FMedSci,[a,b] and Mireille B. Toledano, PhD[a,b]

*[a]Department of Epidemiology and Biostatistics and [b]MRC-HPA Centre for Environment and Health, Imperial College London, London, United Kingdom; [c]Center for Research in Environmental Epidemiology, Barcelona, Spain; [d]Municipal Institute of Medical Research Foundation, Barcelona, Spain; [e]Center for Biomedical Investigation Network of Epidemiology and Public Health, Barcelona, Spain; and [f]Phrisk Ltd, London, United Kingdom*

**KEY WORDS**

hypospadias, drinking water, disinfection byproducts, trihalomethanes, water consumption

**ABBREVIATIONS**

DBP—disinfection byproduct
THM—trihalomethane
TTHM—total trihalomethane
OR—odds ratio
CI—confidence interval

www.pediatrics.org/cgi/doi/10.1542/peds.2009-3356

doi:10.1542/peds.2009-3356

Accepted for publication Nov 17, 2010

Address correspondence to Professor Paul Elliott, MRC-HPA Centre for Environment and Health, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, St Mary's Campus, Norfolk Place, London W2 1PG, United Kingdom. E-mail: p.elliott@imperial.ac.uk

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).



**FINANCIAL DISCLOSURE:** *The authors have indicated they have no financial relationships relevant to this article to disclose.*

**WHAT'S KNOWN ON THIS SUBJECT:** Few epidemiological studies, which included varied exposure assessment, have investigated the relation between drinking-water–disinfection byproducts such as trihalomethanes and hypospadias, and their results have been inconclusive.

**WHAT THIS STUDY ADDS:** Little evidence was found for an association between trihalomethanes and hypospadias, but a novel association between water consumption and hypospadias was found. Factors that influence maternal water consumption, or other contaminants in tap or bottled water, might explain this finding.

## abstract

**OBJECTIVES:** Hypospadias is a congenital anomaly that affects up to 70 in 10 000 males. Ingestion of drinking-water–disinfection byproducts such as trihalomethanes (THMs) has been associated with hypospadias in a small sample. We examined risk of hypospadias and exposure to THMs through water consumption and use.

**METHODS:** Between September 2000 and March 2003, we interviewed mothers of 471 boys with hypospadias and 490 controls in southeast England about maternal water consumption, dishwashing, showering, bathing and swimming. We obtained residential THM concentrations from the water companies and linked them by using Geographical Information Systems, which provided data on 468 case-subjects and 485 controls.

**RESULTS:** THM exposures, except for ingestion of $\geq$6 $\mu$g/day of bromodichloromethane (odds ratio [OR]: 1.65 [95% confidence interval (CI): 1.02–2.69]), were not associated with risk of hypospadias. Elevated risk of hypospadias was associated with estimates of consumption of cold tap water at home (OR: 1.71 [95% CI: 1.07–2.76]), total water (OR: 1.70 [95% CI: 1.09–2.67]), bottled water (OR: 1.64 [95% CI: 1.09–2.48]), and total fluid (OR: 1.55 [95% CI: 1.01–2.39]) for the highest versus the lowest categories; the first 2 showed dose-response trends.

**CONCLUSIONS:** Evidence for an association between maternal water consumption and risk of hypospadias did not seem to be explained by THM exposure. Factors that influence maternal water consumption or other contaminants in tap or bottled water might explain this finding. It is important that women maintain an adequate fluid intake during pregnancy. *Pediatrics* 2011;127:e389–e397

Hypospadias is a common urogenital congenital anomaly that affects infant boys.[1] Prevalence estimates are 4 to 24 in 10 000 male births across Europe[2] and 70 in 10 000 male births in the United States.[3] Identified risk factors include low birth weight and family history of hypospadias.[3–5] Chemical exposures have been postulated as a possible cause, specifically antiandrogens[6] and phthalates.[7] Folate supplementation during early pregnancy may have a protective effect.[7]

Disinfection byproducts (DBPs) such as trihalomethanes (THMs) result from a reaction between chlorine and natural organic matter in the water supply.[8] THMs can be taken up through ingestion, inhalation, and skin absorption during drinking, showering, bathing, and swimming.[9] THMs may affect fetal development through a number of mechanisms,[10] including an antiandrogenic mechanism.[11] Maternal bromodichloromethane exposure has been associated with reductions in progesterone levels.[12,13] Progesterone receptors play a direct role in normal genital tubercle development[6,14] and could potentially be influenced by bromodichloromethane exposure. Placental insufficiency[15] and reduced levels of human chorionic gonadotropin[16] have also been implicated in the etiology of hypospadias, and bromodichloromethane has been shown to inhibit human placental trophoblast differentiation, which reduces the secretion of immunoreactive and bioactive chorionic gonadotropin.[17,18]

Results of studies of hypospadias and DBP exposure have been inconsistent. Two studies found no association; however, the exposure measures were crude, the studies were based on routine registry data without detailed individual-level information, and the sample sizes were small.[19,20] The third study found no association overall of hypospadias with exposure to total THM (TTHM), although in a small subset there was an association with intermediate levels of TTHM ingestion.[21]

We examined data from a large case-control study of hypospadias[7,22] to investigate risk of hypospadias in relation to water consumption and use and estimated THM exposure through ingestion, dishwashing, showering, bathing, and swimming. To our knowledge, this study of THMs and hypospadias is the largest to date, and we used information on individual behavior from questionnaires rather than registry data.

## METHODS

The study methods have been reported elsewhere.[7] Briefly, the study region comprised the health regions of North Thames, South Thames, and the Anglian part of Anglia and Oxford in southeast England. Of 41 surgeons who performed operations for hypospadias in the study area, 40 participated in identifying case-subjects born between January 1, 1997, and September 31, 1998. In the United Kingdom, guidelines recommend operation between 6 and 18 months of age[23]; we maximized ascertainment by ensuring that the youngest of the eligible case-subjects would have reached a minimum of 3 years 8 months of age by the end of case ascertainment in May 2002. Cases were eligible if there was an abnormally positioned urethral orifice operated on by the surgeon and no major accompanying anomaly that would suggest it was part of a syndrome. Over the study period there were 191 438 male births; 731 cases of hypospadias were ascertained in the surgeon's register compared with 221 in the national congenital anomalies register.[22] Of 731 invited case-mothers, 610 replied, 471 of whom (77%, or 64% of invited mothers) participated. We randomly selected potential controls from all male births in the study area and period from registers at the Office for National Statistics. Of 1487 invited control mothers, 758 replied, 490 of whom (65%, or 33% of total eligible controls) agreed to participate. We did not provide an incentive for participation. Between September 2000 and March 2003, we interviewed participants by using computer-assisted telephone interviews on a range of topics including parental demographics, family history of disease, pregnancy history, diet, smoking, alcohol use, occupation, and water consumption and use during the first trimester (Supplemental Fig 1). For this study, information on individual water consumption and use was available for mothers of 468 case-subjects and 485 controls, and we estimated exposure measures for water and fluid consumption, THM concentrations, THM ingestion, water-use activities, and uptake of THMs.

The participation of human subjects did not occur until after ethics approval and informed consent was obtained.

### Water- and Fluid-Consumption Estimates

We created estimates for maternal ingestion of cold tap water at home, cold tap water away from home, total cold tap water (home plus away from home), hot beverages made from tap water, and total tap water. We created 2 other variables by combining the amount of bottled water consumed with the total tap-water estimate (referred to as total water consumption) and then adding milk and carbonated-drink intake (total fluid consumption, excluding liquids consumed through foods). Levels of THMs in bottled water were assumed to be negligible.[24]

### THM-Concentration Estimates

Six water companies provided THM data for 140 water zones. We estimated annual average TTHM, total bromi-

nated THM, bromodichloromethane, dibromochloromethane, bromoform, and chloroform concentrations on the basis of quarterly modeled data from Whitaker et al.[25] No THM data were available for 1997; because analysis of quarterly THM data from 1998–2001 showed that THM variation within the water supply can be attributed more to spatial than temporal variation (Supplemental Table 6), we used the 1998 THM data as an exposure measure for mothers of infants born in both 1997 and 1998.

We georeferenced and mapped to the participants' water zone by using ARCMap Geographical Information Systems 9.0.[26] Four hundred twenty-six case-subjects and 444 controls had postal codes that could be georeferenced to 1998 postal code files. Once georeferencing was done, we linked 354 (76%) case-subjects and 336 (69%) controls to their residential water zone and to THM-concentration estimates. Of the 271 participants not linked to THM data, 45 case-subjects and 44 controls were not georeferenced because of invalid postal codes, 15 case-subjects and 13 controls were linked to water zones for which we had no THM data, and another 54 case-subjects and 92 controls fell within water-company boundaries for which we had neither water-zone nor THM data.

### THM-Ingestion Estimates

We multiplied the reported amount of cold tap water drunk at home during the first trimester by the THM-concentration estimates to estimate THM ingestion for mothers of 354 case-subjects and 336 controls.

### Water-Use Activities and THM-Uptake Estimates

We estimated average weekly duration of water use through dishwashing, showering, bathing, and swimming. We then estimated THM exposure for each activity by multiplying the THM-concentration estimates by the weekly duration of each activity. THM concentrations in swimming pools were based on median values from a previous study.[27] Finally, we multiplied the THM-ingestion estimates and the THM-exposure estimates for water-use activities by the corresponding uptake factor (Supplemental Table 7). These estimates were combined according to the method developed by Whitaker et al[28] to obtain estimates for individual and total THM uptake.

### Exposure Categories

For the exposure metrics cold tap water at home, total cold tap water, dishwashing, showering, and bathing, we created 1 category for zero exposure and divided the remaining exposure distribution into tertiles. For THM concentrations, total tap water, total water, total fluid, and THM uptake, because there were small numbers with zero exposure, we divided the exposure distribution into quartiles.

### Statistical Analyses

We assessed correlations between variables by using Goodman-Kruskal's $\gamma$ and Cramer's $V$. We used univariate and multiple logistic regression to estimate risk of hypospadias and calculated crude and adjusted odds ratios (ORs) and confidence intervals (CIs) in R 2.2.0.[29] We included family income and birth weight as potential confounders and then added in stepwise fashion folate-supplement use during pregnancy, maternal smoking during weeks 6 through 18 of pregnancy, and maternal occupational exposure to phthalates as judged from a job-exposure matrix[7] and assessed whether they improved the fit of the adjusted model when using Akaike information criterion.[30] The categorical cut points for these variables are shown in Table 1. We included swimming as a confounder in the model for the consumption and THM-ingestion estimates, because it is an important route of THM uptake and may affect fluid consumption. We excluded positive family history of hypospadias and previous stillbirth from the multiple logistic regression models, because such history only applied to 1 and 2 controls, respectively. We conducted sensitivity analyses by excluding, separately, mothers with gestational diabetes and women who drank high levels of bottled water or high levels of cold tap water at home. We checked for interactions between exposures and the potential confounders in our model. We present uncorrected $P$ values without adjustments for multiple testing.

## RESULTS

### Maternal Characteristics

Mothers of boys with hypospadias drank significantly more cold water at home, total tap water, total water, and total fluid than mothers of controls (Table 1). Lower income, low birth weight, and maternal smoking were associated with an increased risk of hypospadias[7] (Table 1). Correlations between the potential confounders and water intake, THM concentrations, and water-use variables were all $\gamma <$ 0.33 (Supplemental Table 8). There were no substantial differences in the social-class profiles of the women with THM-exposure data and those without.

### THM Concentration

There were no associations between THM concentrations in the maternal residential water zone and risk of hypospadias (Table 2).

### Water and Fluid Consumption

With adjustment for the highest versus lowest categories, we found significant excess risk of hypospadias for cold tap water at home (OR: 1.71 [95% CI: 1.07–2.76]), bottled water (OR: 1.64

**TABLE 1** Mean Water and Fluid Consumption and Descriptive Data for the Study Population

| | Cases ($N = 468$) | Controls ($N = 485$) | OR (95% CI) |
|---|---|---|---|
| Mean (±SD) water and fluid consumption, L | | | |
| Cold tap water at home | 0.78 (±0.80) | 0.67 (±0.69) | — |
| Total cold tap water | 1.07 (±1.10) | 0.94 (±1.02) | — |
| Total tap water | 1.78 (±1.24) | 1.59 (±1.11) | — |
| Bottled water | 0.45 (±0.90) | 0.35 (±0.63) | — |
| Total water | 2.22 (±1.50) | 1.95 (±1.23) | — |
| Total fluid | 2.84 (±1.70) | 2.49 (±1.36) | — |
| Descriptive data for the study population, *n* (%) | | | |
| Maternal age | | | |
| 15–24 y | 61 (13.1) | 46 (9.5) | 1.64 (1.06–2.54) |
| 25–29 y | 127 (27.3) | 105 (21.6) | 1.49 (1.07–2.08) |
| 30–34 y | 163 (35.1) | 201 (41.4) | 1.00 |
| 35–39 y | 95 (20.4) | 109 (22.5) | 1.07 (0.76–1.52) |
| 40–50 y | 19 (4.1) | 24 (4.9) | 0.98 (0.51–1.84) |
| Income | | | |
| Less than £10 000 | 55 (12.3) | 27 (5.7) | 2.89 (1.62–5.25) |
| £10 000–£20 000 | 130 (29.0) | 108 (22.8) | 1.71 (1.10–2.67) |
| More than £20 000–£30 000 | 125 (27.9) | 131 (27.6) | 1.35 (0.88–2.10) |
| More than £30 000–£50 000 | 88 (19.6) | 137 (28.9) | 0.91 (0.58–1.43) |
| More than £50 000 | 50 (11.2) | 71 (15.0) | 1.00 |
| Birth weight | | | |
| Low (<2.5 kg) | 57 (13.8) | 38 (8.6) | 1.71 (1.11–2.66) |
| Normal (≥2.5 kg) | 356 (86.2) | 406 (91.4) | 1.00 |
| Maternal smoking (6–18 wk) | | | |
| 0/d | 353 (80.8) | 396 (82.8) | 1.00 |
| ≤5/d | 39 (8.9) | 57 (11.9) | 1.16 (0.78–1.71) |
| >5/d | 45 (10.3) | 25 (5.2) | 2.01 (1.22–3.39) |
| Folate during first 3 mo of pregnancy | | | |
| No | 102 (21.8) | 76 (15.7) | 1.00 |
| Yes | 346 (74.1) | 402 (82.9) | 0.64 (0.46–0.89) |
| Maternal occupational exposure to phthalates | 19 (4.1) | 7 (1.4) | 2.02 (0.84–5.4) |
| No | 327 (70.5) | 343 (71.9) | 1.00 |
| Yes | 14 (3.0) | 4 (0.8) | 3.67 (1.30–13.50) |
| Unemployed | 123 (26.5) | 130 (27.3) | 0.99 (0.74–1.33) |

[95% CI: 1.09–2.48]), total water (OR: 1.70 [95% CI: 1.09–2.67]), and total fluid (OR: 1.55 [95% CI: 1.01–2.39]). Dose-response relations were found for maternal consumption of cold tap water at home ($P_{trend} = .01$) and total water ($P_{trend} = .02$) but not for bottled water or total fluid. There was little evidence of excess risks for total cold tap water, total tap-water consumption (Table 3), cold tap-water consumption away from home, and consumption of hot tap water (eg, coffee and teas) (Supplemental Table 9).

### THM Ingestion

After adjustment, ingestion of ≥6 μg/day of bromodichloromethane was associated with a higher risk of hypospadias (OR: 1.65 [95% CI: 1.02–2.69]), although there were no dose-response relations between THM-ingestion estimates and risk of hypospadias (Table 4).

### Water-Use Activities and THM Uptake

There were no trends for elevated risk of hypospadias associated with duration of dishwashing, showering, bathing, or bathing and showering combined; with adjustment, there was a borderline significant ($P = .05$) reduced risk of hypospadias among children of mothers who reported swimming during pregnancy (OR: 0.74 [95% CI: 0.54–1.00]) (Table 5 and Supplemental Table 9). Estimates of specific and total THM-uptake estimates also did not show elevated risk of hypospadias (OR: 0.73 [95% CI: 0.55–1.19] for the highest category of TTHM uptake) (Supplemental Table 9).

There were no significant interactions between exposures and potential confounders.

### Sensitivity Analyses

There was little correlation ($\gamma = -0.130$) between drinking bottled water and cold tap water at home. Excluding women in the highest category of bottled-water consumption from the cold-tap-water-at-home analysis, and vice versa, or including both variables in the same model did not materially affect the results. There was little association between gestational diabetes and hypospadias risk, and excluding mothers with gestational diabetes did not materially affect the results (Supplemental Tables 10 and 11).

## DISCUSSION

We investigated risk of hypospadias and exposure to THMs and incorporated individual-level data on water consumption, dishwashing, showering, bathing, swimming, and fluid intake. We found a dose-response relation between risk of hypospadias and cold tap-water consumption at home and total water consumption.

To our knowledge, no previous studies have shown an association between water consumption and risk of hypospadias. Lower income has previously been associated with increased cold tap-water intake during pregnancy[31] and increased risk of congenital anomalies,[32] but the association has been inconsistent for hypospadias.[7,33] Although there was no evidence of selection bias in our study resulting from differential participation of case-subjects and controls according to socioeconomic status,[34] we found a

**TABLE 2** Case/Control Prevalence According to THM Concentration and Unadjusted and Adjusted ORs of Hypospadias Risk

| | Cases ($N = 354$), *n* (%) | Controls ($N = 336$), *n* (%) | OR (95% CI) | Adjusted OR (95% CI)[a] |
|---|---|---|---|---|
| TTHM | | | | |
| 0–11 μg/L | 81 (22.9) | 79 (23.5) | 1.00 | 1.00 |
| 12–23 μg/L | 100 (28.2) | 75 (22.3) | 1.30 (0.85–2.00) | 1.20 (0.74–1.95) |
| 24–36 μg/L | 80 (22.6) | 93 (27.7) | 0.84 (0.54–1.29) | 0.78 (0.47–1.27) |
| 37–105 μg/L | 93 (26.3) | 89 (26.5) | 1.02 (0.67–1.56) | 0.93 (0.57–1.50) |
| Chloroform | | | | |
| 0.0–0.9 μg/L | 50 (14.1) | 53 (15.8) | 1.00 | 1.00 |
| 1.0–2.9 μg/L | 103 (29.1) | 78 (23.2) | 1.40 (0.86–2.28) | 1.17 (0.67–2.03) |
| 3.0–6.9 μg/L | 104 (29.4) | 99 (29.5) | 1.11 (0.69–1.79) | 0.99 (0.57–1.69) |
| 7–90 μg/L | 97 (27.4) | 106 (31.5) | 0.97 (0.60–1.56) | 0.84 (0.49–1.46) |
| Total brominated THM | | | | |
| 0–10 μg/L | 86 (24.3) | 83 (24.7) | 1.00 | 1.00 |
| 11–18 μg/L | 92 (26.0) | 80 (23.8) | 1.11 (0.73–1.70) | 1.02 (0.63–1.65) |
| 19–24 μg/L | 82 (23.2) | 88 (26.2) | 0.90 (0.59–1.38) | 0.82 (0.51–1.34) |
| 25–70 μg/L | 94 (26.6) | 85 (25.3) | 1.07 (0.70–1.63) | 1.06 (0.66–1.71) |
| Bromodichloromethane | | | | |
| 0.0–1.0 μg/L | 87 (24.6) | 90 (26.8) | 1.00 | 1.00 |
| 1.1–5.0 μg/L | 88 (24.9) | 65 (19.3) | 1.40 (0.91–2.17) | 1.15 (0.71–1.88) |
| 6–9 μg/L | 85 (24.0) | 94 (28.0) | 0.94 (0.62–1.42) | 0.83 (0.51–1.35) |
| 10–23 μg/L | 94 (26.6) | 87 (25.9) | 1.12 (0.74–1.69) | 1.05 (0.65–1.68) |
| Dibromochloromethane | | | | |
| 0–3 μg/L | 87 (24.6) | 85 (25.3) | 1.00 | 1.00 |
| 4–7 μg/L | 81 (22.9) | 73 (21.7) | 1.08 (0.70–1.68) | 1.00 (0.61–1.64) |
| 8–10 μg/L | 97 (27.4) | 89 (26.5) | 1.06 (0.70–1.61) | 0.91 (0.56–1.47) |
| 11–34 μg/L | 89 (25.1) | 89 (26.5) | 0.98 (0.64–1.49) | 0.92 (0.57–1.49) |
| Bromoform | | | | |
| 0.0–2.4 μg/L | 92 (26.0) | 82 (24.4) | 1.00 | 1.00 |
| 2.5–3.9 μg/L | 70 (19.8) | 70 (20.8) | 0.89 (0.57–1.39) | 0.94 (0.56–1.58) |
| 4.0–6.9 μg/L | 83 (23.4) | 84 (25.0) | 0.88 (0.58–1.35) | 0.88 (0.54–1.45) |
| 7–27 μg/L | 109 (30.8) | 100 (29.8) | 0.97 (0.65–1.45) | 1.06 (0.66–1.69) |

[a] Adjusted for family income, low birth weight, folate-supplement use during pregnancy, maternal smoking during weeks 6 through 18 of pregnancy, and maternal occupational exposure to phthalates. Adjusted estimates were based on data for 289 cases and 292 controls.

lower risk of hypospadias among children of mothers who swam during pregnancy, which potentially reflects social-class differences between case and control mothers. Although we adjusted for family income as a proxy for social class, it remains possible that the association of hypospadias with water consumption might reflect residual confounding by social class or related variables, and it is important that women maintain an adequate fluid intake during pregnancy.

We estimated maternal water consumption from average water use at the time of interview and when pregnant. Interviews were between 2½ and 6 years after pregnancy, so participants could have overestimated or underestimated their consumption, which could have led to exposure misclassification. Recall bias was possible; however, we consider it unlikely that there was differential misclassification between cases and controls, because water consumption was not the main focus of the study and there was no reason for mothers of case-subjects to systematically overestimate water consumption compared with control mothers. We found little association between hypospadias and cold tap water consumed away from home, possibly because water consumption outside the home is difficult to estimate.[35] In our study, only 23% of reported cold tap-water consumption was drunk away from home. We found little association between hypospadias and hot tap-water consumption; boiling water reduces THM concentrations by up to 98%.[36]

Although there was a dose response for water consumption and risk of hypospadias, there was none for THM ingestion. Previous studies mostly found no association of THMs with hypospadias.[19–21] Luben et al[21] found an association of hypospadias with estimated ingestion of TTHM at an intermediate level (>0–32.5 μg/day) but not for high levels (>32.5 μg/day). THMs are volatile, and dermal and inhalation exposures are important routes of uptake.[9,37] We did not find an association of hypospadias with dermal and inhalation THM estimates or with total THM-uptake estimates, which supports previous findings.[21] This result suggests that our finding of increased risk of hypospadias associated with the highest level of bromodichloromethane ingestion may reflect the association with quantity of cold tap water consumed rather than THM exposure.

We used various exposure metrics, some of which were based on individual behavioral information, some on area-level THM concentrations, and some on combination of both. These exposure estimates are subject to random error from both classical error (ie, error in sampling measurements of THMs and quantity of water consumed by individual participants) and Berkson error (ie, assigning modeled area-level THM concentration to individual participants); therefore, exposure misclassification may not simply attenuate risk.[38] Exposure misclassification will also increase the uncertainty in our estimates, which is reflected by wide CIs. THM-concentration information was based on the water zone in which the woman lived at the time of conception. Exposure misclassification from residential mobility during pregnancy is possible,[39] although lessened if mothers remained within the same water zone. THM esti-

**TABLE 3** Unadjusted and Adjusted ORs for Hypospadias Risk and Reported Tap-Water and Fluid Consumption

| | Cases ($N = 468$), $n$ (%) | Controls ($N = 485$), $n$ (%) | OR (95% CI) | Adjusted OR (95% CI)[a] | $P_{trend}$ |
|---|---|---|---|---|---|
| Cold tap water at home | | | | | |
| 0.0 L | 67 (14.3) | 84 (17.3) | 1.00 | 1.00 | — |
| 0.001–0.4 L | 126 (26.9) | 157 (32.4) | 1.01 (0.68–1.50) | 1.22 (0.76–1.94) | — |
| 0.5–0.9 L | 121 (25.9) | 117 (24.1) | 1.30 (0.86–1.96) | 1.65 (1.02–2.68) | — |
| >1.0 L | 154 (32.9) | 127 (26.2) | 1.52 (1.02–2.27) | 1.71 (1.07–2.76) | 0.01 |
| Total cold tap water, home, and away from home | | | | | |
| 0.0 L | 60 (12.8) | 71 (14.7) | 1.00 | 1.00 | — |
| 0.001–0.6 L | 134 (28.6) | 152 (31.5) | 1.04 (0.69–1.58) | 1.25 (0.77–2.03) | — |
| 0.7–1.2 L | 135 (28.8) | 134 (27.8) | 1.19 (0.78–1.81) | 1.50 (0.93–2.45) | — |
| 1.3–13.0 L | 139 (29.7) | 125 (25.9) | 1.32 (0.87–2.01) | 1.26 (0.77–2.07) | 0.36 |
| Total tap water | | | | | |
| 0.0–0.9 L | 95 (20.4) | 127 (26.4) | 1.00 | 1.00 | — |
| 1.0–1.4 L | 117 (25.1) | 124 (25.8) | 1.26 (0.87–1.82) | 1.33 (0.87–2.02) | — |
| 1.5–2.1 L | 120 (25.8) | 124 (25.8) | 1.29 (0.90–1.87) | 1.18 (0.78–1.80) | — |
| 2.2–14.2 L | 134 (28.8) | 106 (22.0) | 1.69 (1.17–2.45) | 1.43 (0.93–2.20) | 0.17 |
| Bottled water | | | | | |
| 0.0 L | 214 (46.8) | 225 (47.2) | 1.00 | 1.00 | — |
| 0.001–0.289 L | 73 (16.0) | 92 (19.3) | 0.83 (0.58–1.19) | 0.92 (0.59–1.40) | — |
| 0.29–0.79 L | 70 (15.3) | 84 (17.6) | 0.88 (0.61–1.27) | 0.94 (0.62–1.44) | — |
| 0.8–10.5 L | 100 (21.9) | 76 (15.9) | 1.38 (0.97–1.97) | 1.64 (1.09–2.48) | 0.05 |
| Total water | | | | | |
| 0.0–1.1 L | 79 (17.3) | 115 (24.3) | 1.00 | 1.00 | — |
| 1.2–1.7 L | 106 (23.2) | 123 (25.9) | 1.25 (0.85–1.85) | 1.32 (0.85–2.05) | — |
| 1.8–2.4 L | 133 (29.2) | 128 (27.0) | 1.51 (1.04–2.21) | 1.44 (0.94–2.22) | — |
| 2.5–16.2 L | 138 (30.3) | 108 (22.8) | 1.86 (1.27–2.73) | 1.70 (1.09–2.67) | 0.02 |
| Total fluid | | | | | |
| 0.0–1.173 L | 93 (20.6) | 137 (29.1) | 1.00 | 1.00 | — |
| 1.174–2.392 L | 114 (25.2) | 117 (24.8) | 1.44 (0.99–2.08) | 1.45 (0.96–2.21) | — |
| 2.393–3.210 L | 113 (25.0) | 118 (25.1) | 1.41 (0.98–2.04) | 1.35 (0.89–2.06) | — |
| 3.211–16.800 L | 132 (29.2) | 99 (21.0) | 1.96 (1.36–2.85) | 1.55 (1.01–2.39) | 0.07 |

[a] Adjusted for family income, low birth weight, folate-supplement use during pregnancy, maternal smoking during weeks 6 through 18 of pregnancy, maternal occupational exposure to phthalates, and swimming. Adjusted estimates were based on data for 367 cases and 408 controls.

mates were based on annual averages of quarterly modeled data for 1998 regardless of whether the year of birth was 1997 or 1998. Although the modeled individual THM estimates were robust[25] and our analysis revealed that spatial was more important than temporal variation, trimester-specific estimates would have been preferable to 1998 annual averages.

Although there have been limited studies on THMs and hypospadias, a number of studies have investigated other congenital anomalies. Chlorinated water and THM concentrations have been associated with an increased risk of urinary system defects[40,41] and neural tube defects.[41–43] Folate intake may reduce risk of congenital malformations such as neural tube defects[44] and hypospadias.[7] An interaction between vitamin use, TTHM, and risk of neural tube defects has been reported[43]; DBPs may interfere with folate metabolism,[45] but we found no interaction between folate supplementation, THMs, and the risk of hypospadias.

Overall, exposure to THMs does not seem to explain the significant association of hypospadias with water consumption. Water consumption may be a proxy for exposure to other compounds in the water. DBPs such as haloacetic acids, which are nonvolatile and mainly ingested,[9] have been associated with neural tube defects[46,47] and urogenital malformations in laboratory animals.[48,49] We did not have data on other DBPs, which have not consistently correlated with THMs.[50] Endocrine-disrupting chemicals have also been implicated in hypospadias,[6,7,51] although the contribution of tap water to overall exposure to endocrine-disrupting chemicals is of minor importance compared with other exposure routes.[52] Endocrine-disrupting chemicals, possibly phthalates, leached from plastic bottles may help explain the increased risk seen with consumption of large quantities of bottled water and could be confounding the effect seen for cold tap water at home. We did not have data to explore whether the women drank water from plastic or glass bottles or on phthalate levels in bottled water. Furthermore, phthalates in bottled water do not represent a significant exposure pathway,[53] although water packaged in plastic bottles has produced unexplained estrogenic effects in animals.[54] Excluding women in the highest category of bottled water from the cold tap-water analysis and vice versa, and including both variables in the same model, did not materially affect these results; also, there was no correlation between bottled water and cold tap water at home, which suggests that these are independent effects.

Our findings may not be a result of particular agents in the water supply; rather, increased tap-water or bottled-water intake may indicate a problematic pregnancy, such as a metabolic disorder (ie, "reverse causality"). Polydipsia is a symptom of several endocrine-related disorders including diabetes mellitus, diabetes insipidus, and renal disorders. We found no evidence for an association between gestational diabetes and hypospadias. Infants born to women with preexisting (but not gestational) diabetes may be at greater risk of hypospadias.[55,56] We did not have information on

**TABLE 4** Unadjusted and Adjusted ORs for Hypospadias Risk and Estimated THM Ingestion at Home

| | Cases ($N = 354$), *n* (%) | Controls ($N = 336$), *n* (%) | OR (95% CI) | Adjusted OR (95% CI)[a] | $P_{trend}$ |
|---|---|---|---|---|---|
| TTHM | | | | | |
| 0.0 μg/d | 52 (14.7) | 62 (18.5) | 1.00 | 1.00 | — |
| >0.0–8.4 μg/d | 92 (26.0) | 102 (30.4) | 1.08 (0.68–1.71) | 1.23 (0.73–2.11) | — |
| 8.5–21.0 μg/d | 95 (26.8) | 90 (26.8) | 1.26 (0.79–2.01) | 1.31 (0.77–2.24) | — |
| 22–190 μg/d | 115 (32.5) | 82 (24.4) | 1.67 (1.05–2.67) | 1.55 (0.91–2.66) | 0.11 |
| Chloroform | | | | | |
| 0.0 μg/d | 93 (26.3) | 109 (32.4) | 1.00 | 1.00 | — |
| >0.0–1.4 μg/d | 90 (25.4) | 75 (22.3) | 1.41 (0.93–2.13) | 1.26 (0.79–2.01) | — |
| 1.5–4.2 μg/d | 81 (22.9) | 83 (24.7) | 1.14 (0.76–1.73) | 1.12 (0.70–1.79) | — |
| 4.3–65.0 μg/d | 90 (25.4) | 69 (20.5) | 1.53 (1.01–2.33) | 1.36 (0.84–2.22) | 0.30 |
| Total brominated THM | | | | | |
| 0.0 μg/d | 52 (14.7) | 62 (18.5) | 1.00 | 1.00 | — |
| >0.0–7.1 μg/d | 91 (25.7) | 99 (29.5) | 1.10 (0.69–1.75) | 1.25 (0.73–2.14) | — |
| 7.2–17.4 μg/d | 98 (27.7) | 95 (28.3) | 1.23 (0.77–1.96) | 1.26 (0.75–2.15) | — |
| 17.5–180.0 μg/d | 113 (31.9) | 80 (23.8) | 1.68 (1.06–2.69) | 1.59 (0.93–2.73) | 0.10 |
| Bromodichloromethane | | | | | |
| 0.0 μg/d | 79 (22.3) | 101 (30.1) | 1.00 | 1.00 | — |
| >0.0–1.0 μg/d | 91 (25.7) | 78 (23.2) | 1.49 (0.98–2.28) | 1.50 (0.93–2.44) | — |
| 2–5 μg/d | 84 (23.7) | 86 (25.6) | 1.25 (0.82–1.90) | 1.09 (0.67–1.77) | — |
| 6–50 μg/d | 100 (28.2) | 71 (21.1) | 1.80 (1.18–2.76) | 1.65 (1.02–2.69) | 0.13 |
| Dibromochloromethane | | | | | |
| 0.0 μg/d | 52 (14.7) | 62 (18.5) | 1.00 | 1.00 | — |
| >0.0–2.4 μg/d | 93 (26.3) | 104 (31.0) | 1.07 (0.67–1.70) | 1.21 (0.71–2.07) | — |
| 2.5–7.1 μg/d | 99 (28.0) | 88 (26.2) | 1.34 (0.84–2.14) | 1.33 (0.78–2.28) | — |
| 7.2–85.0 μg/d | 110 (31.1) | 82 (24.4) | 1.60 (1.00–2.56) | 1.55 (0.91–2.66) | 0.10 |
| Bromoform | | | | | |
| 0.0 μg/d | 52 (14.7) | 62 (18.5) | 1.00 | 1.00 | — |
| >0.0–1.8 μg/d | 89 (25.1) | 101 (30.1) | 1.05 (0.66–1.68) | 1.13 (0.66–1.93) | — |
| 1.9–4.4 μg/d | 106 (29.9) | 87 (25.9) | 1.45 (0.91–2.32) | 1.49 (0.87–2.55) | — |
| 4.5–60.0 μg/d | 107 (30.2) | 86 (25.6) | 1.48 (0.93–2.37) | 1.49 (0.87–2.59) | 0.08 |

[a] Adjusted for family income, low birth weight, folate-supplement use during pregnancy, maternal smoking during weeks 6 through 18 of pregnancy, maternal occupational exposure to phthalates, and swimming. Adjusted estimates were based on data for 289 cases and 292 controls.

**TABLE 5** Unadjusted and Adjusted ORs for Hypospadias Risk and Reported Dishwashing, Bathing, Showering, and Swimming

| | Cases ($N = 468$), *n* (%) | Controls ($N = 485$), *n* (%) | OR (95% CI) | Adjusted OR (95% CI)[a] |
|---|---|---|---|---|
| Dishwashing washing[b] | | | | |
| 0 min | 37 (8.0) | 44 (9.3) | 1.00 | 1.00 |
| 1–7 min | 204 (44.2) | 200 (42.2) | 1.22 (0.75–1.96) | 1.22 (0.69–2.20) |
| 8–17 min | 92 (19.9) | 136 (28.7) | 0.80 (0.48–1.34) | 0.78 (0.42–1.44) |
| 18–140 min | 129 (27.9) | 94 (19.8) | 1.63 (0.98–2.73) | 1.49 (0.80–2.78) |
| Bathing[b] | | | | |
| 0 min | 70 (15.3) | 84 (17.8) | 1.00 | 1.00 |
| 1–64 min | 106 (23.1) | 139 (29.4) | 0.92 (0.61–1.37) | 0.93 (0.59–1.47) |
| 65–139 min | 134 (29.2) | 111 (23.5) | 1.45 (0.97–2.18) | 1.28 (0.81–2.04) |
| 140–840 min | 149 (32.5) | 139 (29.4) | 1.29 (0.87–1.91) | 1.06 (0.67–1.68) |
| Showering[b] | | | | |
| 0 min | 195 (42.7) | 170 (36.0) | 1.00 | 1.00 |
| 1–39 min | 94 (20.6) | 130 (27.5) | 0.63 (0.45–0.88) | 0.73 (0.49–1.08) |
| 40–74 min | 100 (21.9) | 111 (23.5) | 0.79 (0.56–1.10) | 1.00 (0.67–1.47) |
| 75–420 min | 68 (14.9) | 61 (12.9) | 0.97 (0.65–1.45) | 0.94 (0.60–1.48) |
| Swimming | | | | |
| No | 294 (63.4) | 245 (51.4) | 1.00 | 1.00 |
| Yes | 149 (32.1) | 209 (43.8) | 0.59 (0.45–0.78) | 0.74 (0.54–1.00) |
| Cannot remember | 21 (4.5) | 23 (4.8) | 0.76 (0.41–1.41) | 0.71 (0.34–1.44) |

[a] Adjusted for low birth weight, folate-supplement use during pregnancy, maternal smoking during weeks 6 through 18 of pregnancy, maternal occupational exposure to phthalates and family income. Adjusted estimates were based on data for 370 cases and 411 controls.

[b] Average minutes per week during first trimester of pregnancy.

preexisting diabetes; however, because prevalence of diabetes in women in the United Kingdom was 2.5% in 1998,[57] it is unlikely to account for our findings. Maternal BMI is another potentially important factor associated with hypospadias[15] that may affect water consumption; however, we did not have this information.

We also had no information on paternal factors that have been observed in the etiology of hypospadias.[58,59] Our study may have been limited by our pragmatic approach to hypospadias case identification based on surgical referral and operation, precluding us from investigating any possible relation between the most severe cases and THM exposure.

## CONCLUSIONS

We found some evidence for an association between maternal water consumption and risk of hypospadias, which did not seem to be explained by THM exposure. Factors that influence maternal water consumption or other contaminants in tap or bottled water might explain this finding. Those who perform studies of water contaminants and reproductive outcomes need to consider social class, lifestyle, and anthropometric factors in pregnancy that may influence water consumption. It is important that women maintain an adequate fluid intake during pregnancy.

## ACKNOWLEDGMENTS

This study was funded by a grant from the UK Department of Health. Dr Nelson was supported by a Wellcome Trust Research Training Fellowship in clinical epidemiology and also in part by the North Thames Training Programme in Public Health Medicine. We acknowledge the National Institute for Health Research Comprehensive Biomedical Research Centre, Imperial College Healthcare NHS Trust, Imperial College London. Dr Elliott is a National Institute for Health Research senior investiga-

tor. The study sponsors had no role in the study design, data collection, analysis or interpretation, or writing of the article.

We thank Marie-Louise Dudley and Claire Brown for conducting the interviews; James Stewart-Evans for database-cleaning; the Small Area Health Statistics Unit, namely Cornelis de Hoogh for assistance with Geographical Information Systems and James Bennett for modeling the trihalomethane data; John Fawell for helpful comments on an earlier draft of the manuscript; the water companies for providing trihalomethane data; the Office for National Statistics for providing the names and contact details of the subjects; and the surgeons, general practitioners, and mothers who participated in the study.

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# Water Consumption and Use, Trihalomethane Exposure, and the Risk of Hypospadias

Nina Iszatt, Mark J. Nieuwenhuijsen, Paul Nelson, Paul Elliott and Mireille B. Toledano

*Pediatrics* 2011;127;e389-e397; originally published online Jan 10, 2011;
DOI: 10.1542/peds.2009-3356