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Drinking Water Disinfection by-Products and Congenital Malformations: A Nationwide Register-Based Prospective Study

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Background: Drinking water chlorination by-products have been associated with adverse reproductive outcomes, although the findings for congenital malformations are still inconclusive.

Objective: We conducted a nationwide register-based prospective study to assess whether first trimester maternal exposure to the four most common trihalomethanes [total trihalomethanes (TTHM)] via municipal drinking water was associated with risk of congenital malformation among newborns.

Methods: We included all births during 2005–2015 (live and stillbirths) of mothers residing in Swedish localities having >10,000 inhabitants, two or fewer operating water works, and sufficient municipal TTHM monitoring data. Individual maternal first trimester exposure was obtained by linking TTHM measurements to residential information, categorized into no chlorination and <5, 5–15, and >15 μg TTHM/L. We also made chlorination treatment-specific analyses (exclusive use of chloramine or hypochlorite). Outcomes and covariates were obtained via linkage to health care and administrative registers. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by logistic regression.

Results: Based on 623,468 births and a prevalence of congenital malformation of ∼2 cases/100 births, we observed associations between TTHM exposure in areas using chloramine and malformations of the nervous system (OR = 1.82; 95% CI: 1.07, 3.12), urinary system (OR = 2.06; 95% CI: 1.53, 2.78), genitals (OR = 1.77; 95% CI: 1.38, 2.26), and limbs (OR = 1.34; 95% CI: 1.10, 1.64), comparing the highest exposed category with the unexposed. No associations were observed in areas using exclusively hypochlorite as the primary water treatment method. By contrast, for malformations of the heart, a significant inverse association was observed only in areas using hypochlorite.

Discussion: TTHM exposure was associated with the increased risk of malformations of the nervous system, urinary system, genitals, and limbs in areas exclusively using chloramine. An association between chloramine-related chlorination by-products and congenital malformations has not previously been highlighted and needs further attention. https://doi.org/10.1289/EHP9122

Introduction

Drinking water chlorination is an efficient health intervention, used for decades to inactivate pathogens in the drinking water and to reduce microbial growth in the water distribution system. Owing to its strong oxidative properties, chlorine reacts with substances in the water (e.g., natural organic matter), resulting in the formation of hundreds of chlorination by-products (CBPs) (Richardson et al. 2007). Epidemiological evidence is increasing that CBPs are associated with adverse reproductive outcomes, such as intrauterine growth retardation (Cao et al. 2016; Grazuleviciene et al. 2011; Hinckley et al. 2005; Kramer et al. 1992; Levallois et al. 2012; Lewis et al. 2006; Smith et al. 2016; Säve-Söderbergh et al. 2020; Wright et al. 2003, 2004). Likewise, some epidemiological studies suggest associations may exist between CBP exposures and malformations of the neural tube (Dodds and King 2001; Klotz and Pyrch 1999), urogenital systems (Grazuleviciene et al. 2013; Magnus et al. 1999), and circulatory system (Cedergren et al. 2002; Chisholm et al. 2008; Grazuleviciene et al. 2013; Hwang et al. 2002). However, as reported in a meta-analysis, epidemiological evidence on congenital anomalies resulting from gestational exposure to CBPs remains inconclusive (Nieuwenhuijsen et al. 2009). Because embryonic development is complex and congenital malformations are rare, there is a delicate balance between limited power and pooling of conceivably etiologically heterogenic outcomes. In any case, accurate classification of the exposure is perhaps an even greater challenge that requires careful consideration of any potential bias introduced by misclassifications (Waller et al. 2001; Wright and Bateson 2005).

We conducted a large prospective nationwide register-based cohort study in Sweden to assess the association of the exposure during the first trimester of gestation to the sum of the four most common CBPs, total trihalomethanes (TTHM: chloroform, bromoform, bromodichloromethane, and dibromochloromethane), via drinking tap water, with congenital malformations. All areas included were provided with municipal tap drinking water (chlorinated or nonchlorinated). We also performed chlorination treatment-specific analyses by the two major chlorination treatment methods because they may lead to the formation of different CBPs.

Methods

Study Area and Population

We initially mapped all localities (coherent and densely populated urban areas) in Sweden having a population of >10,000 inhabitants ($n = 118$, representing ∼60% of the country's population) with respect to their drinking water production and raw water source during the period 2005–2015. We then excluded localities if there had been changes in chlorination treatment during 2005–2015 or if the locality or municipality were supplied by three or more water utilities. For localities supplied by nonchlorinated drinking water, we excluded those where CBPs still happened to be detected in the tap water when monitored. Among the localities supplied by chlorinated tap water, we excluded localities in which differences in the mean CBP concentrations between two utilities serving the locality exceeded 10 μg/L and

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those in which CBPs were measured for a period of <4 y during the study period (2005–2015). In total, 83 localities remained as our study area (Figure 1). We used a similar study design as in a study assessing TTHM exposure in relation to small for gestational age and preterm delivery (Säve-Söderbergh et al. 2020).

The study population was identified as mothers having their official residential registration in one of the 83 localities at any time during a pregnancy that resulted in a childbirth (live or stillbirth) in Sweden between 1 January 2005 and 31 December 2015. By use of the maternal personal identification number (a unique identification number assigned to all Swedes), health care data linkage was performed by the Swedish Medical Birth Register at the National Board of Health and Welfare. Administrative data linkage included the Longitudinal Integration Database for Health Insurance and Labor Market Studies and a national register for regional divisions based on real estate (Geografidatabasen), both databases at Statistics Sweden. In total, 738,538 newborns (including 2,578 stillbirths) of 457,524 mothers were identified as living in the study area during the pregnancy (Figure 1). Among these mothers, 15% changed locality at some point during their pregnancy, and 7% did so during the first trimester.

Although mothers of full-term newborns were included if they had their residential address in the area at the same locality during a consecutive period of between 6 and 10 months prior to delivery, mothers of preterm newborns were included if they had their residential address in the study area during the entire pregnancy (at birth and 10 months prior to birth). We excluded mothers with a potential high occupational TTHM exposure, that is, if they were registered at the antenatal care as professional swimmers, coaches, or swimming pool personnel ($n = 262$). The study was approved by the regional ethics review board in Stockholm. Because the study was only register-based, no informed consent was required for the data linkage.

Exposure and Covariates

TTHM is a commonly used indicator of the total CBP exposure because trihalomethanes (THMs) are often generated in the highest concentrations (Richardson et al. 2007). We obtained TTHM exposure by summing the concentrations of chloroform, bromoform, bromodichloromethane, and dibromochloromethane in tap water sampled at the end user in the municipal monitoring program from

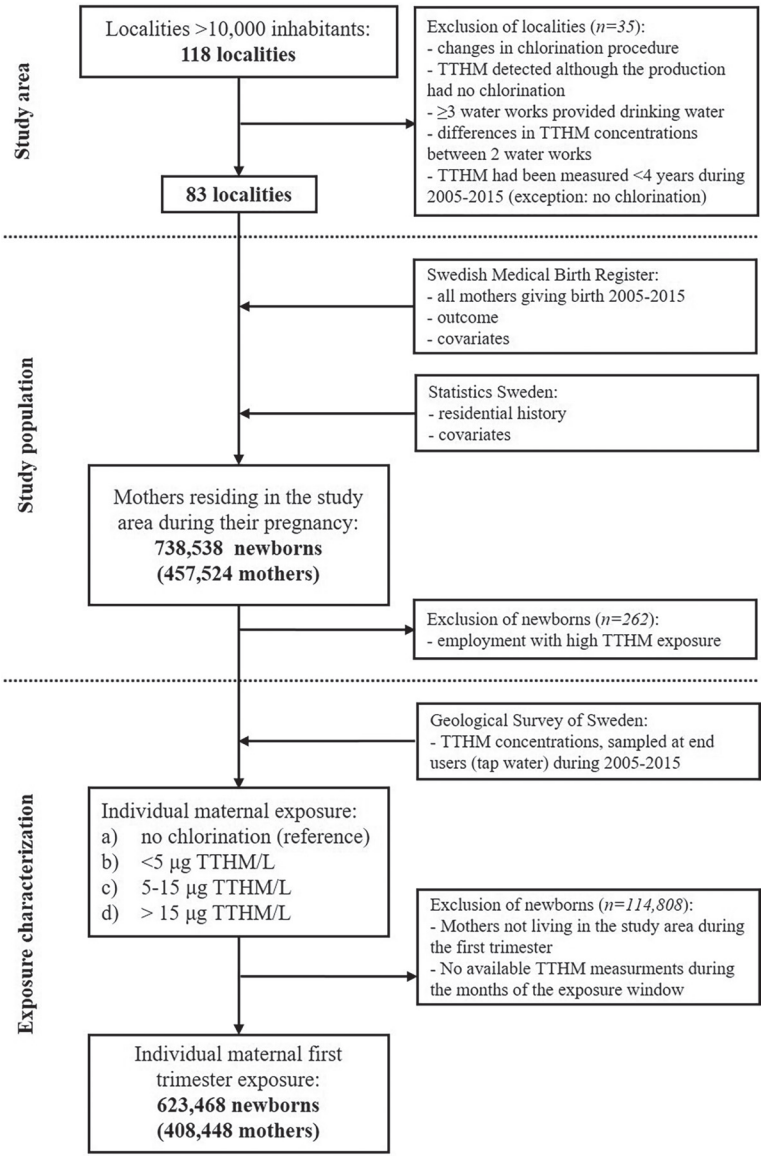

Figure 1. Study area, study population, and exposure categorization. TTHM, average of the four most common trihalomethanes (total trihalomethanes).

a nationwide database managed by the Geological Survey of Sweden {$n = 3{,}887$ using confirmed TTHM analyses [in exposed areas: mean (standard deviation) = 7.2 (11.1) μg TTHM/L, median <level of detection, maximum = 105 μg TTHM/L]}. The sampling made in the municipal monitoring program was done according to the national drinking water regulations (SLVFS 2001:30). Thus, a minimum of four yearly end-user tap water samples were available, with three additional samplings per every 1,000 m^3 drinking water produced per day (TTHM should not exceed 100 μg/L in drinking water). We estimated a trimester-specific 3-month average TTHM exposure for each individual pregnancy by using a locality-specific and multiannual monthly average of TTHM [as outlined by Säve-Söderbergh et al. (2020)]. Briefly, by using a multiannual average for each month and locality for assigning the exposure, we *a*) accounted for seasonal variations (Andersson et al. 2019), *b*) reduced the weight of single extreme values and the influence of locality-specific variations in monitoring programs, as well as *c*) minimized the number of pregnancies excluded due to missing exposure information for a specific month or year.

We used the first trimester because this is the critical window for the development of most human organs and, thus, the effect-window for teratogens (Moore et al. 2016). We are confident that regular consumption of tap water is likely applicable to almost all mothers (Säve-Söderbergh et al. 2018). Based on each individual's locality-specific and multiannual 3-month average TTHM, the maternal exposure was then categorized into one of the following categories: *a*) no chlorination (only mothers in localities with no chlorination), *b*) <5 μg TTHM/L, *c*) 5–15 μg TTHM/L, and *d*) >15 μg TTHM/L.

From the Swedish Medical Birth Register, we obtained maternal information on age, body mass index (BMI), and smoking at registration to antenatal care, parity, self-reported pregestational diabetes, and self-reported use of teratogenic drugs (Class 3) (Nörby et al. 2013). From Statistics Sweden, we obtained data on country of birth, household income, and highest attained education. We also collected locality-related information, such as raw water source, size of the locality, and chlorination treatment used from drinking water producers and the Swedish Water & Wastewater Association.

Outcomes

Information on the diagnosis of congenital malformations [categorized according to the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10 codes Q00–Q99; WHO 2016)] was obtained from the Swedish Medical Birth Register, which covers diagnoses made during the first 28 days postpartum. Major congenital malformations were classified by organ system according to the European Surveillance of Congenital Anomalies (EUROCAT 2014) into nervous system defects, congenital heart defects, orofacial clefts, digestive system defects, urinary system defects, genital defects, and defects in the limbs, as well as chromosomal defects.

Statistical Analyses

We used multivariable logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of exposure to TTHM and the risk of major congenital malformations. To reduce dependency on multiple births, the analyses were clustered by anonymized maternal identification number (intragroup correlation), as received by the data provider.

We used inverse probability weighting to account for missing data and for confounding, that is, we used the inverse of the product of selection and exposure probabilities (Hernán and Robins 2020). Confounders included into the model were selected based on prior knowledge of potential risk factors for congenital malformations. Thus, models were adjusted for maternal age (<25, 25−<30, 30−<35, 35−<40, ≥40 y), BMI (at registration to antenatal care: <18.5, 18.5−<25, 25−<30, ≥30 kg/m^2), maternal self-reported pregestational diabetes (yes/no), any use of teratogenic drugs (yes/no), parity (nulliparous, 1, 2, ≥3), smoking at registration to antenatal care (no smoking, 1–9 cigarettes/d, >9 cigarettes/d), highest attained education (elementary school/secondary education/postsecondary education) and household income (yearly quartiles by year of birth). Despite the locality-specific differences, given the risk of overadjusting, we did not cluster by locality because locality was highly linked to the drinking water treatment method.

The median TTHM concentrations for each exposure category was used to assess linear trends. In the main analyses, we used those living in localities with nonchlorinated municipal drinking water as the reference because they represented the most appropriate unexposed population (pregnant women in densely populated areas provided with municipal drinking water, i.e., no private wells). Previous studies generally used the lowest exposed category as the reference [e.g., Nieuwenhuijsen et al. (2008) and Chisholm et al. (2008)]. For comparison and to assess the potential impact of any contextual confounding linked to the use of chlorination, we also performed analyses in which the lowest TTHM category was used as the reference (<5 μg/L), excluding localities using nonchlorinated water.

In addition, we performed separate analyses for pregnant women in localities that used either hypochlorite or chloramine as the exclusive drinking water treatment method because these treatments may have varying impact on the formation of CBPs. Statistical significance level was set at 0.05, and all statistical analyses were performed using Stata (Release 14.2; StataCorp).

Results

During 2005–2015, we ascertained 623,468 newborns (live and stillbirths) among mothers assigned to a first trimester TTHM exposure (Figure 1). Of those, 65,154 were newborns of mothers receiving nonchlorinated municipal tap water, whereas 133,071 and 247,497 newborns had mothers receiving tap water chlorinated with only hypochlorite or chloramine, respectively, as drinking water treatment. The total prevalence of major congenital malformations was 20 cases/1,000 births (Table S1). The prevalence per group of major malformation ranged from ∼0.5 cases/1,000 births for malformation on the nervous system up to ∼8 cases/1,000 births of congenital heart defects. Major malformations with a prevalence of <∼0.5 cases/1,000 births (i.e., malformations of the ear, face and neck, eye, respiratory, and abdominal wall), as well as minor malformations (prevalence >1.5 cases/10,000 births) were presented only by their prevalence in (Table S1).

We observed some differences in baseline maternal characteristics across the exposure groups, especially for maternal age, attained education, and household income (Table 1). In areas with chlorinated water, the mothers assigned to the lowest exposure category (<5 μg TTHM/L) were older, had higher household incomes, lower BMIs, and were less often smokers and diabetics, as compared with those in the highest category (>15 μg TTHM/L). Similar differences were also observed among mothers in areas receiving drinking water treated with chloramine alone (Table 1). In contrast, in areas receiving water chlorinated with hypochlorite only, the mothers in the lowest exposed category were younger and had both lower attained educations and household incomes, as compared with those in highest exposure category. Although there were no major overall differences in maternal characteristics between the

Table 1. Baseline population characteristics and locality-specific characteristics, by individual first trimester maternal average exposure to the four most common trihalomethanes (TTHM) for all and by chlorination treatment expressed as proportions of all included newborns (%).

			All chlorinated areas			Hypochlorite			Chloramine		
Variables	Categories	No chlorination	<5 μg TTHM/L	5–15 μg TTHM/L	>15 μg TTHM/L	<5 μg TTHM/L	5 – 15 μg TTHM/L	>15 μg TTHM/L	<5 μg TTHM/L	5 – 15 μg TTHM/L	>15 μg TTHM/L
Births included	(*n*)	65,154	289,915	179,182	89,217	30,883	54,144	48,044	188,428	18,934	40,135
Average TTHM	(μg TTHM/L)	—	0.67	9.3	24	1.2	10	22	0.60	9.0	25
Maternal characteristics											
Age (y)	<25	16	10	12	14	17	16	14	9	10	14
	25–<30	33	26	29	30	33	32	32	24	25	28
	30–<35	33	38	37	36	32	34	35	39	38	37
	35–<40	15	21	18	17	15	15	16	23	22	18
	>40	3.0	4.9	3.9	3.5	3.3	3.2	3.3	5.4	5.4	3.6
BMI (kg/m^2)	<18.5	2.2	2.6	2.4	2.4	2.4	2.3	2.2	2.7	2.8	2.6
	18.5–<25	54	59	57	58	54	56	57	61	61	59
	25–<30	24	21	22	23	24	24	24	20	21	23
	≥30	12	8.8	10	11	13	12	12	7.8	8.4	9.8
	Missing data	7.1	8.5	8.2	5.7	6.7	6.0	6.1	9.0	7.3	5.3
Pregestational diabetes[a]	Yes	1.9	1.3	1.7	2.7	1.5	1.9	1.9	1.2	2.0	3.6
	No	98	99	98	97	98	98	98	99	98	96
Parity	Nulliparous	43	45	46	45	42	44	44	46	48	46
	1	37	38	37	37	37	37	37	37	35	37
	2	13	13	12	13	15	13	13	12	12	12
	≥3	5.9	4.8	5.1	6.0	6.9	5.9	6.3	4.5	4.6	5.5
Smoking[a]	No smoking	90	90	90	91	89	90	91	91	92	91
	1–9 cigarettes/d	4.7	3.6	4.2	4.5	5.8	4.8	4.2	3.0	3.3	4.8
	>9 cigarettes/d	1.2	1.0	1.1	1.4	1.8	1.2	1.2	0.81	0.83	1.7
	Missing data	4.1	5.2	4.4	3.4	3.7	3.5	4.1	5.6	3.7	2.5
Use of teratogenic drugs[a]	Yes	0.055	0.049	0.056	0.053	0.052	0.054	0.058	0.050	0.037	0.045
	No	99	99	99	99	99	99	99	99	99	99
Highest attained educational level	Elementary school	11	10	11	12	16	12	11	9.4	10	12
	Secondary education	39	32	32	31	40	35	33	29	28	28
	Postsecondary education	50	58	57	58	45	53	56	61	62	60
Household income (quartiles by year of birth)	1	16	15	17	20	19	17	15	15	20	26
	2	29	22	26	27	29	28	28	21	22	26
	3	40	30	35	34	36	38	38	28	27	29
	4	15	33	22	19	16	18	19	36	32	18
Locality-specific characteristics											
Water source	Groundwater	95	15	21	43	84	63	58	3.2	4.4	26
	Surface water	5.2	85	79	57	16	37	42	97	96	74
Population in locality (*n*)	<20,000	24	1.5	2.8	3.4	7.5	8.0	6.0	0.47	0.0053	0
	20,000–200,000	76	62	34	41	92	63	51	73	72	30
	>200,000	0	37	64	56	0	29	43	27	28	70

Note: The study included a total of 623,468 children born during 2005–2015 to mothers living in large urban areas (>10,000 inhabitants) in Sweden. There were no missing data, with the exception of BMI (8%) and smoking status (6%).
—, Not applicable; BMI, body mass index; TTHM, average of the four most common trihalomethanes (total trihalomethanes).
[a]As reported at registration to antenatal care.

nonchlorinated and chlorinated study areas, the mothers in the nonchlorinated areas tended to be more similar to those in the highest than the lowest TTHM exposure category (Table 1). For the locality-related characteristics, we observed that areas with nonchlorinated drinking water were generally smaller and their raw water source was more often groundwater as compared with those with chlorinated drinking water. These differences were especially marked when the areas with nonchlorinated drinking water were compared with those using chloramine treatment.

When not differentiating by chlorination treatments, a statistically significant increased risk of urinary and genital malformations was observed, multivariable-adjusted OR = 1.44 (95% CI: 1.10, 1.89; $p_{trend} = 0.20$) and OR = 1.47 (95% CI: 1.18, 1.81; $p_{trend} = 0.01$), respectively, when comparing the highest TTHM exposure category with unexposed (Table 2). When considering the areas using chloramine treatment exclusively, associations with significantly increased risk of malformations of both the nervous and the urinary systems, as well as of the genitals and limbs, were found: multivariable-adjusted OR = 1.82 (95% CI: 1.07, 3.12; $p_{trend} = 0.006$), OR = 2.06 (95% CI: 1.53, 2.78; $p_{trend} = 0.001$), OR = 1.77 (95% CI: 1.38, 2.26, $p_{trend} < 0.001$), and OR = 1.34 (95% CI: 1.10, 1.64; $p_{trend} = 0.02$), respectively, when comparing the highest TTHM exposure with unexposed (Table 2). Except for urinary malformations, these associations remained when changing the reference category from unexposed to the lowest exposed category (<5 μg TTHM/L) (Table S2). When considering the areas using hypochlorite treatment, no consistent associations were found.

On the other hand, comparing the highest exposed mothers (>15 μg TTHM/L) to those unexposed (nonchlorinated areas), a significant inverse association was observed for heart defects among the newborns, multivariable-adjusted OR = 0.87 (95% CI: 0.77, 0.99; $p_{trend} = 0.002$; Table 2). In the chlorination treatment-specific analyses, the inverse association remained only for areas using hypochlorite. However, when the lowest TTHM-exposed area (<5 μg TTHM/L) was used as a reference, this association was attenuated and a significant positive association was observed among areas using chloramine, multivariable-adjusted OR = 1.24 (95% CI: 1.09, 1.41; $p_{trend} = 0.001$; Table S2). No clear indications of any associations were observed for the development of orofacial clefts, malformations of the digestive system, or chromosomal abnormalities.

Discussion

In this large-scale nationwide register-based cohort including over 620,000 newborns of mothers living in areas provided with municipal drinking water, we assessed maternal drinking water-related TTHM exposure during pregnancy and subsequent congenital malformations. Based on the first trimester average TTHM tap water concentrations, we observed an increased risk of malformations of the urinary system and of the genitals among newborns of mothers in the highest exposure category. When analyses were separated by type of chlorination treatment, TTHM was associated with an increased risk of malformations of the nervous system, urinary system, genitals, and limbs in areas using chloramine, but not in areas using exclusively hypochlorite as the primary water treatment method. Except for malformations of the urinary system, these associations were robust and remained after changing the reference from the unexposed women to the lowest exposure category (<5 μg TTHM/L). The potential association between TTHM exposure and congenital heart defects was unstable—pointing mainly toward an inverse association—and no clear indications of existing links were observed for the development of orofacial clefts, malformations of the digestive systems, or chromosomal abnormalities.

Based on the most recent meta-analyses of epidemiological studies, evidence of an association between TTHM and congenital malformations is limited (Nieuwenhuijsen et al. 2009). Although some previous studies have reported TTHM exposure (or the use of chlorination as such) to be associated with an increased risk of malformation of the nervous system (Bove et al. 1995; Dodds and King 2001; Klotz and Pyrch 1999), urogenital system (Grazuleviciene et al. 2013; Magnus et al. 1999), and limbs (Kaufman et al. 2020), most studies have reported null findings overall (Chisholm et al. 2008; Dodds et al. 1999; Hwang et al. 2002, 2008; Iszatt et al. 2011; Källén and Robert 2000; Luben et al. 2008; Nieuwenhuijsen et al. 2008; Shaw et al. 2003).

As reviewed by Graves et al. (2001), animal studies lend no support to a suggested association between TTHM exposure and congenital malformations. From animal studies, especially studies on the rat, indications of teratogenic effects affecting heart, limbs, kidney, or urogenital malformations have, however, been observed for CBPs other than TTHM, with the strongest support existing for haloacetic acids and haloacetonitriles (Graves et al. 2001). Nevertheless, even these findings were mainly inconsistent (Graves et al. 2001) and the mechanisms are not yet fully understood (Colman et al. 2011). A proposed pathway is, however, that some CBPs may inhibit methionine synthesis, affecting folic acid metabolism (Dow and Green 2000), which is commonly linked to the development of, for example, neural tube defects. These suggested teratogenic CBPs were not measured in the municipal exposure monitoring programs used in the present study, and thus we cannot exclude that these CBPs were present in the drinking water. Because the method of chlorination treatment affects the types and amount of CBPs formed (Amy et al. 2000), we performed separate analyses for hypochlorite and chloramine, to provide additional support in the interpretations of the findings. Accordingly, we observed treatment-specific differences given that associations were observed for malformations of the nervous system, urinary system, genitals, and limbs in areas using chloramine exclusively, but not hypochlorite. Hypothetically, this could be a result of a proportionally higher formation of potentially teratogenic CBPs, such as haloacetic acids, in areas using chloramine, as compared with hypochlorite, despite similar detected TTHM levels (Sakai et al. 2016). Considering the limited combined evidence from animal and epidemiological studies, we can only speculate on the potential reason behind the chlorination treatment-specific associations observed for chloramine in this study. One potential explanation could be concomitant exposure to CBPs other than those included in the TTHM definition. Alternatively, the chlorinated drinking water may have contained higher levels of single THMs, rather than TTHM, which we were not able to separately account for in this study.

Of all malformations, congenital heart defects have the strongest support for an association with CBP exposure based on experimental and epidemiological studies (Graves et al. 2001; Nieuwenhuijsen et al. 2009). In the present study, however, we observed an inverse association for TTHM exposure and heart defects. One possible explanation for this inverse association observed could be selection bias, commonly introduced when birth records of live births are used (Hernán et al. 2002). Although we were able to include both live and stillbirths in our cohort, there is no information on miscarriage or termination of pregnancies available in the Medical Birth Register. Malformation is common among early pregnancy losses (Philipp et al. 2003), thus any differences in the area-dependent rate of miscarriages or termination of pregnancies due to malformations could also introduce a bias. Although there is no information on the rate of miscarriages, there are indications of regional variations in the rate of termination of pregnancies due to severe malformations in Sweden (NBHW

Table 2. Associations between total trihalomethanes (TTHM) in municipal drinking water during the first trimester of pregnancy and major congenital malformations, expressed as odds ratios (ORs) and 95% confidence intervals (CIs) and using nonchlorinated densely populated areas as reference.

Groups of congenital malformations	Categories		Total births (*n*)	Nonchlorinated (OR)	<5 μg TTHM/L [OR (95% CI)]	5–15 μg TTHM/L [OR (95% CI)]	>15 μg TTHM/L [OR (95% CI)]	p_{trend}
Nervous system	All	Cases (*n*)	623,468	37	129	67	58	0.5
		Noncases (*n*)		65,117	289,786	179,115	89,159	
		Crude		1.00 (Ref)	0.78 (0.54, 1.13)	0.66 (0.44, 0.98)	1.14 (0.76, 1.73)	
		Multivariable-adjusted		1.00 (Ref)	0.87 (0.56, 1.34)	0.71 (0.44, 1.14)	1.27 (0.78, 2.05)	
	Hypochlorite	Cases (*n*)	198,225	37	22	30	20	0.3
		Noncases (*n*)		65,117	30,861	54,114	48,024	
		Crude		1.00 (Ref)	1.26 (0.74, 2.13)	0.98 (0.60, 1.58)	0.73 (0.43, 1.26)	
		Multivariable-adjusted		1.00 (Ref)	1.35 (0.75, 2.45)	1.07 (0.62, 1.84)	0.73 (0.39, 1.37)	
	Chloramine	Cases (*n*)	312,651	37	78	9	36	0.006
		Noncases (*n*)		65,117	188,350	18,925	40,099	
		Crude		1.00 (Ref)	0.73 (0.49, 1.08)	0.84 (0.40, 1.73)	1.58 (0.99, 2.50)	
		Multivariable-adjusted		1.00 (Ref)	0.85 (0.53, 1.36)	0.89 (0.35, 2.21)	1.82 (1.07, 3.12)	
Heart defects	All	Cases (*n*)	623,468	586	2,218	1,185	723	0.002
		Noncases (*n*)		64,568	287,697	177,997	88,494	
		Crude		1.00 (Ref)	0.85 (0.77, 0.93)	0.73 (0.66, 0.81)	0.90 (0.81, 1.00)	
		Multivariable-adjusted		1.00 (Ref)	0.82 (0.74, 0.91)	0.70 (0.63, 0.79)	0.87 (0.77, 0.99)	
	Hypochlorite	Cases (*n*)	198,225	586	262	453	372	0.03
		Noncases (*n*)		64,568	30,621	53,691	47,672	
		Crude		1.00 (Ref)	0.94 (0.81, 1.09)	0.93 (0.82, 1.05)	0.86 (0.75, 0.98)	
		Multivariable-adjusted		1.00 (Ref)	0.91 (0.78, 1.07)	0.92 (0.81, 1.05)	0.85 (0.74, 0.98)	
	Chloramine	Cases (*n*)	312,651	586	1,355	139	345	0.8
		Noncases (*n*)		64,568	187,073	18,795	39,790	
		Crude		1.00 (Ref)	0.80 (0.72, 0.88)	0.81 (0.68, 0.98)	0.96 (0.84, 1.09)	
		Multivariable-adjusted		1.00 (Ref)	0.75 (0.67, 0.85)	0.74 (0.60, 0.91)	0.92 (0.79, 1.06)	
Orofacial clefts	All	Cases (*n*)	623,468	107	385	246	117	0.3
		Noncases (*n*)		65,047	289,530	178,936	89,100	
		Crude		1.00 (Ref)	0.81 (0.65, 1.00)	0.84 (0.66, 1.05)	0.80 (0.61, 1.04)	
		Multivariable-adjusted		1.00 (Ref)	0.84 (0.66, 1.06)	0.86 (0.67, 1.11)	0.85 (0.64, 1.13)	
	Hypochlorite	Cases (*n*)	198,225	107	44	87	64	0.4
		Noncases (*n*)		65,047	30,839	54,057	47,980	
		Crude		1.00 (Ref)	0.87 (0.61, 1.23)	0.98 (0.74, 1.30)	0.81 (0.59, 1.11)	
		Multivariable-adjusted		1.00 (Ref)	0.88 (0.61, 1.28)	0.94 (0.69, 1.27)	0.87 (0.63, 1.20)	
	Chloramine	Cases (*n*)	312,651	107	247	27	51	0.4
		Noncases (*n*)		65,047	188,181	18,907	40,084	
		Crude		1.00 (Ref)	0.80 (0.63, 1.00)	0.87 (0.57, 1.33)	0.77 (0.55, 1.08)	
		Multivariable-adjusted		1.00 (Ref)	0.83 (0.64, 1.08)	0.95 (0.61, 1.49)	0.80 (0.55, 1.15)	
Digestive system	All	Cases (*n*)	623,468	87	312	198	132	0.3
		Noncases (*n*)		65,067	289,603	178,984	89,085	
		Crude		1.00 (Ref)	0.81 (0.63, 1.03)	0.83 (0.64, 1.07)	1.11 (0.84, 1.46)	
		Multivariable-adjusted		1.00 (Ref)	0.90 (0.68, 1.18)	0.89 (0.66, 1.19)	1.20 (0.88, 1.64)	
	Hypochlorite	Cases (*n*)	198,225	87	37	70	77	0.2
		Noncases (*n*)		65,067	30,846	54,074	47,967	
		Crude		1.00 (Ref)	0.90 (0.61, 1.32)	0.97 (0.70, 1.33)	1.20 (0.88, 1.64)	
		Multivariable-adjusted		1.00 (Ref)	0.94 (0.62, 1.44)	0.96 (0.67, 1.37)	1.25 (0.88, 1.77)	
	Chloramine	Cases (*n*)	312,651	87	202	14	54	0.5
		Noncases (*n*)		65,067	188,226	18,920	40,081	
		Crude		1.00 (Ref)	0.80 (0.62, 1.04)	0.55 (0.31, 0.98)	1.01 (0.72, 1.42)	
		Multivariable-adjusted		1.00 (Ref)	0.92 (0.68, 1.23)	0.62 (0.33, 1.17)	1.14 (0.78, 1.68)	

Table 2. (*Continued.*)

Groups of congenital malformations	Categories		Total births (*n*)	Nonchlorinated (OR)	<5 μg TTHM/L [OR (95% CI)]	5–15 μg TTHM/L [OR (95% CI)]	>15 μg TTHM/L [OR (95% CI)]	p_{trend}
Urinary	All	Cases (*n*)	623,468	101	932	259	195	0.2
		Noncases (*n*)		65,053	288,983	178,923	89,022	
		Crude		1.00 (Ref)	2.08 (1.69, 2.55)	0.93 (0.74, 1.17)	1.41 (1.11, 1.80)	
		Multivariable-adjusted		1.00 (Ref)	2.15 (1.70, 2.73)	0.95 (0.73, 1.23)	1.44 (1.10, 1.89)	
	Hypochlorite	Cases (*n*)	198,225	101	63	72	62	0.2
		Noncases (*n*)		65,053	30,820	54,072	47,982	
		Crude		1.00 (Ref)	1.31 (0.96, 1.80)	0.86 (0.63, 1.16)	0.83 (0.61, 1.14)	
		Multivariable-adjusted		1.00 (Ref)	1.39 (0.99, 1.94)	0.88 (0.64, 1.22)	0.90 (0.65, 1.26)	
	Chloramine	Cases (*n*)	312,651	101	668	66	128	0.001
		Noncases (*n*)		65,053	187,760	18,868	40,007	
		Crude		1.00 (Ref)	2.29 (1.86, 2.83)	2.25 (1.65, 3.07)	2.06 (1.58, 2.68)	
		Multivariable-adjusted		1.00 (Ref)	2.37 (1.85, 3.04)	2.33 (1.64, 3.29)	2.06 (1.53, 2.78)	
Genital	All	Cases (*n*)	623,468	161	843	491	325	0.01
		Noncases (*n*)		46,993	289,072	178,691	88,892	
		Crude		1.00 (Ref)	1.18 (0.99, 1.40)	1.11 (0.93, 1.33)	1.48 (1.22, 1.79)	
		Multivariable-adjusted		1.00 (Ref)	1.18 (0.97, 1.42)	1.14 (0.93, 1.39)	1.47 (1.18, 1.81)	
	Hypochlorite	Cases (*n*)	198,225	161	97	167	145	0.09
		Noncases (*n*)		46,993	30,786	53,977	47,899	
		Crude		1.00 (Ref)	1.27 (0.99, 1.64)	1.25 (1.00, 1.55)	1.22 (0.97, 1.53)	
		Multivariable-adjusted		1.00 (Ref)	1.36 (1.04, 1.77)	1.30 (1.03, 1.64)	1.24 (0.97, 1.58)	
	Chloramine	Cases (*n*)	312,651	161	544	63	178	<0.001
		Noncases (*n*)		64,993	187,884	18,871	39,957	
		Crude		1.00 (Ref)	1.17 (0.98, 1.40)	1.35 (1.01, 1.81)	1.80 (1.45, 2.23)	
		Multivariable-adjusted		1.00 (Ref)	1.15 (0.93, 1.41)	1.45 (1.05, 1.98)	1.77 (1.38, 2.26)	
Limbs	All	Cases (*n*)	623,468	274	1,299	742	430	0.3
		Noncases (*n*)		64,880	288,616	178,440	88,787	
		Crude		1.00 (Ref)	1.07 (0.93, 1.22)	0.98 (0.86, 1.13)	1.15 (0.98, 1.34)	
		Multivariable-adjusted		1.00 (Ref)	1.04 (0.89, 1.20)	0.95 (0.82, 1.11)	1.14 (0.96, 1.34)	
	Hypochlorite	Cases (*n*)	198,225	274	146	230	194	0.5
		Noncases (*n*)		64,880	30,737	53,914	47,850	
		Crude		1.00 (Ref)	1.12 (0.92, 1.38)	1.01 (0.85, 1.21)	0.96 (0.80, 1.16)	
		Multivariable-adjusted		1.00 (Ref)	1.12 (0.90, 1.38)	0.98 (0.82, 1.19)	0.96 (0.79, 1.17)	
	Chloramine	Cases (*n*)	312,651	274	864	91	232	0.02
		Noncases (*n*)		64,880	187,564	18,843	39,903	
		Crude		1.00 (Ref)	1.09 (0.95, 1.25)	1.14 (0.90, 1.45)	1.38 (1.15, 1.64)	
		Multivariable-adjusted		1.00 (Ref)	1.06 (0.91, 1.25)	1.02 (0.78, 1.33)	1.34 (1.10, 1.64)	
Chromosomal	All	Cases (*n*)	623,468	88	381	229	119	0.6
		Noncases (*n*)		65,066	289,534	178,953	89,098	
		Crude		1.00 (Ref)	0.97 (0.77, 1.23)	0.95 (0.74, 1.21)	0.99 (0.75, 1.30)	
		Multivariable-adjusted		1.00 (Ref)	0.87 (0.67, 1.14)	0.87 (0.66, 1.15)	0.92 (0.68, 1.25)	
	Hypochlorite	Cases (*n*)	198,225	88	39	61	68	0.8
		Noncases (*n*)		65,066	30,844	54,083	47,976	
		Crude		1.00 (Ref)	0.93 (0.64, 1.37)	0.83 (0.60, 1.16)	1.05 (0.76, 1.44)	
		Multivariable-adjusted		1.00 (Ref)	0.87 (0.57, 1.31)	0.81 (0.56, 1.15)	0.99 (0.70, 1.40)	
	Chloramine	Cases (*n*)	312,651	88	245	24	49	0.6
		Noncases (*n*)		65,066	188,183	18,910	40,086	
		Crude		1.00 (Ref)	0.96 (0.75, 1.23)	0.94 (0.60, 1.48)	0.90 (0.64, 1.28)	
		Multivariable-adjusted		1.00 (Ref)	0.83 (0.62, 1.10)	0.66 (0.38, 1.13)	0.89 (0.61, 1.30)	

Note: The study included a total of 623,468 children born during 2005–2015 to mothers living in large urban areas (>10,000 inhabitants) in Sweden. Models multivariable-adjusted for the following factors: maternal age, BMI, diabetes, any use of teratogenic drugs, parity, smoking at registration to the antenatal care, highest attained education, and household income using inverse probability weighting. BMI, body mass index; Ref, reference; TTHM, average of the four most common trihalomethanes (total trihalomethanes).

2018). In some regions with larger cities, there is a higher rate of pregnancies terminated due to some malformations, especially heart defects, compared with less densely populated regions. Potential region-dependent differences in termination of pregnancies may be a reason to the inverse association indicated for heart defects. Unmeasured confounding, such as exposures to teratogens (i.e., chemicals, pathogens, or other stressors) resulting in chlorination- or locality-related differences in, for example, maternal infections could also be an explanation (Ye et al. 2019). Yet, despite the effort to scrutinize the different scenarios, the full explanation for the inverse association observed for heart defects in the present study and whether drinking water chlorination is involved remains ambiguous, but we consider it not to be a result of TTHM exposure per se.

The limitation related to the lack of individual assessments of TTHM exposure in the present study needs special consideration. First, because of the register-based study design, we were forced to use a crude measure of the exposure, potentially resulting in exposure misclassification. However, given that it is estimated that 99.8% of the adult population in Sweden are consumers of unheated tap water (Säve-Söderbergh et al. 2018), locality-specific estimates likely provide a valid individual estimation of TTHM exposure via the consumption of tap water. Still, we cannot fully exclude that there could be regional differences in individual consumption patterns or modification of the consumption due to pregnancy.

Moreover, TTHM exposure unrelated to the consumption of drinking water could also be important, such as exposure via the lung and skin during various water-related activities (e.g., showering) (Backer et al. 2000; Xu et al. 2002). Although we have no information on these activities in our study population, we can still assume that it is likely that women in the unexposed area were exposed to chlorinated water to a much lesser extent, as compared with women living in the exposed areas. An additional asset in reducing exposure misclassification was the availability of data enabling the exclusion of women with high occupational TTHM exposure (professional swimmers or coaches and swimming pool personnel). Second, we used a locality-specific, multiannual, and trimester-specific average of TTHM exposure. This may not fully capture the true external exposure in each first trimester but both handles potential missing exposure data due to variations in municipal sampling strategies (i.e., potentially leading to dropout of pregnancies) and reduces the impact of single extreme values. This strategy has evolved owing to the fact that season is by far the most important determinant of TTHM formation in Northern Europe, peaking in spring and fall (when the natural organic matter content is higher due to rainfalls, snow melting, and low water temperature). Thus, a multiannual monthly TTHM average—as compared with using average of consecutive months—will better capture the trimester-specific exposure.

The use of a single locality-specific average was supported by the fact that most water treatment plants were small, with a fairly rapid turnover time in the drinking water distribution systems, resulting in a low spatial TTHM variation. Thus, although certain exposure misclassification is inevitable in the exposed populations, the inclusion of an unexposed reference area with nonchlorinated drinking water likely considerably reduces its overall impact.

We included only malformations diagnosed up to 28 days postpartum. Although most severe cases are diagnosed during this period, assuring a high specificity, some less severe cases are likely diagnosed later in life. Still, the overall prevalence of major congenital malformations was 2 cases/100 births (Table S1), which agrees well with the reported national prevalence (2.1 cases/100 births, excluding terminated pregnancies) during 2007–2015 (EUROCAT 2020).

The present study has several strengths. To begin with, this is one of the largest prospective studies assessing TTHM exposure and the risk of congenital malformations. The Swedish health care and administrative registers that were included have a coverage of close to 100% (Källén and Källén 2003; Ludvigsson et al. 2016), reducing the risk of selection bias due to missing data. This is explained by the publicly funded antenatal, delivery, and pediatric care and the mandatory reporting to the registers. In addition, the exclusive use of a unique personal identification number in both health care and administrative registers enabled data linkage with high reliability, including information on migratory patterns during gestation, which previous studies were not able to take into account. We observed a high migration rate among the pregnant women, in line with previous findings (Miller et al. 2010), highlighting the relevance of obtaining this information. The extensive data collected in the registers enabled us to adjust for most relevant individual confounders. Although we cannot rule out unmeasured confounders, because the confounders had little impact on the risk estimates, it is unlikely that these potential unmeasured confounders would have affected the results. There may be exceptions, however, such as differences in the use of folic acid, which was not included in any of the models in the present study because it is estimated to be highly underreported in the Medical Birth Register (NBHW 2018). The use of folic acid supplements during early gestation is recommended by authorities because it prevents the formation of malformations, such as neural tube defects (Czeizel et al. 2013), but the population uptake likely varies by socioeconomic factors (Murto et al. 2017). We handled this by controlling for several individual socioeconomic-related factors (e.g., highest attained educational level, household income) as surrogate confounders. In addition, the prevalence of neural tube defects was low in our population (~ 0.2 cases/1,000 births), indicating that it is unlikely that folic acid would be an important risk factor.

In conclusion, we observed that first trimester maternal TTHM exposure was associated with the risk of malformations of the nervous and urinary systems, as well as of the genitals and limbs, among the newborns in areas using chloramine as drinking water treatment. There were no indications that TTHM in areas using hypochlorite was associated with congenital malformations among the newborns. This may indicate that chlorination treatment-specific levels of single THMs or other CBPs that are not included in the TTHM definition were formed when treating drinking water with chloramine may be the main CBPs responsible for the associations observed with increased risk of congenital malformations. Congenital malformations linked to a CBP originating from chloramine use has not previously been highlighted, and there is a clear need for further attention.

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