

Exposure to Drinking Water Chlorination by-Products and Fetal Growth and Prematurity: A Nationwide Register-Based Prospective Study

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BACKGROUND: Chlorination is globally used to produce of safe drinking water. Chlorination by-products are easily formed, and there are indications that these are associated with adverse reproductive outcomes.

OBJECTIVES: We conducted a nationwide register-based prospective study to assess whether gestational exposure to the four most common chlorination by-products [total trihalomethanes (TTHMs)] via tap water was associated with risk of small for gestational age (SGA), preterm delivery, and very preterm delivery. To date, this is one of the largest studies assessing drinking water TTHM-associated adverse reproductive outcomes.

METHODS: We included all singleton births 2005–2015 (live and stillbirths) of mothers residing in Swedish localities having >10,000 inhabitants, ≤2 operating waterworks, adequate information on chlorination treatment, and a sufficient number of routine TTHM measurements in tap water. Individual maternal second and third trimester exposure was obtained by linking TTHM measurements to residential history, categorized into no chlorination, <5, 5–15, and >15 µg TTHM/L. Outcomes and covariates were obtained via the linkage to Swedish health and administrative registers. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by logistic regression using inverse probability weighting. We stratified the analyses by chlorination treatment (chloramine, hypochlorite).

RESULTS: Based on approximately 500,000 births, we observed a TTHM dose-dependent association with increased risk of SGA, confined to treatment with hypochlorite, corresponding to a multivariable-adjusted OR = 1.20 (95% CI: 1.08, 1.33) comparing drinking water TTHM >15 µg to the unexposed. Similar results were obtained when, instead of unexposed, the lowest exposure category (<5 µg/L TTHM) was used as reference. No clear associations were observed for preterm delivery and very preterm delivery.

DISCUSSION: Chlorination by-products exposure via drinking water was associated with increased risk of SGA in areas with hypochlorite treatment. <https://doi.org/10.1289/EHP6012>

Introduction

Chlorine is globally used in drinking water treatment owing to its high efficiency in inactivating microbial pathogens and reducing microbial growth in the distribution system. As a strong oxidant, chlorine reacts with natural organic matter and other substances in the water, generating hundreds of chlorination by-products (CBPs) (Richardson et al. 2007). There is increasing evidence that some CBPs are genotoxic and carcinogenic (Boorman 1999; Richardson et al. 2007) but also indications that CBP exposure, such as trihalomethanes (THMs), may be associated with increased risk of adverse reproductive outcomes (Bove et al. 2002; Colman et al. 2011; Graves et al. 2001; Grellier et al. 2010; Nieuwenhuijsen et al. 2000; Tardiff et al. 2006). From epidemiological studies, the strongest support of an association is for intrauterine growth retardation, resulting in, for example, small for gestational age (SGA) (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; Wright et al. 2003, 2004), but the results are inconclusive, with several studies indicating no association (Hoffman et al. 2008; Ilek-Priouzeau et al. 2015; Iszatt et al. 2014; Jaakkola et al. 2001; Kogevinas et al. 2016; Patelarou et al. 2011; Porter et al. 2005; Rivera-Núñez and Wright 2013; Villanueva et al. 2011). On

the other hand, indications of inverse associations—although mostly statistically nonsignificant—have been observed for some other specific adverse reproductive outcomes such as preterm delivery and very preterm delivery (Grellier et al. 2010).

Assessing the association between CBP exposure and adverse reproductive outcomes is challenging because of the potential of exposure misclassification. Given that the formation of CBPs has a seasonal variation, linked to the content of organic matter, a correct timing of the exposure in relation to the relevant gestational effect-window is crucial (Mercier Shanks et al. 2013; Uyak et al. 2008). Moreover, correct residential information is important because there are also spatial variations, and approximately 20% of pregnant women move and often resettle in a new county (Miller et al. 2010). The selection of a suitable unexposed reference area is another challenge. Because chlorination of public drinking water is commonplace, most assigned unexposed reference areas are those with private wells in rural areas, potentially introducing, for example, contextual confounding. The alternative has been to use municipal areas with low, but not zero, CBP exposure as the reference group (Hrudey 2009), resulting in reduced exposure contrast and an increased probability of misclassified exposure.

With strong emphasis on reducing the aforementioned shortcomings, we conducted a nationwide register-based prospective cohort study among singleton births in Sweden during 2005–2015 in order to assess the association between gestational exposure to the four most common CBPs, the total trihalomethanes (TTHMs: chloroform, bromoform, bromodichloromethane, and dibromochloromethane), in drinking water and the risk of SGA, preterm, and very preterm delivery.

Methods

Study Area and Study Population

As study area, we selected all localities (coherent and densely populated areas) in Sweden having a population of >10,000

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inhabitants (~60% of the total population) in order to be able to include a large study population with a wide range of CBP exposure while avoiding inclusion of areas not receiving municipal drinking water. Localities were excluded if *a*) there were changes in chlorination treatment of the drinking water between 1994 and 2010 (SWWA 1996, 2014); *b*) CBPs were detected in the drinking water, but no chlorination was reported in the drinking water production; *c*) three or more water utilities provided drinking water to the locality or within municipal borders; *d*) two different utilities provided drinking water with differences in mean CBP concentrations >10 µg/L; or *e*) CBPs were measured for a period of <4 y during 2005–2015 (with the exception of utilities with no chlorination). In total, 83 localities were included in the study area (~40% of the total Swedish population) (Figure 1).

The study population was identified as all mothers giving birth (live and stillbirths) from 1 January 2005 to 31 December 2015 with an official residential registration in any of the localities in the study area during their pregnancy. Data was provided by the Swedish Medical Birth Register (at the National Board of Health and Welfare), linked to the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA; Statistics Sweden) and a national register for regional divisions based on real estate (Geografidatabasen; Statistics Sweden) by the personal identification number (a unique 10-digit number assigned to all Swedes) (Figure 1). From the 738,538 newborns (including 2,578 stillbirths) and 457,524 mothers, we excluded nonsingleton births and all mothers with occupational TTHM exposure (registered as professional swimmers or coaches and swimming pool lifeguards). Because this was a register-based study, where the individuals are nonidentifiable after matching, informed consent was not obtained. The study was approved by the Regional Ethics Review Board in Stockholm.

Exposure and Covariates

The CBP drinking water concentrations, sampled at the end users (tap) in the study area, were obtained from a register administered by the Geological Survey of Sweden ($n=4,272$ confirmed TTHM analyses). The drinking water utilities in Sweden are obliged to follow the national drinking water regulations [SLVFS 2001:30 (Swedish National Food Agency 2001)], at least measuring four tap water samples yearly at the end user, preferably distributed over time and over the distribution system, with three additional samplings per every 1,000 m³ of drinking water produced per day (the TTHM should not exceed 100 µg/L). Although a strong effort was made in assigning an appropriate and as robust as possible CBP exposure for each individual pregnancy, no additional collection of household water samples or data on drinking water consumption was performed. For the exposure, we used a multiannual monthly average of TTHM for each locality (i.e., with one or two waterworks). By using a multiannual average for each month and locality, we *a*) accounted for seasonal variations (Andersson et al. 2019b), *b*) reduced the weight of single extreme values, and by reducing the influence of locality-specific differences in monitoring programs we also *c*) minimized the number of pregnancy dropouts. The multiannual monthly average TTHM were then used to estimate a trimester-specific (3 months) average for each single pregnancy.

The third trimester was considered the most relevant effect-window for SGA, but we also assessed exposure during the second trimester because this time period could be relevant (Lewis et al. 2006). For preterm and very preterm delivery, we focused only on the second trimester exposure because the short exposure period in the third trimester for the children born preterm increases the likelihood of missing data on TTHM exposure (dropouts) among the exposed preterm or very preterm delivery

cases. Because season highly affects the occurrence of natural organic matter and other substances in raw water in Sweden (the precursor materials for CBP formation), estimating a mean TTHM for the total gestation (all three trimesters) was not considered appropriate.

The individual maternal TTHM exposure was then categorized into *a*) no chlorination (reference, only mothers living in localities with no chlorination), *b*) <5 µg TTHM/L, *c*) 5–15 µg TTHM/L, and *d*) >15 µg TTHM/L. We were unable to assess the exposure to single CBPs/THMs due to the too low concentrations (chloroform was the principal THM, whereas other THMs often were below the limit of detection). Due to a combination of seasonal differences in birth rates and the frequency of tap water monitoring, a higher number of pregnancies were assigned third trimester exposure, compared with second trimester exposure. In total, 11% of the pregnant women changed locality during the second or third trimester. In cases where the woman had moved outside the study area or had changed locality during the exposure-relevant effect-window (third or second trimester for SGA, and second trimester for preterm or very preterm delivery), the birth was excluded from that particular analysis (this also applied to women in the reference area). Moving within a locality did not result in exclusion.

We obtained information on the sex and year of birth for each child and the following maternal covariates from the Swedish Medical Birth Register: age, body mass index (BMI), previous miscarriages, parity, smoking (gestational week 30–32), use of drugs with suspected teratogenic effects (Class 3) (Nörby et al. 2013), sick leave/being on disability as reported by the mother, and maternal diagnosis of pregnancy-related conditions categorized according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10; WHO 2016): preexisting and pregnancy-related diabetes (ICD-10 codes O24.0–24.9), preeclampsia (ICD-10 code O14), preexisting and pregnancy-related hypertension (ICD-10 codes O10 and O13.9), and high weight gain (ICD-10 code O26.0)/low weight gain (ICD-10 code O26.1) as reported by antenatal care. From LISA we obtained information on country of birth, highest attained education, and household income. We also collected locality-related information such as raw water source, size of the locality, and permanent chlorination treatment used. The latter enabled separate assessments of newborns of mothers living in localities with water treatment plants using exclusively chloramine or hypochlorite (the two most commonly used disinfectants in the study area).

Outcomes

The outcomes were term SGA (excluding preterm delivery for both cases and noncases), preterm delivery (born before gestational week 37) and very preterm delivery (born before gestational week 32). SGA was registered at delivery care defined as <–2 standard deviations (SDs) from the average weight at the gestational age and sex at partus (Maršál et al. 1996). Preterm and very preterm delivery were defined according to the registered days of gestation made at antenatal care (calculated based on ultrasound evaluations and/or date for last menstrual period).

Statistical Analyses

Logistic regression was used to estimate the odds ratios (ORs) and corresponding 95% confidence intervals (CIs). To reduce dependency for multiple births by the same mother, we clustered the models (intragroup correlation) by anonymized maternal identification as received by the data provider. Confounders were selected based on current knowledge of risk factors for SGA, preterm, and very preterm delivery and on available data in the

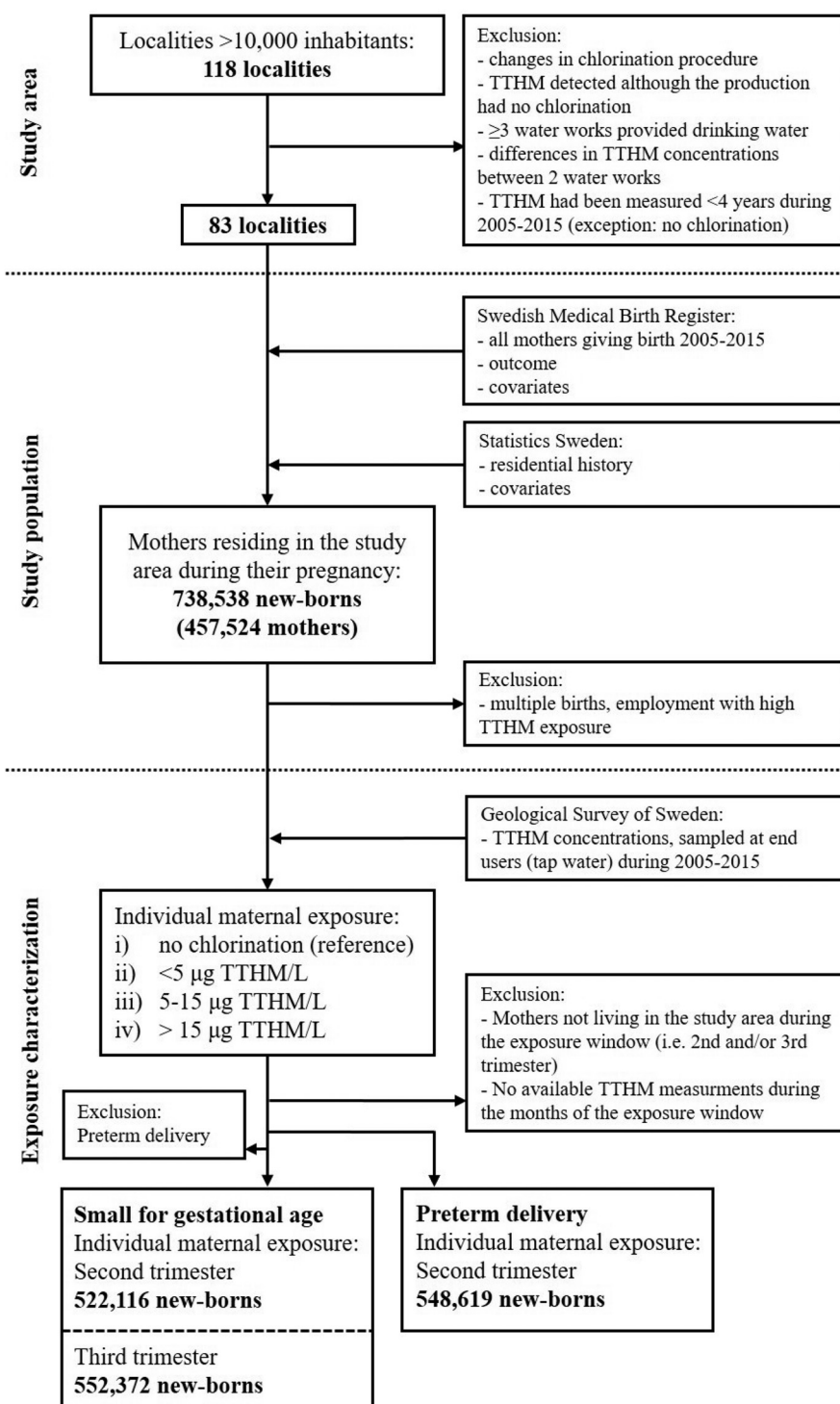


Figure 1. Study area, study population, and exposure categorization (average of the four most common trihalomethanes). Note: TTHM, total trihalomethanes.

registers. We used standardization (inverse probability weight) to adjust for confounding in order to reduce bias due to missing data on covariates (Hernán and Robins 2020). First, models were adjusted for the risk factors considered most relevant (Model 1): maternal age (<25, 25–<30, 30–<35, 35–<40, ≥40 y), BMI (at registration to antenatal care: <18.5, 18.5–24.9, 25–29.9, ≥30 kg/m²), birth region (Nordic/Europe/Africa/North and South America/Asia/other), attained education (elementary school/secondary education/postsecondary education), household income (yearly quartiles by year of birth), and smoking at gestational week

30–32 (no, 1–9, >9 cigarettes/d). Second, in Model 2, we further adjusted for additional risk factors related to the outcome: previous miscarriages (yes/no), parity (nulliparous, 1, 2, ≥3), sick leave/being on disability, use of teratogenic drugs (yes/no), maternal diabetes (yes/no), preeclampsia (yes/no), maternal hypertension (yes/no), maternal weight gain (high/normal/low weight gain) and year of birth (continuous). Linear trends across categories were tested using the median TTHM concentration within categories as a continuous variable. In a sensitivity analysis, we assigned the <5-µg TTHM/L exposure category as the reference in order to minimize

any impact of possible contextual confounding linked to the localities using no chlorination treatment. All analyses were performed on live and stillbirths combined because conditioning the analyses to live births may introduce a bias via the opening of new pathways through unmeasured confounding. Nevertheless, for some assessments we performed additional analyses excluding stillbirths for comparison. All statistical analyses were performed using Stata (version 14.1; Stata Corporation) and the statistical significance level was set at 0.05.

Results

Among 576,483 pregnancies with third trimester exposure information, we ascertained 10,887 cases of term SGA. Among 548,619 pregnancies with second trimester exposure, we ascertained 25,874 and 4,046 cases of preterm and very preterm delivery, respectively (Table 1). We observed some differences in baseline population characteristics across the exposure groups for maternal age, country of birth, attained educational level, household income, and sick leave/disability pension (Table 1). As expected, groundwater was a common source of raw water in localities with no chlorination (the unexposed reference) (Table 2). In localities with the exclusive use of chloramine treatment, groundwater was uncommon, whereas it was the dominating source in areas using hypochlorite. The size of the localities differed between the exposed and the areas with no chlorination, mainly because drinking water producers in large cities generally use chlorination, especially chloramine.

Small for Gestational Age

Based on exposure during the third trimester, comparing the highest TTHM exposure ($>15 \mu\text{g TTHM/L}$) to the unexposed for all chlorination treatments, we observed statistically significant associations with increased odds of SGA in the crude and multivariable-adjusted Model 1, corresponding to $\text{OR} = 1.21$ (95% CI: 1.11, 1.31, $p_{\text{trend}} < 0.001$) and $\text{OR} = 1.13$ (95% CI: 1.04, 1.24, $p_{\text{trend}} < 0.001$), respectively. After further multivariable-adjustment (Model 2), the OR for SGA was 1.05 (95% CI: 0.95, 1.16) when comparing the highest exposure to unexposed (Table 3).

In the assessments stratified by chlorination treatment, we observed for hypochlorite statistically significantly increased odds of SGA comparing the highest TTHM exposure group with the unexposed reference, $\text{OR} = 1.20$ (95% CI: 1.08, 1.33, $p_{\text{trend}} < 0.001$). If we excluded stillbirths from these analyses, the results remained very similar, $\text{OR} = 1.19$ (95% CI: 1.07, 1.32). Excluding the unexposed group from the analysis and instead assigning the lowest TTHM exposure group (i.e., $<5 \mu\text{g TTHM/L}$) as the reference, the OR for the highest TTHM exposure remained essentially the same: $\text{OR} = 1.21$ (95% CI: 1.09, 1.35, $p_{\text{trend}} < 0.001$) (Table 3). When chloramine was used as the disinfection treatment, we observed $\text{OR} = 0.91$ (95% CI: 0.80, 1.03, $p_{\text{trend}} = 0.4$) comparing the highest TTHM exposure group to the unexposed reference (Table 3). These results did not appreciably change when we assigned the lowest TTHM exposure group (i.e., $<5 \mu\text{g TTHM/L}$) as the reference.

Changing the assessment from third to second trimester exposure gave essentially the same results: no overall association with risk of SGA, comparing the highest exposures to the unexposed reference (see Table S1). In agreement with the third trimester exposure, there was a statistically significantly increased risk in areas using hypochlorite: $\text{OR} = 1.15$ (95% CI: 1.03, 1.28, $p_{\text{trend}} = 0.007$). When $<5 \mu\text{g TTHM/L}$ was used as reference, we observed $\text{OR} = 1.09$ (95% CI: 0.98, 1.22) for the highest TTHM exposure group. No associations were observed for chloramine.

Preterm and Very Preterm Delivery

For all different chlorination treatments combined, TTHM exposure during the second trimester, the OR for preterm delivery from Model 1 indicated associations with lower risk, comparing the highest TTHM exposure to the unexposed reference [$\text{OR} = 0.93$ (95% CI: 0.88, 0.99)] (Table 4). In the further multivariable-adjusted model (Model 2), the OR was 0.94 (95% CI: 0.88, 1.00). In localities having exclusive treatment with chloramine, the corresponding OR for preterm delivery was 0.90 (95% CI: 0.83, 0.98) (Table 4). However, no association was observed when $<5 \mu\text{g TTHM/L}$ was assigned as the reference (excluding the unexposed group from the analysis). Likewise, in localities having exclusive treatment with hypochlorite, we observed no association between TTHM exposure and preterm delivery when comparing the highest exposure to $<5 \mu\text{g TTHM/L}$ [$\text{OR} = 0.95$ (95% CI: 0.88, 1.02)]. For very preterm delivery and all chlorination treatments combined, the multivariable-adjusted OR (Model 2) indicated a significant inverse association, $\text{OR} = 0.82$ (95% CI: 0.69, 0.98, $p_{\text{trend}} = 0.04$), comparing the highest TTHM exposure to the unexposed reference (Table 4). However, in the analyses stratified by chlorination treatment (chloramine or hypochlorite), we observed no clear associations, although the number of cases was limited and the confidence intervals wide.

Discussion

The present nationwide register-based cohort, including $>500,000$ singleton births, is one of the largest studies assessing CBP exposure and adverse reproductive outcomes. Based on address and average-trimester-linked TTHM concentrations in tap water, we observed dose-dependent associations with increased risk of SGA, confined to treatment with hypochlorite but not to chloramine. For preterm and very preterm delivery, the results indicated no clear associations, although there were some indications of an inverse association.

Although several epidemiological studies have indicated that CBP exposure is associated with an increased risk of SGA (Tardiff et al. 2006), reproductive and developmental animal studies generally show no indication of adverse reproductive effects, alternatively, showing that the effect is secondary to any adverse toxicological effect occurring in the dams (Colman et al. 2011). However, CBPs formed by the drinking water treatment are numerous, and there is experimental evidence where individual CBPs (e.g., THMs) have caused lower fetal body weight or growth retardations as the primary effect (Schwetz et al. 1974; Smith et al. 1987, 1989, 1992). The toxicity of the majority of the CBPs is likely due to the formation of reactive intermediates (Colman et al. 2011) and linked to the indications that to some CBPs have the potential to pass placental barrier (Christian et al. 2001).

Most previous epidemiological studies assessing CBP exposure and adverse reproductive outcomes did not consider different chlorination treatments. Several studies in which hypochlorite was the only treatment indicated an association between TTHM exposure and increased risk of SGA (Aggazzotti et al. 2004; Grazuleviciene et al. 2011; Källén and Robert 2000), although no association has also been observed (Villanueva et al. 2011). In comparison with previous studies, the TTHM concentrations in the present study were low, irrespective of the type of chlorination treatment. Although the THMs are mainly formed after treatment with hypochlorite, lower concentrations of THMs are also produced by chloramine being hydrolyzed into free chlorine (Hua and Reckhow 2007). Accordingly, in the present study the prevalence of high TTHM exposure ($>15 \mu\text{g/L}$) was considerably more common in areas using hypochlorite (44%) as compared with chloramine (15%). In addition to the fact that

Table 1. Baseline population characteristics by individual maternal average exposure to the four most common trihalomethanes (TTHMs), during the second ($n = 548,619$) and third trimester ($n = 576,483$), expressed as proportions (%).

Variables	Categories	No chlorination	Second trimester			Third trimester		
			<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
<i>n</i>		66,008	262,177	138,672	81,762	263,687	168,449	78,439
Average Outcome	µg TTHM/L	—	0.76	9.0	24	0.75	9.2	24
	SGA ^a	1.8	1.9	2.2	2.0	1.9	2.2	2.1
	Preterm delivery	5.1	3.8	4.1	4.0	3.8	4.1	4.0
	Very preterm delivery	0.80	0.27	0.24	0.38	0.27	0.25	0.38
Sex of child	Female	51	52	51	51	52	51	51
Year of birth	2005	8.2	8.1	7.7	7.4	8.2	7.6	7.2
	2006	8.6	8.3	8.1	7.9	8.3	8.0	7.8
	2007	8.8	8.4	8.4	8.3	8.4	8.4	8.3
	2008	8.9	8.9	8.7	8.8	8.8	8.8	8.9
	2009	9.3	8.9	9.2	9.1	8.8	9.3	9.2
	2010	9.5	9.7	9.8	9.8	9.7	9.7	9.9
	2011	9.3	9.4	9.4	9.6	9.4	9.4	9.6
	2012	9.3	9.5	9.6	9.7	9.5	9.6	9.8
	2013	9.2	9.6	9.6	9.5	9.7	9.5	9.6
	2014	9.3	9.7	9.8	9.9	9.7	9.8	9.9
	2015	9.4	9.5	9.8	10	9.5	9.8	9.8
Maternal age (y)	<25	17	10	11	14	10	12	14
	25–29	33	26	28	30	26	29	30
	30–34	32	38	37	35	38	37	35
	35–39	15	22	19	17	22	18	17
	>40	2.9	4.9	4.1	3.6	4.8	3.9	3.5
Maternal BMI (kg/m ²)	<18.5	2.4	2.8	2.7	2.5	2.9	2.6	2.6
	18.5–<25	59	65	63	61	65	63	61
	25–<30	26	22	23	25	22	24	25
	≥30	13	10	11	12	9	11	12
Prior miscarriages	Yes	20	22	21	21	22	21	21
Parity	Nulliparous	44	45	47	45	45	46	45
	1	37	37	37	37	38	37	36
	2	13	13	12	13	13	12	13
	≥3	5.6	4.7	4.7	5.9	4.7	5.0	6.1
Country of birth	Nordic	80	73	73	70	73	73	69
	Europe, other	6.3	6.4	7.1	9.1	6.3	7.0	9.3
	Africa	2.9	5.3	5.4	4.3	5.2	5.3	4.3
	North/South America	1.0	2.5	1.8	1.5	2.5	1.6	1.5
	Asia	9.4	13	13	16	13	13	16
Attained education	Elementary school	11	11	11	12	10	11	12
	Secondary education	39	32	32	31	32	32	31
	Postsecondary education	50	58	58	57	58	57	57
Household income (quartile)	First	16	16	17	21	15	17	22
	Second	29	22	25	28	22	26	27
	Third	40	30	34	33	30	35	33
	Fourth	15	33	23	18	33	22	18
Sick leave/early retirement	Yes	0.22	0.15	0.11	0.11	0.2	0.1	0.1
Smoking: gestational week	1–9	3.9	2.6	3.3	3.3	2.6	3.3	3.5
	>9	0.94	0.94	0.87	0.95	0.69	0.89	1.0
	30–32 (cigarettes/d)							
Drugs (suspected teratogens)	Yes	0.053	0.043	0.043	0.051	0.046	0.042	0.047
Maternal diagnosis	Diabetes	1.9	1.3	1.5	2.7	1.3	1.6	2.7
	Preeclampsia	2.9	2.5	2.6	2.6	2.4	2.5	2.5
	Hypertension	1.5	1.8	1.2	1.6	1.9	1.2	1.6
	High weight gain	0.014	0.012	0.014	0.097	0.012	0.040	0.12
	Low weight gain	0.015	0.0015	0.0051	0.012	0.00076	0.0065	0.013

Note: —, not applicable; BMI, body mass index; NA, not possible to evaluate the coverage; SGA, small for gestational age, excluding preterm delivery; TTHM, total trihalomethanes. ^aExcluding preterm delivery: based on $n = 548,619$ for second trimester exposure and $n = 552,372$ for third trimester exposure. There was no missing information except for BMI, sick leave, and smoking (8%, 13%, and 6% respectively).

Table 2. Area-specific characteristics by average total trihalomethane (TTHM) exposure (second and third trimester) and chlorination treatments for all births, expressed as proportions (%).

Variables ^a	All			Chloramine			Hypochlorite			
	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
Second trimester										
<i>n</i>	66,008	262,177	138,672	81,762	172,320	15,240	33,996	27,803	28,768	43,893
Average µg TTHM/L	—	0.76	9.0	8.0	0.67	8.0	25	1.3	10	23
Water source										
Surface water	5	87	83	57	97	99	80	17	25	41
Groundwater	95	13	17	43	3	0.0066	20	83	75	59
Chlorination treatment										
Chloramine	0	86	17	45	100	100	100	—	—	—
Hypochlorite	0	15	25	55	—	—	—	100	100	100
Chlorine dioxide ^b	0	1.8	60	0.18	—	—	—	—	—	—
Chlorine gas	0	0	1.6	0.0013	—	—	—	—	—	—
Population (<i>n</i>)										
<20,000	25	1.2	1.4	3.5	0.48	0	0	7.9	5.1	6.3
20,000–200,000	75	60	34	41	71	85	25	92	83	50
>200,000	0	39	65	56	28	15	75	0	12	44
Third trimester										
<i>n</i>	66,008	263,687	168,449	78,439	173,265	22,204	34,237	28,527	48,731	42,477
Average µg TTHM/L	—	0.75	9.2	8.9	0.66	8.9	25	1.3	10	22
Water source										
Surface water	5	97	80	56	97	96	74	18	38	40
Groundwater	95	13	20	44	3.2	4.5	26	83	62	60
Treatment										
Chloramine	0	86	19	44	100	100	100	—	—	—
Hypochlorite	0	16	34	56	—	—	—	100	100	100
Chlorine dioxide ^b	0	2.0	50	0.36	—	—	—	—	—	—
Chlorine gas	0	0.0011	1.5	0.010	—	—	—	—	—	—
Population (<i>n</i>)										
<20,000	25	1.2	2.8	3.5	0.49	0.0090	0	8.2	8.2	6.1
20,000–200,000	75	60	35	40	72	72	29	92	65	48
>200,000	0	39	62	57	28	28	71	0	27	46

Note: —, not applicable; TTHM, total trihalomethanes.

^aNo missing data.

^bUsed in combination with chlorite or chlorite and chlorine gas.

Table 3. Associations between average trihalomethane (TTHM) exposure (third trimester) for full-term small for gestational age expressed as odds ratios (ORs) and 95% confidence intervals (CIs).

Treatment	Components	Total births (n)	No chlorine (OR)	<5 µg TTHM/L [OR (95% CI)]	5–15 µg TTHM/L [OR (95% CI)]	>15 µg TTHM/L [OR (95% CI)]	<i>p</i> _{trend} ^a
All chlorination treatments ^b	Cases (n)	552,372	1,100	4,712	3,484	1,592	
	Noncases (n)		61,404	248,494	157,913	73,674	
	Crude		1.00 (ref)	1.06 (0.99, 1.13)	1.23 (1.15, 1.32)	1.21 (1.11, 1.31)	<0.001
	Model 1		1.00 (ref)	1.00 (0.92, 1.08)	1.18 (1.08, 1.27)	1.13 (1.04, 1.24)	<0.001
	Model 2		1.00 (ref)	0.93 (0.85, 1.01)	1.10 (1.01, 1.20)	1.05 (0.95, 1.16)	0.009
Chloramine	Cases (n)	283,385	1,100	3,136	401	667	
	Noncases (n)		61,404	166,953	20,646	32,214	
	Model 1		1.00 (ref)	1.07 (1.00, 1.15)	1.03 (0.91, 1.08)	1.06 (0.91, 1.18)	0.2
	Model 2		1.00 (ref)	0.90 (0.82, 0.99)	0.94 (0.82, 1.08)	0.91 (0.80, 1.03)	0.4
	Model 2		1.00 (ref)	1.00 (ref)	1.01 (0.89, 1.14)	0.96 (0.86, 1.06)	0.4
Hypochlorite	Cases (n)	177,048	1,100	576	988	884	
	Noncases (n)		61,404	26,660	45,489	39,947	
	Model 1		1.00 (ref)	1.11 (1.00, 1.25)	1.16 (1.06, 1.28)	1.18 (1.07, 1.30)	<0.001
	Model 2		1.00 (ref)	1.09 (0.96, 1.23)	1.14 (1.04, 1.26)	1.20 (1.08, 1.33)	<0.001
	Model 2		1.00 (ref)	1.00 (ref)	1.14 (1.03, 1.26)	1.21 (1.09, 1.35)	<0.001

Note: Model 1 was adjusted for maternal age, BMI, household income, attained education, smoking at week 30, and country of birth by inverse probability weighting. Model 2 was as Model 1 additionally adjusted for previous miscarriages, parity, sick leave/early retirement, use of teratogenic drugs, diabetes, preeclampsia, hypertension, weight gain, and year of birth. BMI, body mass index; ref, reference; TTHM, trihalomethanes.

^a*p*_{trend}: linear trends across categories were tested using the median TTHM concentration within categories as a continuous variable.

^bChloramine, hypochlorite, chlorine gas, chlorine dioxide in single or combined treatment.

chloramine is less reactive than hypochlorite, consequently forming fewer CBPs, including TTHMs (Hua and Reckhow 2007), there are also differences in the types of CBPs generated between the two methods (WHO 2000). Thus, our TTHM-associated finding for increased risk of SGA for drinking water treated with hypochlorite, but not chloramine, could be due to quantitative as well as qualitative differences in the formation of CBPs. It could also be due to a lower exposure misclassification in the areas using hypochlorite because it is well established that THMs are reasonably good proxies for total CBPs when this chlorination method is used. Because other CBPs are formed when chloramines are used, TTHMs become less representative of the total CBPs.

In the present study, SGA was predefined in the Swedish Medical Birth Register according to < -2 SD below the sex- and gestational age-specific average weight at partus (corresponding to the 2.3rd percentile). Although this cutoff is more stringent, capturing mainly moderate-to-severe cases of SGA (increasing the specificity—less of a threat to validity) as compared with those studies using the 10th percentile as cutoff, we may not capture the full effect of the CBP exposure.

We observed no clear associations between TTHM and preterm or very preterm delivery in the present study although there were some indications of inverse associations, as also suggested in some previous epidemiological studies (Grellier et al. 2010). Because maternal infections may induce preterm delivery (Pararas et al. 2006), it has been hypothesized that chlorination of drinking water may cause a lower occurrence of maternal infections (Jaakkola et al. 2001), which could potentially explain the inverse associations. Yet, no studies have confirmed this link. An alternative explanation for these previous inverse findings could be selection bias introduced by restricting the analyses to only live births (Hernán et al. 2002; Lewis et al. 2007). Although we were able to include the stillbirths in the present study, we were not able to include pregnancies resulting in spontaneous abortion. Because we observed no clear dose-response and because the results were highly dependent on the choice of reference area, the most reasonable interpretation of our findings is that TTHM, or chlorination per se, was not linked to preterm or very preterm delivery at the TTHM concentrations appearing in the present study.

As in any epidemiological study, the present work suffered from limitations. Foremost, we consider exposure misclassification as the most important issue, which also highlights the complexity of the assessment. First, we were unable to assess the drinking water consumption or the exposure via any other relevant routes. We observed in a previous survey that the vast majority of the adult population in Sweden is consuming unheated tap water (99.8%) (Säve-Söderbergh et al. 2018). On the other hand, the THMs are highly volatile and therefore ingestion, inhalation, and dermal exposure could be equally important routes of exposure (Backer et al. 2000; Xu et al. 2002), indicating that non-consumers of tap water are also exposed to the THMs. Some studies have tried to reduce the misclassification by collecting information on water consumption and on showering/bathing habits (Danileviciute et al. 2012; Grazuleviciene et al. 2013), and others measured the blood concentrations of THMs (Smith et al. 2016; Zhou et al. 2018). However, because THMs are easily absorbed and have a short half-life, the blood concentrations fluctuate, with high peaks of the most volatile CBPs seen shortly after showering, complicating the use of biomarkers of exposure (Backer et al. 2008). Second, we applied the same average TTHM concentration to the whole locality. Because most of the water treatment plants were small (<10% distributed drinking water to localities with more ≥100,000 inhabitants), with a more rapid water distribution turnover, the spatial variation in exposure within the network is likely less pronounced. Third, to avoid the impact of missing CBP tap water data for a specific month and locality, we assigned the trimester average exposure for each pregnancy. Although a more precise exposure period could have been preferable, the knowledge is still limited on the gestational age for the specific effect-windows for the outcomes evaluated in the present study, resulting in the trimester-specific average being the most appropriate. Fourth, we cannot exclude that CBPs other than the four most common THMs were responsible for the observed association because the concentrations and composition of CBPs in Sweden are dependent on several raw water-related factors (Andersson et al. 2019a; Lavonen et al. 2013).

Besides exposure misclassification, confounding needs to be reflected upon. Although we have good information on many important risk factors and have used inverse probability weighting to account for unequal distribution of risk factors, we cannot fully

Table 4. Associations between average trihalomethane (TTHM) exposure (second trimester) for preterm delivery, and very preterm delivery expressed as odds ratios (ORs) and 95% confidence interval (CIs).

Treatment	Components	Total births (n)	No chlorine (OR)	<5 µg TTHM/L [OR (95% CI)]	5–15 µg TTHM/L [OR (95% CI)]	>15 µg TTHM/L [OR (95% CI)]	<i>p</i> _{trend} ^a
Preterm delivery							
All chlorination treatments ^b	Cases (n)		3,394	12,151	6,455	3,874	
	Noncases (n)	548,619	62,614	250,026	132,217	77,888	
	Crude		1.00 (ref)	0.90 (0.86, 0.93)	0.90 (0.86, 0.94)	0.92 (0.87, 0.96)	0.8
	Model 1		1.00 (ref)	0.91 (0.87, 0.96)	0.93 (0.88, 0.98)	0.93 (0.88, 0.99)	0.09
	Model 2		1.00 (ref)	0.92 (0.88, 0.97)	0.94 (0.89, 1.00)	0.94 (0.88, 1.00)	0.1
Chloramine	Cases (n)		3,394	7,810	670	1,684	
	Noncases (n)	285,586	62,614	165,202	14,570	34,845	
	Model 1		1.00 (ref)	0.90 (0.85, 0.94)	0.84 (0.76, 0.93)	0.91 (0.85, 0.99)	0.1
	Model 2		1.00 (ref)	0.90 (0.85, 0.95)	0.85 (0.77, 0.94)	0.90 (0.83, 0.98)	0.06
	Model 2		1.00 (ref)	1.00 (ref)	0.93 (0.85, 1.03)	1.00 (0.93, 1.07)	1.0
Hypochlorite	Cases (n)		3,394	1,474	1,477	2,091	
	Noncases (n)	166,172	62,614	26,329	27,291	41,502	
	Model 1		1.00 (ref)	1.01 (0.94, 1.09)	1.01 (0.94, 1.09)	0.93 (0.88, 1.00)	0.05
	Model 2		1.00 (ref)	1.04 (0.97, 1.13)	1.05 (0.97, 1.13)	0.95 (0.89, 1.02)	0.2
	Model 2		1.00 (ref)	1.00 (ref)	1.04 (0.97, 1.13)	0.95 (0.88, 1.02)	0.2
Very preterm delivery							
All chlorination treatments ^b	Cases (n)		530	1,908	1,028	580	
	Noncases (n)	548,619	65,478	260,269	137,644	81,182	
	Crude		1.00 (ref)	0.91 (0.82, 1.00)	0.92 (0.83, 1.03)	0.88 (0.78, 1.00)	0.4
	Model 1		1.00 (ref)	0.88 (0.77, 1.00)	0.91 (0.79, 1.04)	0.83 (0.71, 0.98)	0.2
	Model 2		1.00 (ref)	0.92 (0.80, 1.06)	0.94 (0.81, 1.09)	0.82 (0.69, 0.98)	0.05
Chloramine	Cases (n)		530	1,390	139	249	
	Noncases (n)	315,749	65,478	194,248	17,435	36,280	
	Model 1		1.00 (ref)	0.86 (0.75, 0.99)	1.04 (0.83, 1.32)	0.81 (0.67, 0.99)	0.2
	Model 2		1.00 (ref)	0.91 (0.78, 1.06)	1.13 (0.89, 1.45)	0.77 (0.62, 0.96)	0.05
	Model 2		1.00 (ref)	1.00 (ref)	1.23 (0.99, 1.52)	0.85 (0.70, 1.02)	0.06
Hypochlorite	Cases (n)		530	225	217	315	
	Noncases (n)	166,172	65,478	27,578	28,551	43,278	
	Model 1		1.00 (ref)	0.87 (0.71, 1.07)	0.83 (0.67, 1.02)	0.84 (0.70, 1.01)	0.07
	Model 2		1.00 (ref)	0.95 (0.76, 1.17)	0.89 (0.71, 1.10)	0.88 (0.73, 1.07)	0.2

Note: Model 1 was adjusted for maternal age, BMI, household income, attained education, smoking at week 30, and country of birth by inverse probability weighting. Model 2 was as Model 1 additionally adjusted for previous miscarriages, parity, sick leave/early retirement, use of teratogenic drugs, diabetes, preeclampsia, hypertension, weight gain, and year of birth. BMI, body mass index; ref, reference; TTHM, total trihalomethanes.

^a*p*_{trend}: Linear trends across categories were tested using the median TTHM concentration within categories as a continuous variable.

^bChloramine, hypochlorite, chlorine gas, chlorine dioxide in single or combined treatment.

exclude that some unmeasured confounding may have affected our results. For example, differences in study area-specific characteristics such as larger localities in exposed areas could not be controlled for in the analyses. However, because the results remained essentially the same by changing the reference area from no chlorination to the lowest exposure category (<5 µg TTHM/L), this potential impact seemed limited.

Several important strengths need to be highlighted. This is one of the largest prospective studies, assessing adverse reproductive outcomes in relation to TTHM exposure, and we were able to adjust for most relevant confounders at an individual level. The Swedish Medical Birth Register and the Statistics Sweden registers have a high coverage, close to 100% (Källén and Källén 2003; Ludvigsson et al. 2016), which, for example, reduced the risk of a biased selection of the pregnancies included. Moreover, because the maternal and delivery care is publicly funded in Sweden, there is likely no bias introduced by mothers not visiting the antenatal care because of their economic situation, resulting in similar data quality of the information gathered during pregnancy across the regions. Despite the aforementioned shortcomings linked to the exposure assessment, strong effort was made to accurately classify the exposure. The individual maternal TTHM exposure assigned was based on residential and temporal information at an exposure-relevant effect-window. In contrast to most previous studies, we were able to include an unexposed reference population that was served by municipal drinking water and not by private wells. This substantially improved the comparability with the exposed populations and minimized the risk of introducing contextual confounding related

mainly to differences between urban and rural areas. Nevertheless, potential remaining contextual confounding related to differences in locality characteristics, such as size, cannot be fully excluded. In any case, the sensitivity analysis performed, based on the lowest exposure (<5 µg TTHM/L) as the reference, supported our conclusion. Moreover, based on detailed information on drinking water production, we were able to stratify our analyses by the chlorination treatment, something that few previous studies have been able to consider.

In conclusion, the results of the present study provide the evidence that CBP exposure via drinking water is associated with increased risk of SGA in areas with hypochlorite treatment, but not chloramine, potentially due to CBP formation differences. There was no clear association for preterm or very preterm delivery.

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