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Original Contribution

Estimated Effects of Disinfection By-products on Birth Weight in a Population Served by a Single Water Utility

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Research has suggested that trihalomethane exposures during pregnancy might impair fetal growth. Most epidemiologic studies, however, relied on relatively crude exposure assessment methods and did not examine racial/ethnic subgroups. During 1999–2001, vital records data were obtained for a large, racially diverse population residing in 27 Massachusetts communities that received drinking water from a single public utility. The water system was monitored weekly for trihalomethanes and, system-wide, it maintained geographically stable total trihalomethane levels during the study period. The authors examined the effects of trimester-specific and pregnancy average exposures to total trihalomethane in drinking water on term low birth weight in all singleton births. A high average total trihalomethane exposure ($\geq$70 μg/liter) during the second trimester increased the risk of term low birth weight (odds ratio = 1.50, 95% confidence interval (CI): 1.07, 2.10). The estimated risk increase for Caucasians during the second trimester was 37% (95% CI: 0.80, 2.36), while for all minority women combined (i.e., African Americans, Hispanics, and Asians) it was 60% (95% CI: 1.03, 2.47). The study data suggest that high levels ($\geq$70 μg/liter) of trihalomethanes experienced during the second trimester and pregnancy overall may affect fetal growth.

birth weight; chloroform; environmental exposure; fetal growth retardation; pregnancy trimester, second; trihalomethanes; water

Abbreviations: CI, confidence interval; OR, odds ratio; TLBW, term low birth weight.

The benefits of chlorine disinfection of drinking water are well established with regard to reducing microbial contamination. In the early 1970s, however, scientists discovered that chlorine reacts with organic matter to form chloroform, referred to as a ''disinfection by-product'' (1). Subsequently, more than 500 disinfection by-products have been identified (2). Some epidemiologic studies suggested that pregnant women exposed to water containing elevated trihalomethane concentrations may be at greater risk for adverse pregnancy outcomes, including birth defects, spontaneous abortion, and fetal growth retardation (3, 4). Researchers estimated mostly small increases in risk for being born low weight at term or small for gestational age when exposure to total trihalomethanes during pregnancy was 60 μg/liter or higher (3–6). In the mid 1980s, women in New Jersey (4) experienced increased risks of term low birth weight (TLBW) at trihalomethane levels above 100 μg/liter (odds ratio (OR) = 1.40, 90 percent confidence interval (CI): 1.0, 2.0) averaged over the whole pregnancy, while for Colorado women in the early 1990s the risk increased when third trimester exposures exceeded 61 μg/liter (OR = 5.9, 95 percent CI: 2.0, 17.0) (4). Wright et al. (5), studying 96 communities in Massachusetts in 1990, reported 13 percent (95 percent CI: 1.03, 1.24) and 14 percent (95 percent CI: 0.95, 1.38) risk increases for term small-for-gestational-age and TLBW infants, respectively, but this time for second trimester levels

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greater than 80 μg/liter. In a later study of 109 Massachusetts communities, the same authors found third trimester exposures of greater than 74 μg/liter to be associated with term small-for-gestational-age infants (OR = 1.13, 95 percent CI: 1.07, 1.20), but they did not present associations for other trimesters (6).

In public water systems serving more than 10,000 people in the United States, regulatory monitoring data consist of samples from four locations that are typically collected once during each quarter. Such limited sampling may not accurately capture the spatial or temporal variability of disinfection by-products in a system. Only three studies published to date that examined the effects of disinfection by-products on fetal growth modeled total trihalomethane exposures more extensively or conducted population surveys to improve exposure assessment (4, 7). The remaining studies relied solely on quarterly monitoring data or on water source or treatment method to create a simple dichotomous exposure variable (3–6, 8, 9). Furthermore, with the exception of four studies (5–7, 9), exposure and risk estimates were generally derived only for the third trimester. Thus, exposures during earlier trimesters or throughout pregnancy were ignored.

A science advisory panel from the US Environmental Protection Agency reviewing the disinfection by-products literature recommended that future epidemiologic studies consider the role of geographic and temporal variability to reduce exposure misclassification (10). Here, we improved exposure assessment by relying on weekly not quarterly monitoring data for total trihalomethanes in water supplied to homes by a single public utility serving multiple communities in Massachusetts. In addition, the water treatment regimens used by this utility minimized the geographic variability of total trihalomethanes, the importance of which is underscored by recent research to develop methods to identify utilities that have low spatial variability of disinfection by-product (11). The selected communities were served with water containing a low level of total trihalomethanes (<20 μg/liter) before 1998, yet changes in treatment processes led to elevated total trihalomethane levels thereafter. Thus, the time frame of our study captures the first time the diverse population living in these communities was exposed to higher levels of total trihalomethanes in the water supply. We examined the effects of trimester-specific and pregnancy average exposures to total trihalomethane in drinking water on TLBW in this population and examined the associations in racial and ethnic subgroups.

MATERIALS AND METHODS

Birth data

Data were obtained from the Registry of Vital Records and Statistics, Massachusetts Department of Public Health. We abstracted 40,514 records of singletons conceived between the beginning of February 1999 and the end of February 2001 and born between August 1999 and December 2001 whose mothers resided at birth in a community served only by the utility we studied. This 2-year period represents the time during which complete pregnancy exposure could be ascertained for all term births. We restricted our analyses to infants born between 37 and 45 gestational weeks with a birth weight between 500 and 5,000 g ($n = 2{,}833$ excluded). Furthermore, if the birth records did not provide information on the infant's sex, maternal age, marital status, race/ethnicity, maternal education, parity, cigarette smoking, payment source, or a maternal disease factor ($n = 1{,}152$), subjects were excluded from analyses, leaving us with 36,529 births. We examine TLBW, defined as weighing less than 2,500 g and born after 36 weeks of gestation; infants born at term with normal weight served as controls. Gestational age was determined from clinical estimates provided in the birth data.

Water quality data

We abstracted trihalomethane data from the Massachusetts Department of Environmental Protection records for 27 communities receiving water from a single supplier (12). Total trihalomethane samples were collected weekly on Mondays in vials containing ascorbic acid as a preservative for the trihalomethane compounds (13). Samples were refrigerated and analyzed within days. Trihalomethane concentrations were determined by US Environmental Protection Agency method 524.2 (13, 14) and consisted of chloroform, bromoform, bromodichloromethane, and dibromochloromethane. The sum of measurements for all constituents represents our measure of total trihalomethane (figure 1). The utility transmission system incorporated major water treatment processes at three locations in the system. Sodium hypochlorite was added at the first point, soda ash, carbon dioxide, and fluoride at a second location, and chlorine and ammonia in a final treatment step (13). Three of the communities conducted their own chloramination as a final step, while the remaining 24 received chloramination from a single facility. In addition, corrosion control treatment regimens created stable trihalomethanes (total trihalomethanes) within the distribution system (13).

Exposure assessment

We based our total trihalomethane exposure estimates on maternal residence at birth, gestational age, and environmental sampling data. We relied on clinical estimates of gestational age reported on the birth certificate for each infant to infer the periods that comprised the first, second, and third trimesters. For comparison purposes, exposure estimates were also generated using the last menstrual period. Relying on weekly total trihalomethane samples, we calculated each mother's trimester-specific and pregnancy average exposure, assuming that the mothers lived at the residence reported on the birth certificate throughout pregnancy. Analytical variability or precision for the total trihalomethane sampling method is estimated at about 20 percent (13). We determined that a range of plus or minus 20 percent of the weekly average of four sampling sites captured nearly all individual sample site values (figure 2) and therefore applied a single average for these sites to 24 of 27 communities. The remaining three communities that conducted their own chloramination treatment were

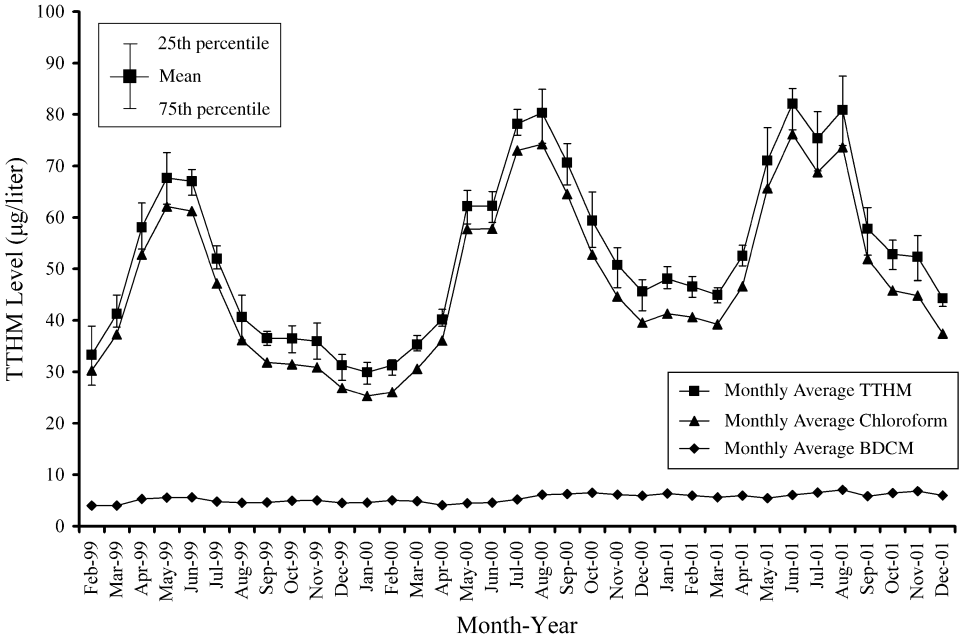

FIGURE 1. Monthly distribution (25th percentile, mean, and 75th percentile) of total trihalomethane (TTHM) and mean values for chloroform and bromodichloromethane (BDCM) from six sample sites served by a single water utility in Massachusetts from February 1999 to December 2001.

assigned weekly total trihalomethane values from two sites (not averaged) within those communities.

The first, second, and third trimesters were represented by gestational days 1–93, 94–186, and from day 187 to the date of birth. Pregnancy length in days was calculated by multiplying the clinical gestational age, presented in weeks, by seven, thus assuming the value represented completed weeks of gestation. Because the total trihalomethane data were highly colinear from week to week, we imposed a standard week structure, defined as Sunday to Saturday, and

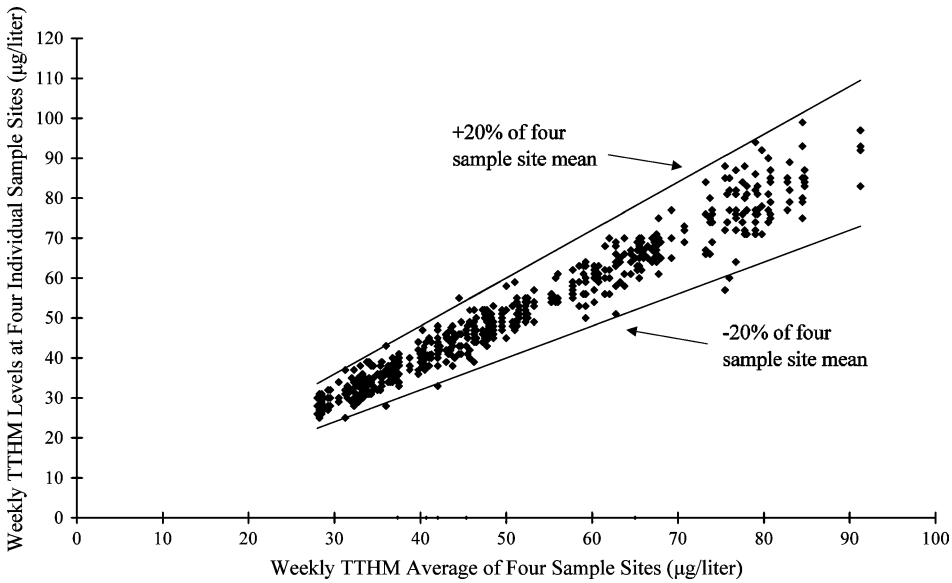

FIGURE 2. Comparison of weekly total trihalomethane (TTHM) levels between four sample sites and the mean of the four sample sites used for exposure assessment with 20% error bars around the mean from February 1999 to December 2001 for a single water utility in Massachusetts.

weighted the contribution of partial weeks to the exposure estimate by using the number of days that contributed to that week divided by seven.

Statistical methods

We used logistic regression to estimate crude and adjusted odds ratios and 95 percent confidence intervals for TLBW. First trimester total trihalomethane exposure was modeled without inclusion of exposure during other trimesters, while second trimester exposure was adjusted for first trimester total trihalomethane exposure, and third trimester exposure was adjusted for both first and second trimester exposures. To assess confounding due to maternal diseases, we entered all available risk factor information into our models and removed those (13 out of 21) variables that did not influence results and/or were extremely rare. All other known or suspected predictors of TLBW were retained in the adjusted models to control for potential confounding.

Categorical variables were used for gestational age in weeks (a linear and a second-order power term), infant's gender, marital status (married, not married, and previously married within 300 days), adequacy of prenatal care (Kessner Index), maternal age (<20, 20–29, 30–34, 35–39, or ≥40 years), maternal race/ethnicity (African American, Asian, Caucasian, Hispanic, or other), maternal education (less than high school, high school degree, associate's degree, bachelor's degree, postgraduate degree), parity (1, 2–3, 4–5, or ≥6), interval since the previous livebirth (≤12 months or >12 months), maternal smoking during pregnancy (0, 1–5, 6–10, or ≥11 cigarettes per day), previous infant who weighed >4,000 g, previous preterm or small-for-gestational-age infant, prenatal care source of payment (private, Healthy Start, or government), conception season (i.e., 3-month length), birth season, and average per capita income of the community as reported in US Census data (<$23,000, $23,000–<$26,000, $26,000–<$33,000, or ≥$33,000) (15). Indicator variables for the following maternal diseases during pregnancy were also included in the adjusted models: anemia, cardiac disease, hydramnios, chronic hypertension, pregnancy-related hypertension, sickle cell anemia, Rh sensitivity, and uterine bleeding. We report race/ethnicity-stratified analyses with and without adjustment for confounders to examine effect modification. Monotonic exposure trends were examined by entering continuous total trihalomethane variables into logistic models. Finally, we used linear regression to model birth weight (in grams).

RESULTS

A total of 894 trihalomethane samples were abstracted for six monitoring sites from 1999 through 2001. The interquartile range of the monthly total trihalomethane distributions was 59 μg/liter (minimum = 28 μg/liter; maximum = 87 μg/liter) (figure 1). The timing and duration of the total trihalomethane peaks varied each year, sometimes occurring as early as May or as late as August. The main component of total trihalomethanes in this water system was chloroform, with the monthly average fraction contributing 83–93 percent of the total trihalomethane (average, 89 percent). Bromodichloromethane ranged from not detected to 9 μg/liter (75th percentile, 6.1 μg/liter). Dibromochloromethane and bromoform were not detectable or were measured at very low levels (<1 μg/liter).

The mean birth weight of the 36,529 singleton term infants included in our analysis was 3,451 g. Among these, 780 (2.1 percent) were classified as low birth weight. The distributions of major predictors of TLBW are shown in table 1. In general, mothers who smoked, had less prenatal care, were of African-American ancestry, or suffered from a disease during pregnancy delivered a higher percentage of TLBW infants. Table 2 also shows a higher percentage of TLBW for mothers with high second trimester and pregnancy average total trihalomethane exposure. Second trimester and pregnancy average total trihalomethane exposure estimates were strongly correlated ($r = 0.87$), while exposures between trimesters were moderately or negatively correlated (range, −0.41 to 0.34). In the total study population, we also noted an unequal exposure distribution, such that a noticeably smaller proportion of fetuses carried to term had experienced a high total trihalomethane exposure (≥70 μg/liter) during the first trimester (9 percent) compared with such exposures during the second (15 percent) and third (20 percent) trimesters (table 2).

Regarding TLBW, with adjustment for potential confounding factors, we observed an increased risk with exposure to high levels of total trihalomethane during the second trimester (OR = 1.50, 95 percent CI: 1.07, 2.10) and during the whole pregnancy (OR = 1.23, 95 percent CI: 0.92, 1.64) (table 3). For the second trimester, a trend was observed per 10-μg/liter increase in total trihalomethane (OR = 1.08, 95 percent CI: 1.00, 1.17). Linear regression suggested a mean decrease in birth weight of −12 g (95 percent CI: −31, 6) at the second highest level of exposure during the second trimester.

Among Caucasians, an association with total trihalomethane exposure of 70 μg/liter or above was suggested for second trimester exposures (OR = 1.37, 95 percent CI: 0.80, 2.36), but the point estimate was lower than for all race/ethnicity combined and the estimate imprecise (table 4). Interestingly, third trimester estimates were in the opposite direction in this group.

Among minority mothers (African Americans, Hispanics, and Asians combined), the adjusted odds ratio for TLBW and exposures of 70 μg/liter or above in the second trimester was 1.60 (95 percent CI: 1.03, 2.47), and the odds ratio for a continuous variable per 10-μg/liter increase in total trihalomethane was 1.10 (95 percent CI: 1.00, 1.22) (table 4). Crude race/ethnicity-specific models indicated that the risk was highest in the Hispanic and African-American populations, but confidence intervals for all race/ethnicity subgroups were wide and overlapped because of small sample sizes in some strata (data not shown). Linear regression showed mean decreases in birth weight of −7 g (95 percent CI: −14, 0), −6 g (95 percent CI: −13, 1), and −12 g (95 percent CI: −21, −3) during the first and second trimesters and the whole of pregnancy, respectively, with increasing levels of total trihalomethane exposure (per 10 μg/liter).

TABLE 1. Demographic characteristics of mothers and their singleton infants* in selected Massachusetts communities served by a single surface-supplied drinking water utility, 1999–2001

	Study population		Mean birth weight (g)	TLBW† (%)
	No.	%		
Total	36,529	100	3,451	100
Infant's gender				
Male	18,694	51	3,515	1.8
Female	17,835	49	3,384	2.5
Parity (no.)				
1	17,570	48	3,402	2.6
2–3	16,644	46	3,499	1.6
4–5	2,022	6	3,479	2.5
≥6	293	1	3,497	2.0
Maternal race/ethnicity				
Caucasian	21,426	59	3,516	1.6
African American	5,553	15	3,352	3.5
Hispanic	5,839	16	3,397	2.6
Asian	3,680	10	3,308	2.4
Other	31	0	3,401	3.2
Maternal age (years)				
<20	2,104	6	3,295	4.0
20–29	13,658	37	3,410	2.4
30–34	12,296	34	3,489	1.5
35–39	6,916	19	3,505	1.9
≥40	1,555	4	3,483	3.2
Highest maternal education				
Some high school	3,932	11	3,349	3.3
Graduated high school	9,765	27	3,407	2.6
Associate's degree	6,625	18	3,452	2.2
Bachelor's degree	9,361	26	3,507	1.5
More than college degree	6,846	19	3,495	1.6
Maternal smoking (cigarettes/day)				
0	34,586	95	3,461	2.0
1–5	867	2	3,293	4.5
6–10	681	2	3,271	4.6
≥11	395	1	3,213	6.6
Prenatal care (Kessner Index)				
Adequate	27,053	74	3,467	1.9
Intermediate	4,907	13	3,398	2.6
Inadequate	958	3	3,325	3.8
Unknown	3,561	10	3,442	2.3
None	50	0	3,107	18.0
Maternal diseases during pregnancy				
One or more	7,411	20	3,407	3.0
None	29,118	80	3,463	1.9

* Term infants (weighing >500 g and <5,000 g) born between 37 and 45 weeks of gestation and conceived from February 1999 to February 2001.

† TLBW, term low birth weight ($n = 780$).

DISCUSSION

We relied on birth certificate information and weekly water quality monitoring data to derive pregnancy-specific total trihalomethane exposure estimates for maternal residences in Massachusetts communities served by a single public utility. We found that exposure to total trihalomethanes of 70 μg/liter or above averaged over the second trimester increased the risk of delivering a TLBW infant by 50 percent. We found a smaller estimate for risk in Caucasians (37 percent) compared with minorities including African Americans, Hispanics, and Asians combined (60 percent). While the 95 percent confidence intervals of second trimester risk largely overlap between Caucasians and non-Caucasians, the lower 95 percent confidence interval excluded the null only for minorities. Currently, no other published study has evaluated risk for TLBW and disinfection by-product exposure by race/ethnicity, perhaps because previous studies were not large or diverse enough to allow conducting race/ethnicity-specific analyses (3–9). However, associations between trihalomethane levels and low birth weight among Hispanics but not other racial/ethnic groups have recently been reported (16).

Similar to previous studies, this study did not distinguish between various pathways of exposure. Substantial exposure to the volatile portion of disinfection by-products might occur through dermal contact and inhalation during showering, bathing, swimming, and hand dish washing, but we were unable to measure the contribution of such exposures in this study (17). Not accounting for individual water use behavior may introduce exposure misclassification. However, the outcome (TLBW) is not expected to influence prior behavior during pregnancy. Thus, we expect the misclassification to be nondifferential for cases and controls, resulting most likely in a bias toward the null. Alternatively, if women choose to avoid tap water because of bad taste when total trihalomethane levels are highest, this may result in a nonlinear dose-response pattern and a drop in the estimated effect at the highest exposure level. Researchers who evaluated individual-level water consumption and showering habits reported inconsistent results for adverse birth outcomes; for example, studies did not find an increase in risk for intrauterine growth restriction or low birth weight with water consumption and/or showering habits (7, 18). Others reported an association for consumption of water with high levels of disinfection by-product and the risk of spontaneous abortion (19).

Our study had several strengths, including a possible reduction in nondifferential exposure misclassification due to the unique conditions of the water system described earlier. In addition, our approach resulted in studying a population's exposure over time rather than comparing populations from different communities with varying exposure levels with each other. Thus, we reduced the risk of confounding by geographic and demographic risk factors; there are far less time-varying risk factors we are aware of that might be associated with total trihalomethane levels and confound risk estimates.

We used maternal address at birth to assign exposures, assuming that this represents the residence for the entire

TABLE 2. Mean birth weight and percentage of term low birth weight by trimester and pregnancy average total trihalomethane level in selected Massachusetts communities served by a single surface-supplied drinking water utility, 1999–2001

	Study population		Mean birth weight (g)	TLBW* (%)
	No.	%		
Total	36,529	100	3,451	100
First trimester total trihalomethane level (μg/liter)				
<40	10,768	29	3,456	2.3
40–<50	10,487	29	3,455	2.0
50–<60	6,963	19	3,446	2.1
60–<70	5,158	14	3,440	2.1
≥70	3,153	9	3,455	2.0
Second trimester total trihalomethane level (μg/liter)				
<40	10,513	29	3,450	2.1
40–<50	9,634	26	3,453	2.0
50–<60	6,178	17	3,465	2.0
60–<70	4,757	13	3,439	2.3
≥70	5,447	15	3,445	2.4
Third trimester total trihalomethane level (μg/liter)				
<40	8,968	25	3,449	2.0
40–<50	7,883	22	3,442	2.3
50–<60	6,167	17	3,448	2.1
60–<70	6,171	17	3,460	2.2
≥70	7,340	20	3,458	2.1
Pregnancy average total trihalomethane level (μg/liter)				
<40	6,675	18	3,442	2.2
40–<50	7,843	21	3,454	2.2
50–<60	17,385	48	3,463	1.9
≥60	4,626	13	3,430	2.7

* TLBW, term low birth weight.

pregnancy. Research indicated that a substantial number (25 percent) of women are likely to move between conception and delivery, although the majority of these women move within the county of residence (20, 21). We do not believe that a large percentage of women moved out of the water service area that we studied, because 24 communities in our study area were adjacent to each other. It is also likely that women relocated to a community served by the same water supply. Thus, their total trihalomethane exposure measure would remain unaffected. The contiguity of these communities also implies that a subset of women who live and work in adjacent communities continue to use the same water supply, further reducing exposure misclassification that would result from using a different water source at the work site. For the women who move into the water service area during pregnancy, we would expect that moving is not affected by (subsequent) outcome status, and therefore effect estimates would most likely be impacted by nondifferential exposure misclassification and bias toward the null (22).

There is a possibility of residual confounding in our study, because of lack of information on selected risk factors such as maternal nutrition, job-related risk factors, maternal infection rates, indoor/outdoor air pollution, and other water contaminants. However, these risk factors for our outcome would have to be associated with total trihalomethane exposure levels to act as confounders. That is, they would have to be varying over time in concert with the total trihalomethane levels. While air pollution is time varying and could be a potential confounder, the air pollutants most often linked in the literature to fetal growth retardation are combustion by-products, which would be expected to be highest in winter (23). This is anticyclic to total trihalomethane levels that increase with water's absorbance of 254-nm ultraviolet light and temperature (13). Thus, we would expect negative confounding of our effects, if any. The same would be true for maternal respiratory infections. Nutrition and job-related factors are likely not seasonal in the population studied.

There are several differences in design between our study and those by Wright et al. (5, 6) that could account for our stronger second trimester effect estimates, including exposure assessment, the type of Massachusetts communities and the time period studied, the methods used to estimate

TABLE 3. Crude and adjusted* odds ratios and 95% confidence intervals for term low birth weight by trimester-specific and pregnancy average total trihalomethane exposure in selected Massachusetts communities served by a single surface-supplied drinking water utility, 1999–2001

Total trihalomethane (μg/liter)	Term low birth weight (all races)							
	First trimester		Second trimester		Third trimester		Pregnancy average	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Crude values								
<40	1.00		1.00		1.00		1.00	
40–<50	0.87	0.72, 1.05	1.04	0.84, 1.29	1.05	0.79, 1.39	1.00	0.79, 1.25
50–<60	0.90	0.73, 1.11	1.01	0.79, 1.29	0.84	0.63, 1.11	0.86	0.70, 1.06
60–<70	0.92	0.73, 1.15	1.17	0.92, 1.49	0.89	0.66, 1.19	1.23	0.98, 1.54
≥70	0.87	0.67, 1.13	1.31	1.03, 1.66	0.96	0.70, 1.32	N/A†	
Adjusted values								
<40	1.00	0.67, 1.13	1.00		1.00		1.00	
40–<50	0.82	0.66, 1.03	1.10	0.81, 1.49	0.87	0.60, 1.26	1.07	0.81, 1.42
50–<60	0.84	0.66, 1.08	1.08	0.79, 1.49	0.79	0.56, 1.12	0.95	0.75, 1.20
60–<70	0.88	0.66, 1.17	1.24	0.92, 1.67	0.84	0.58, 1.21	1.23	0.92, 1.64
≥70	0.87	0.63, 1.21	1.50	1.07, 2.10	0.74	0.44, 1.22	N/A	
Per 10-μg/liter increase	0.97	0.89, 1.04	1.08	1.00, 1.17	0.94	0.85, 1.05	1.03	0.93, 1.13

* Odds ratios were adjusted for gestational age, infant's gender, marital status, adequacy of prenatal care, maternal age, maternal race/ethnicity, maternal education, parity, maternal smoking, prenatal care source of payment, conception season, birth season, per capita income, previous preterm or small for gestational age infant, previous trimester exposure, and maternal disease factors including anemia, cardiac disease, diabetes, hydramnios, chronic hypertension, pregnancy-related hypertension, Rh sensitivity, sickle cell anemia, and uterine bleeding.

† N/A, not available.

gestational age, and the modeling approach. While in fact the communities we studied were a subset of the communities included in the analyses by Wright et al. (5, 6), as described above, none of these communities experienced total trihalomethane levels above 20 μg/liter prior to the end of 1997 (13). Gradual changes in treatment were introduced between September 1997 and July 1998 to improve pathogen inactivation. Therefore, these communities, representing 35 and 55 percent of the state's Hispanic and African-American populations, respectively, would have been counted as unexposed by Wright et al. (5, 6).

Wright et al. used gestational age based on the last menstrual period to identify term birth, while we used clinical estimates (5). We reanalyzed our data by use of the last menstrual period and found that effect estimates at the highest total trihalomethane exposure during the second trimester were lower for all race/ethnicities combined (OR = 1.26, 95 percent CI: 0.90, 1.77) and Caucasians only (OR = 1.08, 95 percent CI: 0.63, 1.84) but less so for minority women (OR = 1.44, 95 percent CI: 0.93, 2.23).

Our models included previous trimester exposure (i.e., second trimester exposure was adjusted for first trimester total trihalomethane exposure). Adjustment for previous trimester exposure assumes that exposures and health impacts from conception through birth are part of a continuous process and that exposures during an earlier period may affect what effect these exposures have during a later period (24, 25). Only Wright et al. (5) reported results for first and second trimester exposures, but they estimated each trimester's exposure effect independent of previous trimester exposures. Gallagher et al. (26) compared exposures based on areas with high and low total trihalomethane levels and calculated trimester-specific total trihalomethane exposures but, because these were highly correlated ($r = 0.67$ to 0.95), reported only the results for the third trimester. In contrast to this study, our trimester-specific exposures were not highly correlated ($r = -0.41$ to 0.34), because we relied on a single water system; thus, exposures did not vary geographically but seasonally and were measured at a high time resolution. When we estimated the effects for each trimester while ignoring previous exposures, the estimates for TLBW at the highest level of total trihalomethane exposure (≥70 μg/liter) during the second trimester were comparable but slightly lower (all races: OR = 1.28, 95 percent CI: 0.96, 1.72; Caucasians: OR = 1.17, 95 percent CI: 0.74, 1.84; non-Caucasians: OR = 1.40, 95 percent CI: 0.95, 2.07). Third trimester effects were null in all races, Caucasians, and non-Caucasians.

Our findings for TLBW are similar to previous results by Bove et al. (4), who had suggested that high total trihalomethane exposure during the entire pregnancy increased the risk for low-weight births at term. Another important similarity to the study by Bove et al. (4) is that they studied a population composed of 72.6 percent Caucasians and 22.5 percent African Americans. If the racial disparity in the effects we observed is due in part to increased susceptibility by African Americans, we would expect researchers studying more diverse populations, such as this one in

TABLE 4. Adjusted* odds ratios and 95% confidence intervals for term low birth weight by trimester-specific and pregnancy average total trihalomethane exposure, stratified by maternal race/ethnicity, in selected Massachusetts communities served by a single surface-supplied drinking water utility, 1999–2001

Total trihalomethane (μg/liter)	First trimester		Second trimester		Third trimester		Pregnancy average	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Caucasians ($n = 343$)								
<40	1.00		1.00		1.00		1.00	
40–<50	0.84	0.60, 1.18	1.11	0.69, 1.78	0.73	0.43, 1.23	1.06	0.70, 1.60
50–<60	0.76	0.54, 1.09	1.10	0.67, 1.79	0.60	0.36, 0.98	0.87	0.62, 1.21
60–<70	0.59	0.38, 0.92	1.22	0.76, 1.97	0.54	0.31, 0.93	1.06	0.69, 1.63
≥70	0.91	0.58, 1.43	1.37	0.80, 2.36	0.43	0.20, 0.94	N/A†	
Per 10-μg/liter increase	0.94	0.84, 1.04	1.06	0.95, 1.20	0.88	0.75, 1.04	0.96	0.84, 1.10
Non-Caucasians (*African Americans, Hispanics, and Asians combined*) ($n = 436$)								
<40	1.00		1.00		1.00		1.00	
40–<50	0.82	0.60, 1.12	1.08	0.73, 1.61	1.04	0.60, 1.80	1.09	0.73, 1.62
50–<60	0.94	0.66, 1.32	1.09	0.72, 1.66	1.06	0.64, 1.74	1.04	0.74, 1.46
60–<70	1.17	0.80, 1.72	1.27	0.86, 1.87	1.26	0.84, 2.12	1.40	0.94, 2.08
≥70	0.84	0.52, 1.36	1.60	1.03, 2.47	1.17	0.59, 2.32	N/A	
Per 10-μg/liter increase	1.00	0.90, 1.11	1.10	1.00, 1.22	0.99	0.85, 1.15	1.10	0.96, 1.25

* Odds ratios were adjusted for gestational age, infant's gender, marital status, adequacy of prenatal care, maternal age, maternal education, parity, maternal smoking, prenatal care source of payment, conception season, birth season, per capita income, previous preterm or small for gestational age infant, previous trimester exposure, and maternal disease factors including anemia, cardiac disease, diabetes, hydramnios, chronic hypertension, and uterine bleeding.

† N/A, not available.

New Jersey, to be more likely to detect adverse outcomes in exposed populations.

The biologic plausibility for trihalomethanes' inducing adverse reproductive outcomes can be derived from animal toxicology, evidence of exposure in humans, and mechanistic pathways. Inhalation and oral exposures to chloroform at various stages of gestation in rats, mice, and rabbits resulted in reduced birth weights and decreased body size in offspring, although the doses administered may have induced maternal toxicity (3). Experimental approaches including models of quantitative structure-activity relations and whole-embryo-culture assays have implicated multiple pathways through which various disinfection by-products might adversely impact animal and human reproductive health (3).

In humans, exposure to disinfection by-products can be demonstrated by measurable levels of chloroform, bromoform, and haloacetic acids or their metabolites in blood, urine, and exhaled breath (17). Transplacental passage of chloroform and other volatile organic compounds in blood has been demonstrated in mice and humans (27, 28). Furthermore, there is evidence that metabolites of chloroform may accumulate in the amniotic fluid of pregnant mice (29).

Bromodichloromethane is correlated with chloroform ($r = 0.56$) in our data set and is a secondary component of total trihalomethane. Research has shown that bromodichloromethane can affect chorionic gonadotrophin secretion in human placental trophoblast cultures (30). Cultures exposed to bromodichloromethane showed a dose-dependent decrease in the secretion of immunoreactive chorionic gonadotropin, as well as bioreactive chorionic gonadotropin (30). This implies that the placenta is a likely target of bromodichloromethane toxicity in humans and that adverse pregnancy outcomes, including those leading to growth retardation, may be due to bromodichloromethane (30).

There is evidence that maternal oxidative stress during pregnancy may play an important role in adverse fetal development (29, 31, 32). Lipid peroxides are generally higher in women with noncomplicated pregnancies than in nonpregnant women, and there is limited evidence that these elevations may occur during the second trimester and taper off later in gestation (33). If this natural rise in oxidative stress during the second trimester occurs simultaneously with elevated exposure to total trihalomethanes, it is plausible that the incompletely developed and already highly stressed antioxidant system of the fetoplacental unit may further impede fetal growth.

The metabolism of chloroform proceeds through a P-450-dependent activation step (34). Chloroform may be oxidatively metabolized and decomposed to electrophilic phosgene, which is highly reactive and will bond to cell components including proteins, phospholipid polar heads, and reduced glutathione (35). This may lead to chromosomal abnormalities, enzymatic malfunction, and disruption of cellular membranes, all of which could interfere with normal uterine development via placental changes or a direct effect on the conceptus. Phosgene may also be hydrolyzed to generate

carbon dioxide and hydrochloric acid (35). Research has shown that cytochrome P-450E1 (CYP2E1) is the primary enzyme involved in the metabolism of low doses of chloroform (34). A recent study found that newborns with a high-metabolism *CYP2E1* gene variant who experienced pregnancy average exposures of more than 29.4 μg/liter for disinfection by-products were at much higher risk (OR = 13.2, 95 percent CI: 1.19, 146.7) of intrauterine growth retardation compared with those without this *CYP2E1* variant (7).

Our results add to a growing body of research about the harmful effects of total trihalomethane exposures on fetal development. We found evidence for a second-trimester and whole-pregnancy exposure to disinfection by-products and effect on fetal growth that may differ by race/ethnicity. Equivocal and inconsistent results from previous epidemiologic research on disinfection by-products may be attributable to the lack of examining susceptible subgroups and limited environmental data leading to crude exposure assessment that did not adequately capture the spatiotemporal variability of total trihalomethane exposures. Future research should include analyses by race/ethnicity and address potential causes of variation in effect estimates.

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