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Prenatal Exposure to Disinfection Byproducts and Intrauterine Growth in a Chinese Cohort

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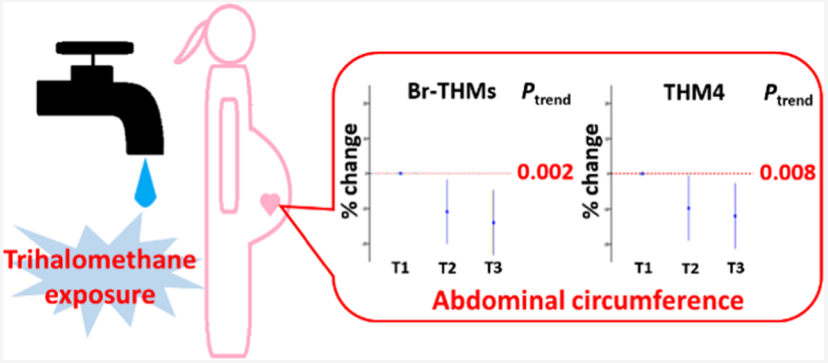

ABSTRACT: Disinfection byproduct (DBP) exposure has been associated with birth size, pregnancy oxidative stress, and other adverse perinatal outcomes. However, little is known about the potential effect of prenatal DBP exposure on intrauterine growth. The present study included 1516 pregnant women from the Xiaogan Disinfection By-Products (XGDBP) birth cohort who were measured for four blood trihalomethanes [i.e., chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM)] and two urinary haloacetic acids [i.e., dichloroacetic acid (DCAA) and trichloroacetic acid (TCAA)] across pregnancy trimesters. Second- and third-trimester fetal ultrasound measures of the abdominal circumference (AC), head circumference, biparietal diameter, femur length, and estimated fetal weight and birth weight were converted into z-scores. After adjusting for potential confounders, linear mixed models showed a decreasing AC z-score across tertiles of blood brominated THM (Br-THMs, the sum of BDCM, DBCM, and TBM) and total THM (THM4, the sum of Br-THMs and TCM) concentrations (both p for trend <0.01). We also observed a decreasing AC z-score across categories of blood TBM during pregnancy trimesters (p for trend = 0.03). Urinary haloacetic acids were unrelated to fetal growth parameters. In summary, prenatal exposure to THMs, particularly during the first trimester, was associated with reduced fetal abdominal circumference.

KEYWORDS: *disinfection byproducts, intrauterine growth, ultrasound measures, blood THMs, urinary HAAs*

INTRODUCTION

Disinfection of drinking water has been extensively used to prevent microbial diseases since the early 20th century. However, disinfection byproducts (DBPs) are formed unintentionally when natural organic matter in raw water reacts with the disinfectants (e.g., chlorine and chlorine dioxide). To date, more than 600 types of DBPs have been identified in drinking water, among which trihalomethanes (THMs) and haloacetic acids (HAAs) are the two most abundant species.[1,2] Human exposure to DBPs is chronic and widespread and occurs via inhalation, ingestion, and dermal absorption in daily water-use activities.[3−5]

Animal studies have shown that some DBPs can pass through the placenta,[6] which can lead to intrauterine growth retardation,[7] decreased birth length and weight,[7−10] and increased birth defects in rodent species.[11,12] Previous epidemiological studies also reported associations between gestational exposure to DBPs and fetal anthropometric measures at delivery, such as birth weight[13−17] and birth length,[18] as well as adverse birth outcomes [e.g., small for gestational age (SGA) and preterm birth].[18−23] However, evidence linking DBP exposure to intrauterine growth is sparse. Repeated ultrasound measures reflect the changing rate of growth in utero and capture specific fetal growth measures such as abdominal circumference (AC), biparietal diameter

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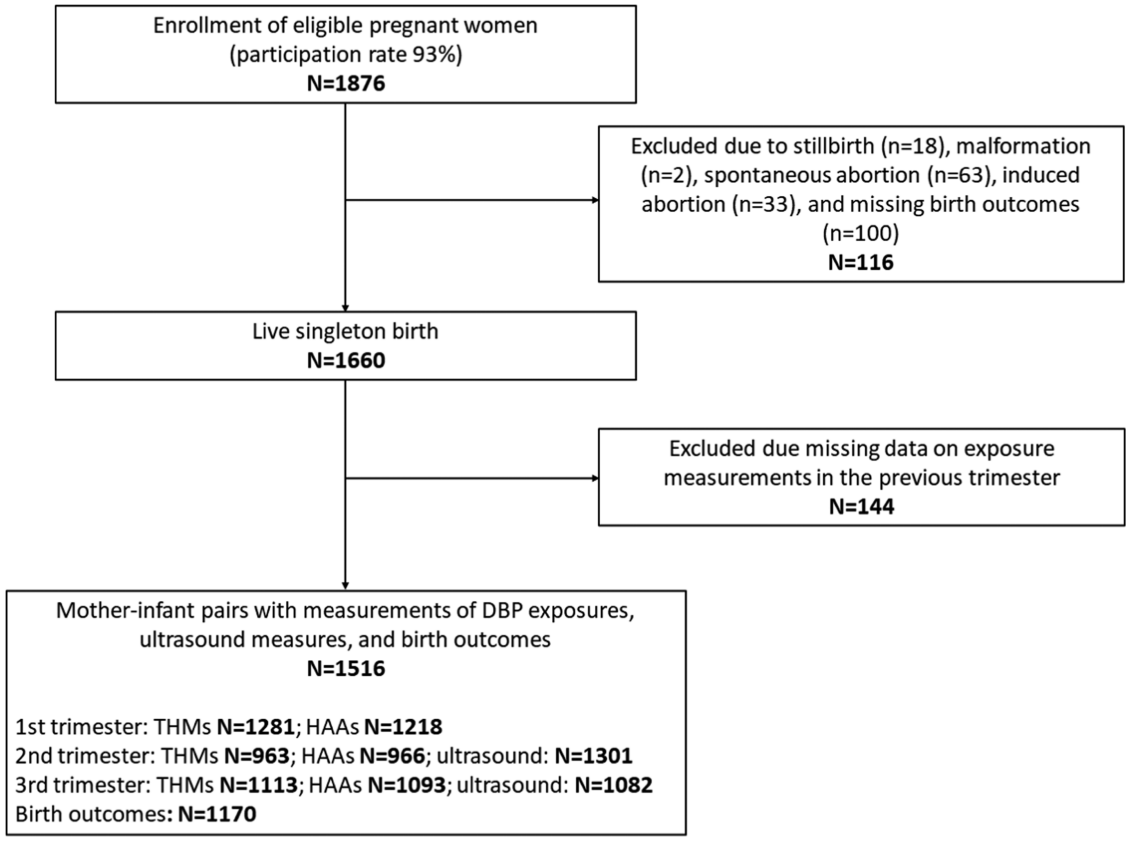

Figure 1. Flow chart for study participants.

(BPD), and femur length (FL), which facilitates an investigation of the effects of DBP exposure on specific anthropometric parameters during different gestational periods. In our previous study, we found an inverse association between the maternal urinary trichloroacetic acid (TCAA) concentration in late pregnancy and fetal BPD, head circumference (HC), and FL among 332 mother−infant pairs.[24] However, no studies to our knowledge have explored the association of exposure to THMs with intrauterine growth parameters. More importantly, the potential windows of vulnerability to exposure, which could lead to improved mechanistic insights for disease development, remain unclear.

Blood biomarkers of THMs and urinary biomarkers of HAAs are sensitive measures to study low levels of exposure.[25,26] While the elimination half-life of THMs in humans is relatively short, exposure biomarkers are considered to reflect steady-state blood concentrations due to the high frequency of daily exposures and slow partitioning out of adipose tissue.[27] Urinary TCAA and dichloroacetic acid (DCAA) are potential biomarkers for ingested HAAs.[22] In the present analysis, we evaluated the association of blood THM and urinary HAA concentrations across pregnancy trimesters with fetal growth assessed by repeated ultrasound measurements during pregnancy in combination with weight at birth. We also explored windows of vulnerability by examining fetal growth parameters in relation to trimester-specific blood THM and urinary HAA concentrations.

MATERIALS AND METHODS

Study Design. This study comprised pregnant women from the Xiaogan Disinfection By-Products (XGDBP) cohort (2015−2017), which has been described in detail previously.[22] Briefly, pregnant women less than 14 gestational weeks were recruited from the Maternal and Child Health Care Service Center of Xiaonan District between 2015 and 2017. Women were eligible if they were between 18 and 40 years of age at time of enrollment, resided in Xiaogan City permanently, were <14 weeks of gestation, had no self-reported psychiatric or laboratory-confirmed endocrine diseases (e.g., diabetes and thyroid diseases), and were carrying a singleton fetus. A total of 2021 women were asked to participate, of whom 1876 (93%) agreed to partake in the study. Each participant completed a self-reported questionnaire, underwent a physical examination, provided a spot urine sample, and had a peripheral venous blood draw during the first [gestational age (GA) <14 weeks, median: 9.0 weeks], second (GA 14−27 weeks, median: 16.9 weeks), and third (GA > 27 weeks, median: 31.6 weeks) trimesters. We excluded 360 women because of spontaneous abortion (n = 63), induced abortion (n = 33), stillbirths (n = 18), malformation (n = 2), or due to missing data on exposure (n = 100) or ultrasound measures (n = 144), leaving 1516 women in our present analysis (Figure 1). All participants provided written consent at enrollment, and the Ethics Committee of Tongji Medical College approved our study protocol.

Sample Collection and Analysis. Procedures for sample collection and DBP quantification have been illustrated in detail in our previous study.[28] In brief, peripheral blood was drawn from the cubital vein and stored at 4°C before analysis. Blood chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM) were quantified using a headspace solid-phase microextraction gas chromatography method.[18,29] Spot urine samples were

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collected using a polypropylene container and frozen at −40 °C until quantification. Urinary DCAA and TCAA were purified using liquid−liquid extraction and then determined by a gas chromatograph (Agilent Technologies 6890N, CA).[30] For quality control, each analysis run included a blank water sample (boiled spring water) and two quality controls spiked with target analytes.[28] The limits of detection (LODs) of TCM, BDCM, DBCM, TBM, TCAA, and DCAA were 1.95 ng/L, 0.45 ng/L, 0.68 ng/L, 2.00 ng/L, 0.50 μg/L, and 1.0 μg/L, respectively. Because specific gravity (SG) has been recommended as a more favorable approach for urinary dilution correction than creatinine,[31,32] we measured urinary SG using a Mindray urine analyzer. Urinary DCAA and TCAA were SG-corrected using the following formula: $P_c = P[(SG_{mean} - 1)/(SG_i - 1)]$, where P_c is the corrected concentration, P is the uncorrected concentration, SG_i is the SG of the participant's urine sample, and SG_{mean} is the mean SG of our study participants.[28]

Ultrasound Measurements and Birth Outcomes. Fetal ultrasound scans were performed to measure the fetal abdominal circumference (AC), head circumference (HC), biparietal diameter (BPD), and femur length (FL) during the second [mean ± standard deviation (SD): 17.7 ± 2.5 gestational weeks] and third trimester (mean ± SD: 32.5 ± 3.0 gestational weeks) by specialized obstetricians at the Maternal and Child Health Care Service Center of Xiaonan District. Estimated fetal weight (EFW) was calculated according to the Hadlock algorithm.[33] Birth outcomes (i.e., infant sex, birth weight, GA at delivery, and delivery mode) were abstracted from the hospital medical records. GA was estimated by a certified obstetrician based on self-reported last menstrual period and ultrasound evaluation at first-trimester prenatal visits.[22] We constructed GA-specific standard deviation scores (z-scores) for fetal growth parameters based on both ultrasound and birth measures using the GAMLSS package in R software.[34,35] Briefly, we modeled AC, HC, BPD, FL, and fetal weight (EFW and birth weight combined) using a cubic spline by GA in days based on our study population after normalizing the parameters using Box−Cox transformations. The fetal growth z-scores were acquired based on the best-fitting models according to Akaike's information criteria, which represented the percentile of the fetal or birth size at any specific GA.[36]

Covariates. At recruitment, we obtained basic characteristics of study participants via self-reported questionnaire, which included age, height, marital status, education level, income, geographic residence setting, sources of drinking water, and reproductive history. At enrollment and during each follow-up visit, we also collected information on lifestyle factors (e.g., smoking status, alcohol consumption, and folic acid usage), second-hand smoke exposure, maternal weight, and water-use activities (e.g., daily tap-water consumption, frequency and duration of bathing/showering, and time interval since last bathing/showering). Maternal weight was measured by certificated obstetricians using a multifunctional anthropometric instrument.

Data Analysis. We performed descriptive statistics for maternal characteristics [e.g., age, body mass index (BMI) at enrollment, income, education level, and gravidity], concentrations of blood THMs and urinary HAAs, ultrasound measures (i.e., AC, HC, BPD, FL, and EFW), and birth outcomes (i.e., birth weight, GA at delivery, delivery mode, and infant sex). Blood THM and urinary HAA concentrations below the LODs were replaced by $LOD/\sqrt{2}$.[37] We also calculated chlorinated THMs (Cl-THMs) as the sum concentration of TCM, BDCM, and DBCM, brominated THMs (Br-THMs) as the sum concentration of TBM, DBCM, and BDCM, and total THMs (THM4) as the sum concentration of Br-THMs and TCM. Correlations between DBP biomarker concentrations were evaluated using Spearman's rank correlation coefficients.

We explored associations of blood THM and urinary HAA concentrations obtained from first, second, and third trimesters with measures of fetal growth z-scores (i.e., AC, HC, BPD, FL, and fetal weight z-scores) evaluated during the second and third trimesters, and at birth, respectively, using linear mixed models,[38] where a random intercept for each participant and a random slope for GA at the time of fetal growth measurement (i.e., an ultrasound scan or delivery) were included. To remain consistent with our previous study,[22] blood TCM, BDCM, Cl-THMs, Br-THMs, and THM4 and SG-adjusted urinary TCAA and DCAA concentrations were categorized into tertiles at each pregnancy trimester. Because of the limited detection rates of blood DBCM and TBM (<49%), a three-level ordinal variable was created by <60th, 60th−80th, and >80th percentiles. P for trend was estimated by modeling DBP tertiles (or categories) as integer values (i.e., 0, 1, and 2). DBP biomarkers with a detection rate of >50% were also modeled as continuous variables after $\log_{10}$-transformation and are presented in the Supporting Information. We separately assessed the associations between blood THM and urinary HAA concentrations in the previous trimester and fetal growth z-scores in the following ultrasound measurement using linear regression models to identify the potential windows of vulnerability. Stratified analyses were performed to test whether the associations between DBP exposures and fetal growth parameters were modified by infant sex by adding interaction terms between biomarker concentrations and infant sex to the models.

Potential confounders were evaluated in a forward stepwise procedure if their inclusion led to a >10% change in the effect estimates for any associations between DBP biomarkers and intrauterine growth parameters. The following covariates were included in the final models: maternal age (continuous), BMI at enrollment (continuous), maternal height (continuous), infant sex (boys vs girls), gravidity (1 vs >1), folic acid usage during pregnancy (ever vs never), smoking status (ever vs never), alcohol intake (ever vs never), and education level (junior school and below, high school, or college and above).

To test the robustness of our results, we conducted several sensitivity analyses. First, we reanalyzed the associations between DBP biomarker concentrations and fetal growth z-scores by excluding women who had ever consumed tobacco or alcohol during pregnancy (N = 90) or by excluding women who had only one THM or HAA measurement during pregnancy (N = 348). Second, we included geographic residence setting (urban vs rural) and household income (<3000, 3000−4999, or ≥5000 Yuan/month) as additional covariates in the mixed regression models to evaluate the influence of maternal socioeconomic status. Third, to assess the influence of recent peak exposure events, we adjusted for the time interval since last showering or bathing due to their strong influence on THM concentrations.[39,40] Fourth, we included a different set of covariates in the final models based on the previous literature according to the directed acyclic graph (DAG):[28,41] maternal age (continuous), BMI at

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enrollment (continuous), geographic residence setting (urban vs rural), household income (<3000, 3000−4999, or ≥5000), and maternal education level (junior school and below, high school, or college and above) (Figure S2). Fifth, to assess the influence of maternal nutritional status, we included maternal weight gain during pregnancy (continuous) as a covariate in the mixed models. Finally, we reanalyzed the associations of blood DBCM and TBM concentrations with fetal growth parameters by categorizing participants into the following new three-level exposure groups: the low-exposure group with concentrations <LOD, the median-, and high-exposure groups that were equally divided among detectable samples. All statistical analyses were performed using R software (version 3.6.0, R Foundation for Statistical Computing, Austria).

RESULTS

Maternal Characteristics. Pregnant women included in the study sample were on average (±SD) 26.4 (±4.2) years of age (Table 1). More than half (64.1%) of mothers reported their education background as less than high school, 52.6% lived in an urban setting, and 86.0% reported income as less than 5000 Yuan/month. Most women (70.6%) had a normal BMI (18.5−24.9 kg/m^2) at enrollment, used folic acid (94.6%), and reported no smoking (97.3%) or alcohol consumption (96.3%) during pregnancy.

Distribution of Blood THMs and Urinary HAAs. During the first, second, and third trimesters of pregnancy, 1281, 963, and 1113 women with blood drawn were quantified for THM concentrations, respectively, and 1218, 966, and 1112 women with urine samples were quantified for HAA concentrations, respectively. Blood TCM and BDCM and urinary DCAA and TCAA were detected in ≥79.2% of the samples collected across pregnancy trimesters, whereas blood DBCM and TBM were detectable in 42.7 and 48.9% of the specimens, respectively (Table 2). The median concentrations of blood TCM, BDCM, Cl-THMs, Br-THMs, and THM4, and SG-corrected urinary TCAA and DCAA across pregnancy trimesters were 10.2 ng/L, 0.81 ng/L, 12.0 ng/L, 4.0 ng/L, 17.3 ng/L, 1.7 μg/L, and 7.1 μg/L, respectively. The correlations between exposure biomarkers are shown in Table S1. While blood TCM, BDCM, DBCM, and TBM concentrations were significantly correlated, all Spearman coefficients were relatively low (all ρ <0.40). We also observed that basic characteristics and mean exposure concentrations were similar between the overall participants included in the present study (N = 1516) and those with full measurements of THMs and HAAs (N = 766) throughout pregnancy (Table S2).

Ultrasound Measurements and Birth Outcomes. A total of 1301 (85.8%) and 1082 (71.4%) infants had ultrasound measurements during the second and third trimesters, respectively (Table 3). The crude distribution of AC, HC, BPD, FL, and fetal weight (EFW and birth weight combined) by GA at the time of measurement (i.e., GA at time of ultrasound measures or at birth) is shown in Figure S1. The mean (±SD) EFW in the second and third trimesters were 222.4 (±165.5) and 1980.8 (±633.3) g, respectively (Table 3). The mean (±SD) birth weight and GA at delivery were 3309.1 (±415.0) g and 39.2 (±1.3) weeks, respectively; overall, 60.1% of pregnant women had cesarean delivery and 51.2% of newborns were male.

DBP Concentrations and Fetal Growth z-Scores. After adjusting for confounding, we found decreasing AC z-scores

Table 1. Characteristics of Study Participants (N = 1516)

maternal characteristics	N	mean ± SD or %
age (years)	1516	26.4 ± 4.2
height (cm)	1505	160.1 ± 4.4
geographic residence setting		
urban	791	52.6%
rural	712	47.4%
gestational age at study measurements (weeks)		
first trimester	1301	9.5 ± 2.3
second trimester	1082	17.7 ± 2.5
third trimester	1170	32.5 ± 3.0
BMI at enrollment (kg/m^2)		
<18.5	323	21.5%
18.5−24.9	1059	70.6%
≥25	119	7.9%
marital status		
married	1445	95.4%
other	69	4.6%
education level		
junior school and below	966	64.1%
high school	351	23.3%
college and above	190	12.6%
income (Yuan/month)		
<3000	610	40.4%
3000−4999	688	45.6%
≥5000	212	14.0%
gravidity		
1	701	46.2%
≥2	815	53.8%
smoking during pregnancy		
ever	41	2.7%
never	1475	97.3%
alcohol use during pregnancy		
ever	56	3.7%
never	1460	96.3%
second-hand smoke exposure		
ever	665	43.9%
never	851	56.1%
folic acid usage during pregnancy		
yes	1434	94.6%
no	82	5.4%
main source of drinking water		
tap water	779	55.0%
bottled/mineral water	487	34.4%
well water	148	10.5%
time-varying factors		
daily tap-water consumption (mL)		
0	1786	52.2%
0−500	407	11.9%
>500	1230	35.9%
frequency of bathing/showering (times/week)		
<2	607	17.7%
2−6	885	25.8%
>6	1934	56.5%
duration of bathing/showering (minutes)		
<10	664	19.4%
10−15	1967	57.4%
>15	795	23.2%
time interval since last bathing/showering (hours)		
<12	144	4.2%
12−24	2295	67.0%
>24	987	28.8%

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Table 2. Maternal Distribution of Blood THM and Urinary HAA Concentrations (N = 1516)[a]

DBP biomarkers	number of samples	%>LOD	arithmetic mean	geometric mean	median	percentile 20%	40%	60%	80%
THM (ng/L)									
TCM	3357	92.6	15.9	9.5	10.2	5.2	8.6	12.1	17.5
BDCM	3357	79.2	0.96	0.80	0.81	0.35	0.71	0.93	1.2
DBCM	3357	42.7	0.91	0.74	<LOD	<LOD	<LOD	0.76	1.2
TBM	3357	48.9	28.8	4.5	<LOD	<LOD	<LOD	3.9	15.7
Cl-THMs	3357	–	17.7	11.7	12.0	6.8	10.2	14.0	19.0
Br-THMs	3357	–	30.7	7.2	4.0	2.7	3.3	5.7	17.6
THM4	3357	–	46.5	20.7	17.3	9.5	14.5	20.9	37.5
HAA (μg/L)									
crude concentrations									
DCAA	3296	95.8	7.7	5.8	7.1	3.4	6.0	8.2	10.5
TCAA	3296	91.4	2.6	1.6	1.6	0.81	1.4	1.9	2.9
SG-adjusted concentrations									
DCAA	3267	–	8.1	6.5	7.1	4.4	6.2	7.9	10.3
TCAA	3267	–	3.0	1.7	1.7	1.1	1.4	2.0	2.7

[a]Abbreviations: DBP, disinfection byproduct; THM, trihalomethane; HAA, haloacetic acid; LOD, the limit of detection; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Cl-THMs, chlorinated THMs; Br-THMs, brominated THMs; THM4, total THMs; SG, specific gravity; DCAA, dichloroacetic acid; and TCAA, trichloroacetic acid.

Table 3. Distribution of Ultrasound and Delivery Measures of Fetal Growth in Study Participants (N = 1516)[a,b]

fetal growth parameter	mean (±SD) or n (%)	median	25th–75th
ultrasound measures			
gestational age (weeks)			
second trimester	17.7 (±2.5)	17.0	16.4–17.6
third trimester	32.5 (±3.0)	31.7	30.1–34.3
AC (cm)			
second trimester	12.0 (±2.8)	11.0	10.0–12.0
third trimester	28.4 (±3.2)	27.9	26.1–30.5
HC (cm)			
second trimester	13.8 (±3.0)	13.0	12.0–14.0
third trimester	29.0 (±2.2)	29.0	27.0–30.0
BPD (cm)			
second trimester	3.9 (±0.80)	3.6	3.4–3.9
third trimester	8.1 (±0.70)	8.1	7.6–8.6
FL (cm)			
second trimester	2.4 (±0.73)	2.2	2.2–2.5
third trimester	6.1 (±0.62)	6.0	5.7–6.5
estimated fetal weight (g)			
second trimester	222.4 (±165.5)	168.7	147.3–198.9
third trimester	1980.8 (±633.3)	1808.5	1510.9–2338.9
birth outcomes			
gestational age (weeks)	39.2 (±1.3)	39.1	38.4–40.0
birth weight (g)	3312.1 (±413.9)	3300.0	3000.0–3570.0
delivery mode			
vaginal	465 (39.9%)	–	–
cesarean	703 (60.1%)	–	–
infant sex			
male	599 (51.2%)	–	–
female	571 (48.8%)	–	–

[a]We included 1301 and 1082 ultrasound measures in the second and third trimester, respectively, and 1170 birth outcomes in the present analysis. Fetal weight in the second and third trimesters was estimated using the Hadlock algorithm. [b]Abbreviations: AC, abdominal circumference; HC, head circumference; BPD, biparietal diameter; and FL, femur length.

across tertiles of blood Br-THMs and THM4 concentrations during pregnancy (i.e., first and second trimesters) (both p for trend <0.01); the percent change in the AC z-score comparing the extreme Br-THMs and THM4 tertiles was −14.2% (95% CI: −23.6, −4.8%) and −12.6% (95% CI: −21.9, −3.3%), respectively (Table 4). We also found a decreasing AC z-score across categories of blood TBM concentrations during pregnancy trimesters (p for trend = 0.03); the percent change in the AC z-score comparing the second vs first categories of TBM was −13.5% (95% CI: −23.4, −3.6%). Stratified analysis showed slightly more pronounced inverse associations between blood TBM concentrations and the AC z-score among female infants [% change= −20.1% (95% CI: −36.5, −3.7%) comparing extreme TBM categories, p for interaction = 0.12, Table S4]. There was no evidence of any relationship between urinary HAA concentrations and fetal growth parameters (i.e., AC, HC, BPD, FL, and fetal weight z-scores), and between blood THM concentrations and fetal weight z-scores (i.e., EFW and birth weight combined). When trimester-specific associations between DBP exposures and fetal growth z-scores were explored, we found that the inverse associations between blood TBM, Br-THMs, and THM4 concentrations and AC z-scores were more pronounced when DBP biomarkers were measured in the first trimester (Figure 2). Blood THM and urinary HAA concentrations in the third trimester were unrelated to birth weight (Table S5). The associations between THM and HAA concentrations and fetal growth z-scores were materially unchanged when we excluded women who reported smoking or drinking in pregnancy (Table S6), when we excluded women who had only one THM or HAA measurement during pregnancy (Table S7), when we additionally corrected for geographic residence setting and household income, time interval since last bathing/showering, or maternal weight gain during pregnancy, and when we included a different set of covariates according to our prespecified DAG (Tables S8–S11). The inverse associations between TBM and AC z-scores were materially unchanged when we categorized participants with concentrations <LOD in the low-exposure group (Table S12).

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Table 4. Associations of Blood THM and Urinary HAA Concentrations from First, Second, and Third Trimesters with Repeated Parameters of Fetal Growth z-Scores from Second and Third Trimesters, and at Birth, Respectively, Based on Linear Mixed Models (1516 Mother−Infant Pairs, 3553 Measurements)[a,c]

		percent change (95% CI)				
DBP biomarkers	N^b	AC	HC	BPD	FL	fetal weight
Blood THMs (ng/L)						
TCM						
T1 (<7.0)	1119	0	0	0	0	0
T2 (7.0−13.1)	1119	**−13.5 (−23.0, −4.0)**	0.93 (−7.7, 9.5)	−0.86 (−8.5, 6.7)	−9.3 (−18.7, 0.12)	−7.1 (−14.4, 0.18)
T3 (>13.1)	1119	−8.1 (−17.3, 1.1)	−5.1 (−13.7, 3.5)	−0.37 (−7.9, 7.1)	−3.9 (−13.1, 5.3)	−4.1 (−11.3, 3.1)
P for trend	–	0.09	0.24	0.93	0.42	0.27
BDCM						
T1 (<0.62)	1119	0	0	0	0	0
T2 (0.62−0.97)	1119	5.6 (−3.8, 15.0)	−0.75 (−9.5, 7.9)	3.5 (−4.1, 11.1)	−5.3 (−14.7, 4.1)	2.6 (−4.7, 9.9)
T3 (>0.97)	1119	4.7 (−4.6, 14.0)	2.0 (−6.8, 10.8)	4.7 (−2.9, 12.3)	5.4 (−3.9, 14.7)	2.7 (−4.6, 10.0)
P for trend	–	0.32	0.39	0.13	0.25	0.48
DBCM						
<60th (<0.76)	2014	0	0	0	0	0
60th−80th (0.76−1.2)	672	4.7 (−5.2, 14.6)	5.9 (−3.3, 15.1)	4.4 (−3.6, 12.4)	3.0 (−6.9, 12.9)	5.0 (−2.7, 12.7)
>80th (>1.2)	671	1.3 (−8.9, 11.5)	4.0 (−5.5, 13.5)	−3.3 (−11.6, 5.0)	−3.9 (−14.1, 6.3)	2.6 (−5.2, 10.4)
P for trend	–	0.63	0.41	0.68	0.61	0.36
TBM						
<60th (<3.9)	2014	0	0	0	0	0
60th−80th (3.9−15.7)	672	**−13.5 (−23.4, −3.6)**	1.6 (−7.7, 10.9)	−4.2 (−12.3, 3.9)	−4.8 (−14.7, 5.1)	−3.8 (−11.6, 4.0)
>80th (>15.7)	671	−8.3 (−19.0, 2.4)	4.1 (−5.9, 14.1)	−5.6 (−14.3, 3.1)	−0.77 (−11.5, 9.9)	0.98 (−7.0, 9.0)
P for trend	–	**0.03**	0.61	0.15	0.67	0.98
Cl-THMs						
T1 (<9.1)	1119	0	0	0	0	0
T2 (9.1−15.5)	1119	**−12.4 (−21.9, −2.9)**	4.3 (−4.6, 13.2)	0.76 (−7.0, 8.6)	−6.8 (−16.3, 2.7)	−4.7 (−12.1, 2.7)
T3 (>15.5)	1119	−8.9 (−18.2, 0.36)	−4.3 (−13.2, 4.6)	−0.35 (−7.9, 7.3)	−3.0 (−12.3, 6.3)	−0.76 (−8.1, 6.5)
P for trend	–	0.07	0.34	0.93	0.53	0.86
Br-THMs						
T1 (<3.0)	1119	0	0	0	0	0
T2 (3.0−4.1)	1119	**−11.0 (−20.2, −1.8)**	1.7 (−6.8, 10.2)	−4.4 (−11.8, 3.0)	−6.4 (−15.6, 2.8)	−2.7 (−9.9, 4.5)
T3 (>4.1)	1119	**−14.2 (−23.6, −4.8)**	3.8 (−4.8, 12.4)	−7.5 (−15.1, 0.08)	−4.1 (−13.5, 5.3)	−1.9 (−9.2, 5.4)
P for trend	–	**0.002**	0.39	0.06	0.38	0.59
THM4						
T1 (<12.2)	1119	0	0	0	0	0
T2 (12.2−23.0)	1119	**−11.1 (−20.4, −1.8)**	−1.3 (−9.8, 7.2)	−1.9 (−9.4, 5.6)	**−10.3 (−19.6, −1.0)**	−6.6 (−13.8, 0.56)
T3 (>23.0)	1119	**−12.6 (−21.9, −3.3)**	0.36 (−8.3, 9.1)	−3.5 (−11.1, 4.1)	−2.4 (−11.7, 6.9)	−2.9 (−10.3, 4.5)
P for trend	–	**0.008**	0.94	0.36	0.61	0.41
SG-adjusted urinary HAAs (μg/L)						
DCAA						
T1 (<5.7)	1089	0	0	0	0	0
T2 (5.7−8.5)	1089	−4.8 (−14.0, 4.4)	−1.1 (−10.8, 8.6)	−5.7 (−13.6, 2.2)	−5.7 (−15.0, 3.6)	−2.7 (−10.5, 5.1)
T3 (>8.5)	1089	2.6 (−6.8, 12.0)	2.1 (−7.6, 11.8)	−0.25 (−8.2, 7.8)	0.31 (−9.2, 9.8)	1.5 (−6.5, 9.5)
P for trend	–	0.62	0.66	0.93	0.97	0.71
TCAA						
T1 (<1.3)	1089	0	0	0	0	0
T2 (1.3−2.1)	1089	−6.4 (−15.6, 2.8)	**−10.8 (−19.9, −1.7)**	−3.4 (−11.3, 4.5)	−4.8 (−14.2, 4.6)	3.1 (−4.7, 10.9)
T3 (>2.1)	1089	1.1 (−8.3, 10.5)	−0.89 (−10.1, 8.3)	1.6 (−6.5, 9.7)	5.1 (−4.4, 14.6)	2.7 (−5.2, 10.6)
P for trend	–	0.85	0.93	0.70	0.31	0.50

[a]Models were adjusted for age, body mass index at recruitment, maternal height, education level, infant sex, gravidity, folic acid usage during pregnancy, smoking status, and alcohol intake. [b]Number of samples across pregnancy trimesters. [c]Abbreviations: DBP, disinfection byproduct; THM, trihalomethane; HAA, haloacetic acid; AC, abdominal circumference; HC, head circumference; BPD, biparietal diameter; FL, femur length; T, tertile; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Cl-THMs, chlorinated THMs; Br-THMs, brominated THMs; THM4, sum of 4 THMs; DCAA, dichloroacetic acid; and TCAA, trichloroacetic acid.

DISCUSSION

In this prospective birth cohort, we found that women with higher concentrations of blood TBM, Br-THMs, and THM4 across pregnancy trimesters had lower fetal abdominal circumference measurements. Associations were strengthened with blood THM concentrations measured in the first trimester, suggesting that early pregnancy may be a potentially vulnerable window for fetal growth. Urinary HAA concentrations were not associated with fetal growth parameters in this study.

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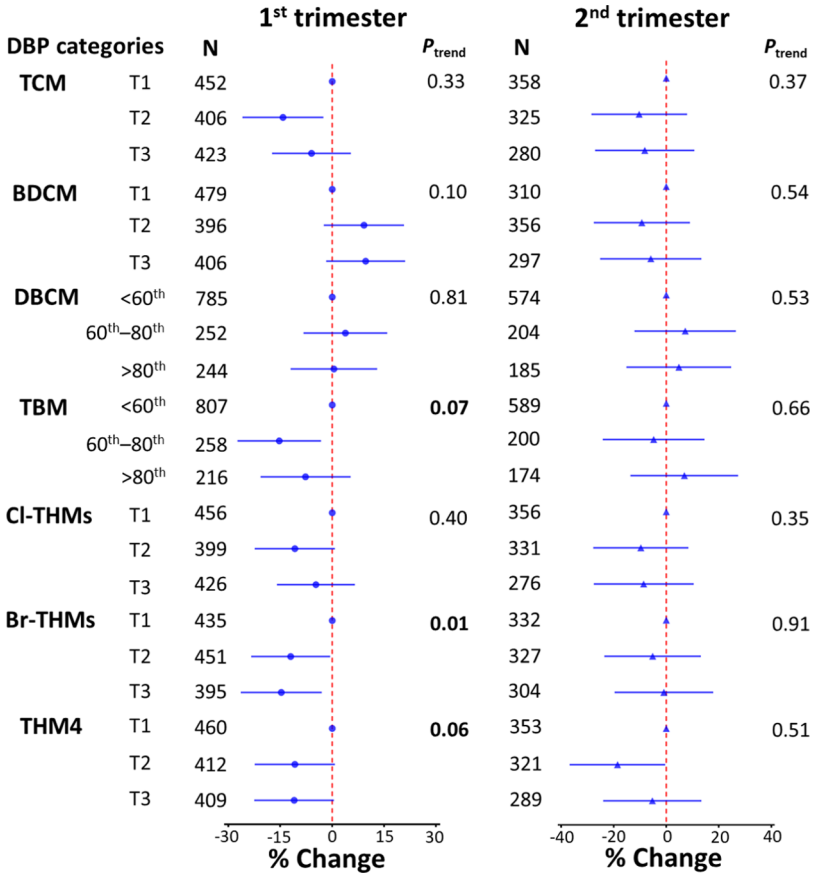

Figure 2. Associations of AC z-scores with blood THM concentrations in the previous trimester (exposure at 1st trimester vs AC at 2nd trimester and exposure at 2nd trimester vs AC at 3rd trimester) stratified by different exposure windows. Abbreviations: DBP, disinfection byproduct; THM, trihalomethane; AC, abdominal circumference; HC, head circumference; BPD, biparietal diameter; FL, femur length; T, tertile; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Cl-THMs, chlorinated THMs; Br-THMs, brominated THMs; and THM4, sum of 4 THMs.

Blood TCM and BDCM and urinary DCAA and TCAA were detected in ≥79.2% of the samples collected across pregnancy trimesters, which is not unexpected given the widespread use of chlorinated water in our study participants.[28] The median concentrations of blood THM4 and urinary TCAA in our study sample were 17.3 ng/L and 1.6 μg/L, respectively, which were lower than that reported among pregnant women in Wuhan City (57.1 ng/L and 7.1 μg/L, respectively),[18,24] United Kingdom (urinary TCAA: 6.1 μg/L),[42] and South Africa (urinary TCAA: 201 μg/L).[43] The difference in exposure may be explained by regional variability in DBP concentrations in the water supply systems.[28] For instance, THM4 concentrations in the water system of Xiaogan City (mean: 7.4 μg/L) were among the lowest levels in previous water studies from Wuhan City (mean: 25.3 μg/L),[44] United Kingdom (mean: 12.2−61.0 μg/L),[45] and South Africa (mean: 72 μg/L).[46] In addition, the differences in population ethnicity, socioeconomic status, and water-use habits may also influence DBP biomarker concentrations.[28,47,48]

Several epidemiological studies have shown that higher THM concentrations are associated with lower fetal anthropometric measures at delivery, such as birth weight,[15,16,49−51] birth length, and small for gestational age.[52] To date, however, few studies have explored the association of DBP biomarker concentrations with ultrasound fetal growth parameters. Deng and colleagues measured urinary TCAA concentrations among 332 pregnant women at the time of delivery and reported inverse associations between urinary TCAA and ultrasound measures of BPD, HC, and FL in male infants only.[24] In contrast, in our present study, we did not find any convincing associations between urinary DCAA and TCAA and ultrasound measures of fetal growth. Inconsistency in findings between our study and other work may be explained by the difference in exposure concentrations among participants. All participants in the Deng study lived in Wuhan City, whose median urinary concentrations of TCAA were substantially higher than that of our present cohort (8.6 vs 2.6 ng/L, respectively). Furthermore, differences in study design (cross-sectional vs prospective study) and the timing of exposure assessment and ultrasound measurements (single vs repeated measures) may account for discrepancies in study findings. In addition, this previous study only included 332 mother−infant pairs, which may have resulted in imprecise estimates.

To our knowledge, this current analysis is the first to investigate the association between prenatal exposure to THMs and ultrasound fetal growth measurements. We found inverse associations between maternal blood TBM, Br-THM, and THM4 concentrations and the AC z-score, which is a sensitive predictor of restricted fetal growth,[53,54] and reflects fetal liver growth and subcutaneous fat accretion.[55] In support of our findings, animal studies have shown that gestational exposure to THMs can lead to intrauterine growth retardation in rodent species,[56,57] probably by disturbing placental vascularization and disrupting immune and inflammatory

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functions.[58−60] Meanwhile, some THM molecules can cross the placental barrier and reach the fetal liver,[6] which can inhibit calcium sequestration and the activity of cytochrome P-450, eventually leading to disrupted fetal liver development.[61,62] Our previous research based on the same cohort found that blood TCM, Br-THMs, and THM4 across pregnancy trimesters were positively associated with urinary oxidative stress biomarkers.[63] Elevated maternal oxidative stress can disrupt normal placentation and nutritional supply to the fetus,[64,65] which may result in delayed adipose accumulation and reduced intrauterine fetal development.[66,67] In addition, we observed that the inverse associations between blood TBM concentrations and the AC z-score were modestly higher among female infants. We previously reported that blood TBM concentrations were associated with DNA hypomethylation in cord blood,[68] which can contribute to impaired fetal growth.[69,70] Female infants have a relatively higher methylation status,[71] which may partially explain a heightened sensitivity to hypomethylation effects.

Interestingly, the inverse associations between blood exposure biomarkers and the AC z-score were stronger for first-trimester blood THM concentrations, suggesting that early pregnancy may be a potentially vulnerable window. This is biologically plausible given that early pregnancy is crucial for the development of the placenta and fetal organs,[72,73] which is sensitive to environmental toxicants.[74−76] Numerous epidemiological studies have found that exposure to certain environmental pollutants during the first trimester was associated with reduced fetal growth parameters.[77−80] Our results also showed that THM exposures can impair fetal growth in the second trimester, possibly via altering hormone regulation, disrupting placental growth and/or triggering the oxidative stress response.[81,82] Early-onset growth retardation is a significant concern given its association with various adverse health outcomes in children and adults.[83,84] However, more mechanistic studies are needed to clarify our observed trimester-specific associations.

The strengths of our study include its prospective design, relatively large sample size, comprehensive determination of exposure biomarkers for two leading DBP species (i.e., THMs and HAAs), and repeated measurements of exposure biomarkers and fetal growth parameters across pregnancy trimesters. However, some limitations should be considered. First, ultrasound fetal growth parameters were measured up to two times for each participant, which may have been insufficient to characterize the intrauterine fetal trajectory throughout pregnancy. Second, blood THM and urinary HAA concentrations were measured at a single time point during each trimester. While our sensitivity analysis showed similar results when we additionally corrected for recent peak exposure events (e.g., showering and bathing), exposure misclassification cannot be fully ruled out.[28] In this case, however, such nondifferential misclassification would tend to bias estimates toward the null. Third, we cannot exclude residual confounding from other unmeasured covariates (e.g., dietary habits, physical activity, and gene polymorphisms)[85−87] and coexposure to other DBP species (e.g., haloacetonitriles, haloketones, and nitrosamines).[88,89] Fourth, the possibility of chance findings cannot be excluded due to multiple testing. Fifth, the generalizability of our results should be interpreted with caution, given that we did not use nationally representative data to estimate the fetal growth z-scores and that a large proportion of our study participants had low socioeconomic status and underwent cesarean delivery (60.1%), the latter being relatively common delivery mode in China.[90] Finally, observational studies such as ours cannot demonstrate causality.

To conclude, we found inverse associations between prenatal blood TBM, Br-THMs, and THM4 concentrations and fetal abdominal circumference measurements among 1516 mother−infant pairs from this Chinese birth cohort. We also found these associations to be stronger for first-trimester blood THM concentrations, suggesting a potentially vulnerable window in early pregnancy. Our findings suggest that intrauterine fetal growth is highly sensitive to THMs, even at low exposure levels.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.1c04926.

Associations between fetal growth parameters and gestational age at measurement (Figure S1), directed acyclic graph (DAG) between prenatal DBP concentrations and intrauterine growth parameters (Figure S2), correlation between blood THM and SG-adjusted urinary HAA concentrations (Table S1), characteristics of women with 3 THM and HAA values and all participants (Table S2), associations of continuous blood THM and urinary HAA concentrations with fetal growth parameters (Table S3), associations between blood THM and urinary HAA concentrations and fetal growth parameters stratified by infant sex (Table S4), and various sensitive analysis (Tables S5−S12) (PDF)

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C.L. and Y.-X.W. drafted the manuscript; C.L. analyzed the data; and Y.-X.W., W.-Q.L., and C.M. led the study design and conception and supervised the work. All authors interpreted the results and critically revised the manuscript.

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Notes

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