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Article

Relationship between Blood Trihalomethane Concentrations and Serum Thyroid Function Measures in U.S. Adults

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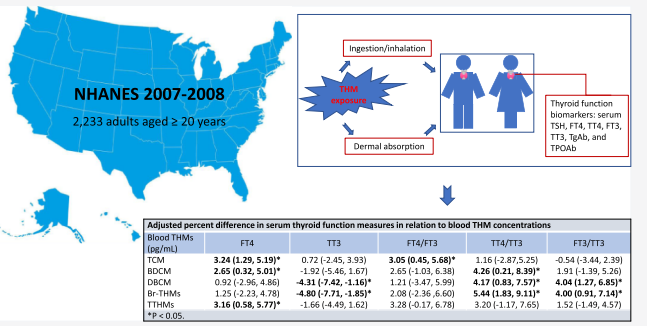
ABSTRACT: Toxicological studies show that exposure to disinfection byproducts, including trihalomethanes (THMs), negatively affects thyroid function; however, few epidemiological studies have explored this link. This study included 2233 adults (ages ≥20 years) from the 2007−2008 National Health and Nutrition Examination Survey (NHANES) who were measured for blood THM concentrations [chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), or bromoform (TBM)] and serum thyroid function biomarkers [thyroid-stimulating hormone, free thyroxine (FT4), total thyroxine (TT4), free triiodothyronine (FT3), total triiodothyronine (TT3), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TgAb)]. Multivariable linear regression models showed positive associations between blood TCM, BDCM, and total THMs (the sum of all four THMs) concentrations and serum FT4, whereas inverse associations were found between blood DBCM and total brominated THM (Br-THM; the sum of BDCM, DBCM, and TBM) concentrations and serum TT3 (all $p < 0.05$). Besides, positive associations were observed between blood TCM concentrations and FT4/FT3 ratio, between BDCM, DBCM, and Br-THM concentrations and TT4/TT3 ratio, and between DBCM and Br-THM concentrations and FT3/TT3 ratio (all $p < 0.05$). Blood THM concentrations were unrelated to the serum levels of thyroid autoantibodies TgAb or TPOAb. In summary, exposure to THMs was associated with altered serum biomarkers of thyroid function but not with thyroid autoimmunity among U.S. adults.



Adjusted percent difference in serum thyroid function measures in relation to blood THM concentrations

Blood THMs (pg/mL)	FT4	TT3	FT4/FT3	TT4/TT3	FT3/TT3
TCM	**3.24 (1.29, 5.19)***	0.72 (-2.45, 3.93)	**3.05 (0.45, 5.68)***	1.16 (-2.87,5.25)	-0.54 (-3.44, 2.39)
BDCM	**2.65 (0.32, 5.01)***	-1.92 (-5.46, 1.67)	2.65 (-1.03, 6.38)	**4.26 (0.21, 8.39)***	1.91 (-1.39, 5.26)
DBCM	0.92 (-2.96, 4.86)	**-4.31 (-7.42, -1.16)***	1.21 (-3.47, 5.99)	**4.17 (0.83, 7.57)***	**4.04 (1.27, 6.85)***
Br-THMs	1.25 (-2.23, 4.78)	**-4.80 (-7.71, -1.85)***	2.08 (-2.36 ,6.60)	**5.44 (1.83, 9.11)***	**4.00 (0.91, 7.14)***
TTHMs	**3.16 (0.58, 5.77)***	-1.66 (-4.49, 1.62)	3.28 (-0.17, 6.78)	3.20 (-1.17, 7.65)	1.52 (-1.49, 4.57)

*P < 0.05.

KEYWORDS: *drinking water, disinfection byproducts, trihalomethanes, thyroid function, NHANES*

1. INTRODUCTION

Thyroid hormones are present in numerous tissues (e.g., heart, fat, brain, pituitary, liver, ovary, and bone) and play a critical role in controlling energy metabolism and physiologic function of reproductive, nervous, and cardiovascular systems.[1−3] The hypothalamus−pituitary−thyroid axis regulates thyroid function by producing thyroxine (T4), triiodothyronine (T3), and thyroid-stimulating hormone (TSH).[4] A fraction (<1%) of circulating T4 and T3 is in unbound form, which is biologically active and can enter cells.[4] Clinical or sub-clinical thyroid diseases, which are usually diagnosed based on circulating thyroid hormones, have been associated with long-term risks of developing diabetes,[5] cardiovascular diseases,[6] and coronary heart disease mortality among adults.[7]

Increasing evidence from in vitro, animal, and human studies shows that exposure to chemicals commonly encountered in our environment, including disinfection byproducts (DBPs) might alter thyroid function via mechanisms related to the disruption of thyroid peroxidase, iodine transport, deiodinases, hepatic catabolism, and receptor binding.[8,9] For instance, Narotsky et al. reported an increased incidence of thyroid follicular cell hypertrophy in female rats when exposed to environmentally relevant levels of the whole mixture of drinking water DBPs.[10] Chu et al. reported that rats exposed to trihalomethanes (THMs) for 90 days had increased epithelial height, reduced follicular size and colloid density, and collapse of follicles in the thyroid glands, which were mostly reversible when exposure was terminated.[9] Adverse thyroid effects have also been reported for certain DBPs, such as iodoacetic acid, bromate, chlorate, and 3-chloro-4-(dichloromethyl)-5-hydroxy2(5*H*)-furanone in rodent species.[11−14] Nevertheless, few population studies have explored the associations of DBPs with thyroid function measures. Lubbers et al.[15] reported reduced serum levels of T4 among three glucose-6-phosphate dehydrogenase deficient adults after daily ingestion of sodium chlorite at a concentration of 5 mg/L for 12 weeks. In a more recent study, Ouhoummane et al.[16]

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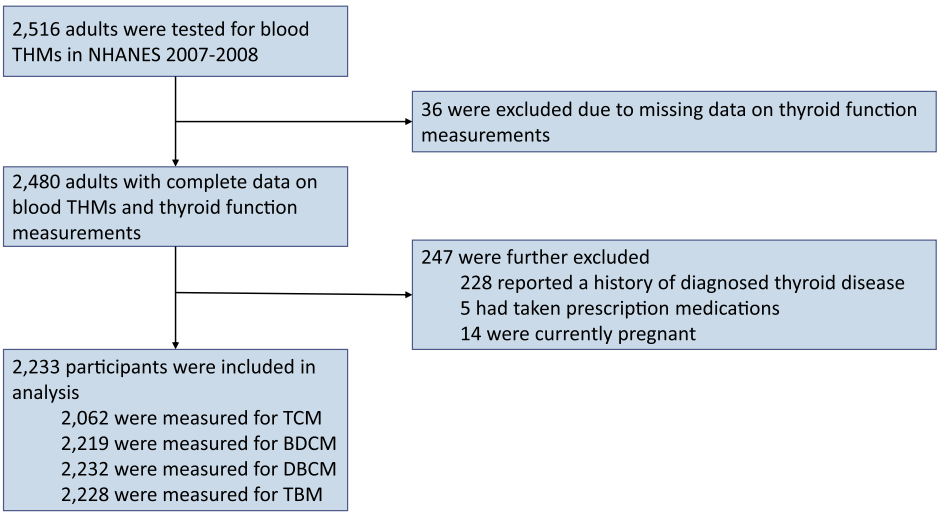

Figure 1. Flow chart of study population exclusion criteria. Abbreviations: THMs, trihalomethanes; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; and TBM, bromoform.

reported higher levels of blood TSH among 2126 low birth weight newborns from municipalities where drinking water was disinfected by chlorine dioxide instead of chlorine. However, the associations of DBPs with thyroid function measures among general adults have not been explored using internal exposure biomarkers.

THMs are the most common species of DBPs in chlorinated water, accounting for 66% of chlorinated DBP compounds.[17] Blood THM concentrations are sensitive to environmental levels of exposure and are believed to reflect steady-state concentrations because of the high frequency of daily exposure events and slow partitioning out of the adipose tissue.[18] Therefore, the present analysis aimed to explore whether blood biomarker concentrations of THMs were associated with thyroid function measures among a representative sample of civilian, non-institutionalized U.S. adults.

2. METHODS

2.1. Study Population. The present study data were obtained from the National Health and Nutrition Examination Survey (NHANES) 2007−2008, which is part of an ongoing cross-sectional survey aimed to assess the nationally representative nutritional and health status of U.S. citizens.[19] Methods of data collection have been described elsewhere.[20] The NHANES study protocol was approved by the research ethics review board of the National Center for Health Statistics and all participants signed the informed consent.

In 2007−2008, 2516 adults (≥20 years) provided blood samples, which were measured for THM concentrations. We excluded adults who had no thyroid function measures (n = 36), reported a previous history of diagnosed thyroid disease (n = 228), had taken prescription medications in the past 30 days which may affect thyroid function (n = 5),[21] or were currently pregnant (n = 14) at time of the survey, leaving 2233 participants in the current analysis (participant flow chart, Figure 1).

2.2. Measurement of Blood THMs. A peripheral venous blood sample was drawn from each participant by venipuncture during scheduled medical examinations, which was immediately processed and stored in the NHANES mobile examination center.[22] Chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM) concentrations in whole blood were measured via solid-phase microextraction gas chromatography and mass spectrometry after a pretreatment that has been previously described in detail.[23] We calculated blood brominated trihalomethanes (Br-THMs) by summing the concentrations of BDCM, DBCM, and TBM; and blood total trihalomethanes (TTHM) by summing TCM and Br-THMs. The limit of detection (LOD) of TCM, BDCM, DBCM, and TBM for our current study population was 2.10, 0.62, 0.62, and 1.0 pg/mL, respectively. Values below LOD were replaced with LOD/$\sqrt{2}$.[24]

2.3. Determination of Serum Thyroid Function and Urinary Iodine. Serum free T4 (FT4), total T4 (TT4), free T3 (FT3), total T3 (TT3), and TSH were measured using various immunoenzymatic assays.[25] Urinary iodine concentration was determined by inductively coupled plasma dynamic reaction cell mass spectroscopy.[26] Serum thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) were measured by the access two-step immunoenzymatic "sandwich" assay.[27] Quality control procedures for all analyses followed a comprehensive data quality assurance program.[28] The ratios of thyroid function measures (FT4/FT3, TT4/TT3, FT4/TT4, and FT3/TT3), which are markers of peripheral thyroid hormone metabolism,[29] were also calculated.

2.4. Covariates. Demographic data such as age, sex, and race/ethnicity were collected in an in-home survey. Body weight and height were measured during mobile physical examination. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Physical examination sessions (morning, afternoon, and evening) and fasting time (≤10 h vs >10 h) were also recorded. Serum cotinine was measured to directly reflect exposure to tobacco smoke (≥10 ng/mL as active smoking, 1−9.9 ng/mL as environmental tobacco smoke exposure, and <1 ng/mL as nonsmoking),[30] using a liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry.[31]

2.5. Statistical Analyses. Descriptive analyses were conducted for participants' characteristics and laboratory measurements of blood THM concentrations and serum thyroid function. Because a large proportion of observations were below the LOD for TBM (76.4%), this exposure

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biomarker was not considered further in subsequent analyses. Multivariable linear regression models were used to explore the association of continuous measures of blood concentrations of TCM, BDCM, DBCM, Br-THM, and TTHM with levels of FT4, TT4, FT3, TT3, and TSH, and ratios of thyroid function measures (FT4/FT3; TT4/TT3; FT4/TT4; and FT3/TT3). Participants were also assigned to quartiles for TCM, BDCM, Br-THM, and TTHM concentrations and categorized into three exposure groups for DBCM (the low-exposure group with concentrations <LOD, and the median-, and high-exposure groups were equally divided among detectable samples) to obtain equally precise estimates in each exposure category.[32] Both blood THM concentrations and thyroid function measures were natural log-transformed because of skewed distribution; the resulting regression coefficients were back-transformed and presented as percent differences in serum thyroid measurements associated with blood THM concentrations using the formula: $[e^{(\ln 10\times\beta)} - 1] \times 100$. We also fit multivariable logistic regression models to estimate odds ratios and 95% confidence intervals (CIs) for the proportion of participants with high levels of TPOAb (>9 IU/mL) or TgAb (>4 IU/mL),[33,34] a marker of immunologic disturbance of thyroid function, according to THM exposure.

Covariates were selected a priori based on previous NHANES findings[35] and were considered in multivariable models if their inclusion modified the estimates by ≥10%. For consistency, all models were finally adjusted for the same set of covariates, including sex (male vs female), age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, and other), BMI (continuous), ln-transformed creatinine-adjusted urinary iodine (continuous), serum cotinine levels (<1, 1−9.9, and ≥10 ng/mL), physical examination session (morning, afternoon, and evening), and fasting time (≤10 h vs >10 h). Missing data on BMI (n = 31), serum cotinine (n = 1), and urinary iodine (n = 77) were replaced by median values.

Four sensitivity analyses were conducted. First, we reanalyzed the associations between blood THM concentrations and thyroid function measures by excluding participants who had high serum levels of TPOAb (>9 IU/mL) or TgAb (>4 IU/mL) to avoid the impact of pre-existing immunologic disturbance of the thyroid tissue. Second, we excluded participants who had low urinary levels of iodine (<100 μg/L) to reduce the influence of potential iodine deficiency.[36] Third, to test the influence of recent peak exposure events, we excluded participants who spent any time at a swimming pool, hot tub, or steam room in the past 72 h given that they are strong predictors of blood THM concentrations. Besides, we additionally added sampling season, source of drinking water, and the time interval since the last bath or shower as covariates in the multivariable models. Fourth, we assessed the influence of co-exposure by all other THMs by mutually adjusting for their summed concentrations as a covariate in the multivariable models. All data analyses were performed using SAS version 9.4 (SAS Institute Inc.), with adjustments for complex survey designs.[37]

3. RESULTS

3.1. Population Characteristics. The characteristics of 2233 adults included in the current analysis are presented in Table 1. Participants' mean age and BMI were 45.9 years (95% CI: 45.0, 46.8) and 28.4 kg/m^2 (95% CI: 28.0, 28.8). A little more than half of the participants were male (52.3%) and 70.0% were non-Hispanic White. Only 605 adults (27.0%) were active smokers; 142 (6.3%) and 208 (10.0%) had high levels of TgAb (>4 IU/mL) and TPOAb (>9 IU/mL), respectively.

Table 1. Characteristics of Study Participants in NHANES 2007−2008 (N = 2233)[a,b]

characteristic[c]	mean (95% CI) or N (%)
age (years)	45.9 (45.0, 46.8)
BMI (kg/m^2)	28.4 (28.0, 28.8)
sex	
male	1189 (52.3)
female	1044 (47.7)
race/ethnicity	
non-Hispanic White	1059 (70.0)
non-Hispanic Black	440 (10.5)
Mexican American	385 (8.2)
other	349 (11.3)
serum cotinine (ng/mL)	
no tobacco smoke exposure (<1.0)	1494 (67.3)
environmental tobacco smoke exposure (1.0−9.9)	133 (5.7)
active smoking exposure (≥10)	605 (27.0)
physical examination sessions	
morning	1091 (48.4)
afternoon	801 (34.0)
evening	341 (17.6)
fasting time (h)	
≤10	1491 (69.1)
>10	665 (30.9)
urinary iodine (μg/g creatinine)	155.7 (5.9)
TgAb (IU/mL)	
normal (≤4)	2087 (93.7)
positive (>4)	142 (6.3)
TPOAb (IU/mL)	
normal (≤9)	2012 (90.0)
positive (>9)	208 (10.0)

[a]Abbreviations: BMI, body mass index; TgAb, thyroglobulin antibody; and TPOAb, thyroid peroxidase antibody. [b]All estimates were accounted for complex survey designs. [c]A total of 31, 1, 77, 4, and 13 participants had missing information on BMI, serum cotinine, urinary iodine, TGAb, and TPOAb, respectively.

3.2. Distribution of Blood THMs and Serum Thyroid Function Measures. Table 2 shows the distribution of blood THM concentrations and serum thyroid function measures. In total, 2062 (92.3%), 2219 (99.4%), 2232 (99.9%), and 2228 (99.8%) adults were quantified for TCM, BDCM, DBCM, and TBM, respectively. The detectable rates of TCM, BDCM, DBCM, and TBM were 82.3, 76.1, 59.2, and 23.6%, respectively. Serum thyroid function measures were detectable in all adults included in the current analysis.

3.3. Blood THMs and Thyroid Function Measures. Multivariable linear regression models showed positive associations between blood TCM, BDCM, and TTHM concentrations and serum FT4, whereas inverse associations were observed between blood DBCM and Br-THMs and serum TT3 (all p < 0.05; Table 3). These findings were confirmed when THM concentrations were modeled as categorical variables (Table S1). Levels of serum FT4 were 4.26% (95% CI: 1.96, 6.82%), 3.02% (95% CI: 0.35, 5.75%), and 4.21% (95% CI: 1.37, 7.14%), higher, respectively, comparing extreme quartiles of TCM, BDCM, and TTHMs.

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Table 2. Distribution of Blood THM Concentrations and Serum Thyroid Function Measurements in NHANES Participants 2007−2008[a]

blood THMs	N	% >LOD[b]	mean	median (IQR)	GM
TCM (pg/mL)	2062	82.3	13.7	6.6 (2.7, 15.0)	6.7
BDCM (pg/mL)	2219	76.1	2.8	1.5 (0.4, 3.2)	1.5
DBCM (pg/mL)	2232	59.2	2.0	0.8 (0.4, 1.9)	1.0
TBM (pg/mL)	2228	23.6	2.1	0.7 (0.7, 0.7)	1.0
Br-THMs (pg/mL)	2213	NA	6.9	3.3 (1.8, 6.6)	4.0
TTHMs (pg/mL)	2043	NA	20.5	11.6 (5.6, 22.4)	11.9
thyroid function					
TSH (μIU/mL)	2233	100	2.0	1.6 (1.1, 2.4)	1.6
FT4 (ng/dL)	2232	100	0.8	0.8 (0.7, 0.8)	0.8
TT4 (μg/dL)	2232	100	7.7	7.6 (6.7, 8.6)	7.6
FT3 (pg/mL)	2230	100	3.2	3.2 (2.9, 3.4)	3.2
TT3 (ng/dL)	2230	100	114.0	111.7 (99.0, 127.0)	111.8

[a]Abbreviations: THMs, trihalomethanes; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Br-THMs, the sum of BDCM, DBCM, and TBM; TTHMs, the sum of TCM and Br-THMs; TSH, thyroid-stimulating hormone; FT4, free thyroxine; TT4, total thyroxine; FT3, free triiodothyronine; TT3, total triiodothyronine; LOD, limit of detection; IQR, interquartile range; GM, geometrical mean; and NA, not applicable. [b]The LODs of TCM, BDCM, DBCM, and TBM for our current study population were 2.10, 0.62, 0.62, and 1.0 pg/mL, respectively.

Levels of TT3 were 4.89% (95% CI: −8.21, −1.44%) lower in the highest compared with the lowest exposure categories of DBCM; and 4.67% (95% CI: −8.08, −1.32%) lower in the highest compared with the lowest Br-THM quartiles (Table S1). There was no meaningful relationship between blood THM concentrations and serum TSH, TT4, or FT3 (Table 3).

3.4. Blood THMs and Ratios of Thyroid Function Measures and Antibodies. When ratios of thyroid function measures were evaluated (Table 4), we observed positive associations between blood TCM concentrations and FT4/FT3, between BDCM, DBCM, and Br-THM concentrations and TT4/TT3, and between DBCM and Br-THM concentrations and FT3/TT3 (all $p < 0.05$), which were confirmed when THM concentrations were modeled as categorical variables (Table S2). However, blood THM concentrations were unrelated to high TgAb or TPOAb levels (Table S3).

Table 4. Adjusted Percent Difference (%) and 95% CI in Ratios of Thyroid Function Measures in Relation to Blood THM Concentrations among NHANES Participants 2007−2008[a,b]

blood THMs (pg/mL)	FT4/FT3%(95% CI)	TT4/TT3% (95% CI)	FT4/TT4% (95% CI)	FT3/TT3% (95% CI)
TCM	3.05 (0.45, 5.68)[c]	1.16 (−2.87,5.25)	1.35 (−1.40, 4.13)	−0.54 (−3.44, 2.39)
BDCM	2.65 (−1.03, 6.38)	4.26 (0.21, 8.39)[c]	0.40 (−2.20, 3.02)	1.91 (−1.39, 5.26)
DBCM	1.21 (−3.47, 5.99)	4.17 (0.83, 7.57)[c]	1.20 (−2.56, 5.03)	4.04 (1.27, 6.85)[c]
Br-THMs	2.08 (−2.36, 6.60)	5.44 (1.83, 9.11)[c]	0.79 (−2.60, 4.22)	4.00 (0.91, 7.14)[c]
TTHMs	3.28 (−0.17, 6.78)	3.20 (−1.17, 7.65)	1.66 (−1.59, 4.96)	1.52 (−1.49, 4.57)

[a]Abbreviations: THMs, trihalomethanes; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Br-THMs, the sum of BDCM, DBCM, and TBM; TTHMs, the sum of TCM and Br-THMs; TSH, thyroid-stimulating hormone; FT4, free thyroxine; TT4, total thyroxine; FT3, free triiodothyronine; and TT3, total triiodothyronine. [b]Estimates were accounted for complex survey designs, with adjustment for age, sex, race, BMI, serum cotinine level, ln-transformed creatinine-adjusted urinary iodine, physical examination sessions, and fasting time. THMs and thyroid function measures were ln-transformed in models. Results are presented as percent differences in serum thyroid function in relation to a 10-unit increase in blood THMs concentrations. Percent differences = $[e^{(\ln 10\times\beta)} - 1] \times 100$. [c]$P < 0.05$.

3.5. Sensitivity analyses. The results of blood THM concentrations in relation to thyroid function measures were materially unchanged when we excluded participants who had high serum levels of TPOAb (>9 IU/mL) or TgAb (>4 IU/mL) ($n = 271$; Table S4), those who had low urinary levels of iodine (<100 μg/L) ($n = 665$; Table S5), or those who spent any time at a swimming pool, hot tub, or steam room in the past 72 h ($n = 62$; Table S6) in subsequent sensitivity analyses. These associations were also robust when we additionally adjusted for sampling season, source of drinking water, and the time interval since the last bath or shower (Table S7), and when we mutually adjusted for potential coexposure confounding by adding the summed concentrations of all other THMs as a covariate in the multivariable models (Table S8).

Table 3. Adjusted Percent Difference (%) and 95% CI in Serum Thyroid Function Measures in Relation to Blood THM Concentrations among NHANES Participants 2007−2008[a,b]

blood THMs (pg/mL)	TSH% (95% CI)	FT4% (95% CI)	TT4% (95% CI)	FT3% (95% CI)	TT3% (95% CI)
TCM	−3.65 (−9.18, 2.01)	3.24 (1.29, 5.19)[c]	1.80 (−1.23, 4.88)	0.17 (−1.44, 1.79)	0.72 (−2.45, 3.93)
BDCM	−2.21 (−7.79, 3.50)	2.65 (0.32, 5.01)[c]	2.22 (−0.15, 4.60)	−0.03 (−1.85, 1.81)	−1.92 (−5.46, 1.67)
DBCM	0.94 (−7.70, 9.92)	0.92 (−2.96, 4.86)	−0.30 (−3.12, 2.55)	−0.35 (−2.17, 1.49)	−4.31 (−7.42, −1.16)[c]
Br-THMs	0.86 (−7.95, 10.01)	1.25 (−2.23, 4.78)	0.43 (−2.59, 3.48)	−0.88 (−3.18, 1.45)	−4.80 (−7.71, −1.85)[c]
TTHMs	−4.46 (−9.73, 0.93)	3.16 (0.58, 5.77)[c]	1.41 (−1.97, 4.84)	−0.15 (−2.10, 1.82)	−1.66 (−4.49, 1.62)

[a]Abbreviations: THMs, trihalomethanes; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Br-THMs, the sum of BDCM, DBCM, and TBM; TTHMs, the sum of TCM and Br-THMs; TSH, thyroid-stimulating hormone; FT4, free thyroxine; TT4, total thyroxine; FT3, free triiodothyronine; and TT3, total triiodothyronine. [b]Estimates were accounted for complex survey designs, with adjustment for age, sex, race, BMI, serum cotinine level, ln-transformed creatinine-adjusted urinary iodine, physical examination sessions, and fasting time. THMs and thyroid function measures were ln-transformed in models. Results are presented as percent differences in serum thyroid function in relation to a 10-unit increase in blood THMs concentrations. Percent differences = $[e^{(\ln 10\times\beta)} - 1] \times 100$. [c]$P < 0.05$.

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4. DISCUSSION

Based on a nationally representative survey of U.S. adults, we found positive associations between blood TCM, BDCM, and TTHM concentrations and serum FT4 and inverse associations between blood DBCM and Br-THM concentrations and serum TT3. When the ratios of thyroid function measures were evaluated, we found positive associations between blood TCM concentrations and FT4/FT3, between BDCM, DBCM, and Br-THM concentrations and TT4/TT3, and between DBCM and Br-THM concentrations and FT3/TT3. These associations persisted when we excluded participants who had high TPOAb or TgAb (a marker of autoimmune hypothyroidism) or low iodine status.

Thyroid hormones play an important role in the physiologic function of every tissue including the heart, fat, brain, and pituitary by affecting energy expenditure and thermogenesis,[38] modulating lipid profiles, endothelial function, and blood pressure[39] and maintaining normal reproductive function.[40] Growing evidence shows that variations of thyroid hormones within the normal range are associated with increased morbidity and mortality in the general population. For instance, higher concentrations of FT4 have been associated with a greater risk of atrial fibrillation,[41,42] sudden death,[43] and atherosclerotic cardiovascular morbidity and mortality.[44] Similarly, lower levels of TT3 or FT3 levels have been related to worse prognosis in acute ischemic stroke,[45] chronic heart failure,[46] and chronic kidney disease.[47] In a recent study conducted among 7116 NHANES adults, Neves, et al.[48] reported an inverse association between serum levels of FT3 within the reference range and risk of cardiovascular mortality.

THM-induced thyroid toxicity has been described in animal studies dating back as far as 1979, including an experiment in female rats that demonstrated an increase in the incidence of thyroid tumors when dosed with TCM.[49] Chu et al. reported reversible biochemical, hematological, and histological changes in the thyroid glands of rats (e.g., reduced follicular size and colloid density, increased epithelial height, and collapse of follicles) after the oral administration of TCM, BDCM, DBCM, and TBM at concentrations of 50−2500 mg/L for 90 days.[9] In a multigenerational toxicity study, Narotsky and colleagues reported that exposure to environmentally relevant levels of the whole mixture of drinking water DBPs caused an increased incidence of thyroid follicular cell hypertrophy in adult female rats and their female F1 offspring.[10] However, apart from species differences, exposure levels, routes, and frequency methods applied in animal studies may differ from real-world human exposure scenarios.

Humans can be exposed to THMs through inhalation, ingestion, and dermal absorption during daily activities (e.g., bathing, showering, drinking, and swimming).[50] Blood concentrations are a common internal measure of exposure to THMs because they are sensitive to low levels of exposure.[18] While the elimination half-life of THMs in the human body is relatively short (minutes or hours), blood THM concentrations are believed to reflect steady-state blood concentrations due to the high frequency of daily exposure events and slower partitioning out of the adipose tissue.[18] Our present study is the first investigation exploring the association between blood THMs and thyroid function measures. In an early study, Lubbers et al.[15] reported reduced serum levels of T4 among three glucose-6-phosphate dehydrogenase-deficient adults after daily ingestion of sodium chlorite for 12 weeks. In a more recent study, Ouhoummane et al.[16] reported increased levels of blood TSH among 2126 low birth weight newborns from municipalities where drinking water was disinfected by chlorine dioxide instead of chlorine, probably as a result of reduced production of THMs.[51] However, these studies cannot be directly compared with our findings due to the significant differences in exposure assessment, research design, and participant characteristics. Future population studies are needed to longitudinally validate our novel findings using repeated measures of internal biomarkers of THM exposure.

The mechanisms underlying the associations of DBP exposure with thyroid disruption are poorly understood. However, they are probably related to the disruption of deiodinases, thyroid peroxidase, iodine transport, hepatic catabolism, and receptor binding, which are commonly influenced by environmental chemicals.[8] In support of this hypothesis, in a previous study evaluating the thyroid disrupting effects of iodoacetic acid, Xia et al. revealed iodoacetic acid exposure significantly downregulated the mRNA expression levels of the sodium/iodide symporter (NIS), the thyrotropin receptor (TSHR), and type I deiodinase and simultaneously reduced the protein expression levels of TSHR and NIS in rats.[14] Atterwill et al. revealed that perchlorate causes a release of accumulated iodide from the thyroid gland.[52] Besides, both in vivo and in vitro studies have demonstrated that many DBPs, including THMs, caused cytotoxicity and mutagenicity,[53,54] which are important pathogenic processes for the development of thyroid tumors.[49]

The strengths of our present study include its nationally representative sample, large sample size, the measurement of internal exposure DBP biomarkers (i.e., blood THM concentrations), and the comprehensive evaluation of thyroid function markers. However, our study also has some limitations. First, causality cannot be determined given the observational nature of this cross-sectional study. Nevertheless, because it is not possible to randomize participants to different exposure levels, well-established observational studies with a thorough collection of confounding factors, such as the present study, provide the best available evidence for evaluating the associations between human DBP exposure and thyroid disruption. Second, we used a single measurement of THMs in blood to reflect the average body burden of THM exposure, which may result in exposure misclassification. Meanwhile, serum thyroid function measures were also determined at a single time point for each participant. We cannot fully exclude the measurement error as a result of a single serum thyroid determination, although a previous study has shown that thyroid hormones are stable within relatively narrow limits over time within an individual.[55] In this case, however, these measurement errors are likely to be non-differential, resulting in associations biased toward the null. Third, while we have adjusted for a large set of potential confounders, our results may be influenced by residual or unmeasured confounding, random error, multiple testing, or uncontrolled bias given that thyroid function comprises a variety of hormonal biomarkers. Finally, we did not explore the influence of other DBP species [e.g., chlorate, bromate, iodoacetic acid, and 3-chloro-4-(dichloromethyl)-5-hydroxy2(5*H*)-furanone] due to a lack of data that might have more toxic effects on the thyroid than THMs.[11−14]

Based on a nationally representative population, we found that higher blood THM concentrations were associated with thyroid disruption among U.S. adults. Given the widespread

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human exposure to THMs, additional research is needed to validate our novel findings and to explore the potential mechanisms of THMs' thyroid toxicity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.1c04008.

Multivariable linear regression models of blood THM exposure categories in relation to serum thyroid function measures, multivariable logistic regression models of blood THM concentrations in realtion to TgAb or TPOAb positivity, and sensitivity analyses (PDF)

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Author Contributions

Y.S. and Y.-X.W. drafted the manuscript. Y.S. analyzed the data. Y.-X.W. and C.M. led the study design and conception and supervised the work. P.-F.X. conducted a technical review by validating the accuracy of data analysis. All authors interpreted the results and critically appraised the manuscript for important intellectual content.

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Notes

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