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Article

Association of Blood Trihalomethane Concentrations with Risk of All-Cause and Cause-Specific Mortality in U.S. Adults: A Prospective Cohort Study

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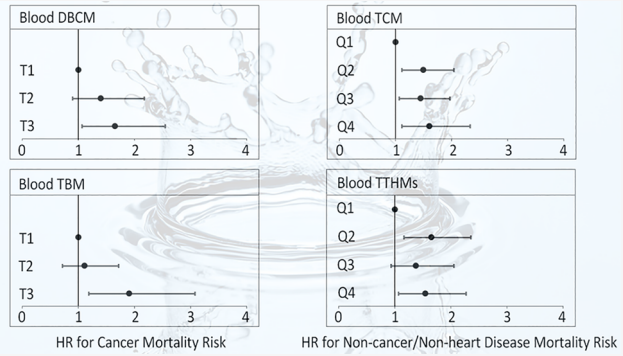
ABSTRACT: Water chlorination can lead to the formation of disinfection byproducts, including trihalomethanes (THMs). However, few epidemiologic studies have explored associations between THM exposure and mortality. This study included 6720 adults aged ≥40 years from the National Health and Nutrition Examination Survey 1999−2012 who had blood THM concentrations quantified. A higher risk of all-cause mortality was found across increasing quartile concentrations of blood chloroform (TCM) and total THMs (TTHMs; sum of all four THMs) (both p for trend = 0.02). Adults in the highest quartile of TCM and TTHM concentrations had hazard ratios (HRs) of 1.35 (95% confidence intervals: 1.05−1.74) and 1.37 (1.05−1.79), respectively, for all-cause mortality, compared with adults in the lowest quartile. When cause-specific mortality was evaluated, a positive relationship was found between blood bromodichloromethane (BDCM), dibromochloromethane (DBCM), bromoform (TBM), total brominated THMs (Br-THMs; sum of BDCM, DBCM, and TBM), and TTHM concentrations and risk of cancer death and between blood TCM and TTHMs and risk of other cause (noncancer/nonheart disease) mortality. Our findings suggest that higher exposure to Br-THMs was associated with increased cancer mortality risk, whereas TCM was associated with a greater risk of noncancer/nonheart disease mortality.



KEYWORDS: *trihalomethanes, adults, mortality, cancer, NHANES*

1. INTRODUCTION

Water disinfection remains one of the most important global public health protection strategies and provides safe drinking water to billions of people by killing disease-causing pathogens.[1] However, when oxidizing agents, including chemical disinfectants, react with organic and inorganic materials in raw water, harmful disinfection byproducts (DBPs) are inadvertently produced.[2] Among the more than 600 identified DBPs, trihalomethanes (THMs) are the most prevalent species in chlorinated water. All four compounds in the THM group, including chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), or bromoform (TBM), have been demonstrated to be genotoxic and carcinogenic in animal models.[3−9] The United States (U.S.) Environmental Protection Agency (EPA) has classified BDCM and TBM as probable human carcinogens and DBCM as a possible human carcinogen[10−12] Due to their high prevalence in drinking water and adverse health effects, the World Health Organization has assigned guideline values for TCM (300 μg/L), BDCM (60 μg/L), DBCM (100 μg/L), and TBM (100 μg/L) in drinking water.[13] The U.S. EPA has regulated total THMs (TTHMs; sum of all four THMs) in drinking water to 80 μg/L.[14] Beyond these limits, the WHO acknowledges that the ultimate objective is to maintain THM levels as low as practical in drinking water.[13]

Epidemiologic studies have revealed associations of THM exposure with cancer mortality, including bladder, colon, and rectal cancers.[15−17] Blood THMs, which are sensitive to low levels of exposure, are considered a reliable matrix to measure steady-state concentrations in human studies.[18] Although blood THMs are eliminated within minutes to hours after exposure, the high frequency of daily exposure and slow partitioning out of adipose tissue are believed to produce steady-state blood concentrations, thus making it a reliable exposure metric.[19] In an early study, Min and colleagues found

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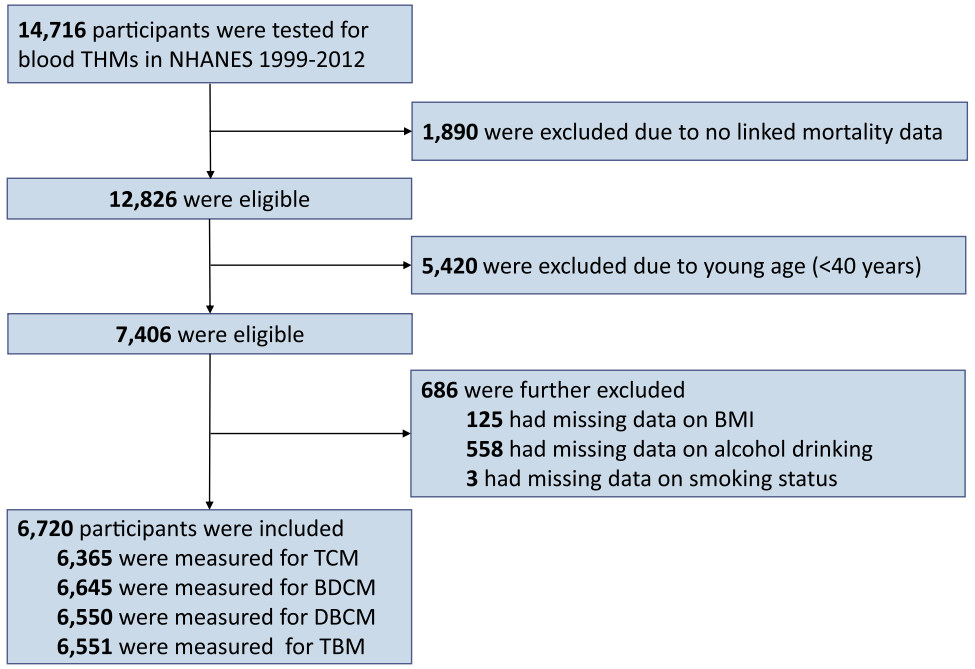

Figure 1. Flowchart of cohort population exclusion criteria.

that higher blood concentrations of BDCM, DBCM, TBM, and total brominated THMs (Br-THMs; sum of BDCM, DBCM, and TBM) were associated with a higher risk of overall cancer mortality among 933 U.S. adults aged 40−59 years from the National Health and Nutrition Examination Survey (NHANES) 1999−2004.[17] Further evidence shows associations of THM exposure with cardiac and hepatic toxicity,[20−22] type 2 diabetes,[23,24] as well as adverse reproductive outcomes (e.g., pregnancy loss),[25] suggesting a potential association of THM exposure with noncancer mortality.[26−28] However, no studies to date have examined associations between THM exposure with all-cause and other non-cancer-related mortality. Therefore, we performed the present analysis by including more recent NHANES data with four additional survey cycles (1999−2012 vs 1999−2004) and seven times the number of participants (6720 vs 933) relative to the study conducted by Min and colleagues, exploring the relationship between blood THM concentrations and mortality due to all causes, heart diseases, cancer, and any other causes.

2. METHODS

2.1. Study Participants. NHANES is a nationally representative program of cross-sectional surveys designed to evaluate the nutritional and health status of adults and children in the United States. NHANES combines interviews with detailed physical examinations and biospecimen collections on a nationally representative sample of the U.S. civilian noninstitutionalized population in 2-year increments.[29] 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 before participation. In our current analysis, data were retrieved for participants who were measured for volatile organic chemicals (VOCs), including blood THMs, between 1999 and 2012 (n = 14 716).[30] We excluded participants who had no linked mortality data (n = 1890). To avoid major reductions in population size while at the same time restricting the analysis to adults at a higher risk of dying,[31,32] we also excluded participants who were less than 40 years of age at time of recruitment (n = 5420). We further excluded participants who had missing data on important lifestyle factors such as body mass index (BMI) (n = 125), alcohol use (n = 558), or smoking status (n = 3), leaving a final sample size of 6720 participants included in subsequent analyses (Figure 1).

2.2. Exposure Assessment. Whole blood samples were collected in gray-top glass vacutainers containing potassium oxalate and sodium fluoride without special instructions (e.g., fasting and the sampling time of a given day). To avoid potential contamination, commercial vacutainers were specially modified by laboratory staff to remove measurable levels of most VOCs.[33] Because THMs are highly volatile, blood was drawn by venipuncture and kept at 4 °C during storage and shipment.[34] A detailed description of the laboratory methods for blood THMs has been reported previously.[33] Briefly, blood TCM, BDCM, DBCM, and TBM concentrations were measured via solid-phase microextraction gas chromatography and mass spectrometry,[35] which are available in the NHANES Laboratory data files.[30] Blood Br-THMs were calculated by summing the concentrations of BDCM, DBCM, and TBM; blood TTHMs were calculated by summing the concentrations of TCM and Br-THMs.[36] Samples with values lower than the analytical limit of detection (LOD) (range: 0.6−2.1 pg/mL) were imputed using LOD/$\sqrt{2}$.[37] To maintain the integrity of laboratory determinations, the NHANES program implemented a comprehensive data quality assurance program, including measuring the analysis of quality control samples at the beginning and at the end of each analytical run.[33] If the quality control results for specific analytes were declared "out of control", the data for all samples analyzed during that analytical run were treated as invalid.

2.3. Covariates. Covariates were obtained during interviews via questionnaires and included age, sex, race/ethnicity, family income, educational level, cigarette smoking, alcohol use, self-reported history of chronic diseases (e.g., diabetes,

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Table 1. Baseline Characteristics of Study Participants in NHANES 1999−2012 [Mean (95% CI) or *N* (%)][a,b]

characteristic[c]	total (*n* = 6720)	censored (*n* = 5905)	event (*n* = 815)	*P*[d]
age (years)	55.1 (54.6, 55.6)	54.1 (53.6, 54.5)	65.2 (63.8, 66.6)	<0.001
BMI (kg/m^2)	29.0 (28.8, 29.2)	29.0 (28.8, 29.3)	28.7 (28.2, 29.2)	0.20
sex				0.006
male	3378 (49.0)	2903 (48.4)	475 (55.0)	
female	3342 (51.0)	3002 (51.6)	340 (45.0)	
race/ethnicity				0.03
non-hispanic white	3374 (75.4)	2888 (75.4)	486 (76.3)	
non-hispanic black	1375 (9.8)	1205 (9.6)	170 (11.9)	
Mexican American	1062 (5.7)	959 (5.7)	103 (5.2)	
other	909 (9.1)	853 (9.3)	56 (6.6)	
educational level				<0.001
less than high school	1919 (17.3)	1581 (15.7)	338 (34.1)	
high school	1595 (25.2)	1383 (24.9)	212 (27.6)	
college or above	3206 (57.5)	2941 (59.4)	265 (38.3)	
family income-to-poverty ratio level				<0.001
0−1.0	1031 (8.8)	875 (8.4)	156 (12.9)	
1.1−3.0	3048 (36.1)	2590 (34.4)	458 (52.9)	
>3.0	2641 (55.1)	2440 (57.2)	201 (34.2)	
cigarette smoking				<0.001
never	3278 (48.4)	2,960 (49.5)	318 (36.7)	
former	2096 (31.2)	1791 (30.9)	305 (34.6)	
current	1346 (20.4)	1154 (19.6)	192 (28.7)	
alcohol use				<0.001
never	2043 (25.2)	1756 (24.5)	287 (32.0)	
low to moderate	4038 (63.6)	3594 (64.4)	444 (56.0)	
heavy	639 (11.2)	555 (11.1)	84 (12.0)	
self-reported chronic diseases				<0.001
hypertension	2524 (33.0)	2093 (31.3)	431 (51.4)	
diabetes	1052 (11.2)	862 (10.2)	190 (21.7)	
cardiovascular diseases	964 (10.8)	689 (8.7)	275 (31.5)	
chronic obstructive pulmonary diseases	573 (8.4)	456 (7.8)	117 (14.9)	
cancer	644 (8.7)	483 (7.8)	161 (17.5)	
self-reported health status				<0.001
very good to excellent	2495 (46.7)	2296 (48.7)	199 (26.3)	
good	2450 (35.1)	2154 (34.9)	296 (37.3)	
poor to fair	1775 (18.2)	1455 (16.4)	320 (37.4)	

[a]Abbreviations: BMI, Body Mass Index; THMs, trihalomethanes; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Br-THMs, sum of BDCM, DBCM, and TBM; TTHMs, sum of TCM and Br-THMs. [b]All estimates were accounted for complex survey designs. [c]6, 489, and 3 participants had missing information on education level, family income-to-poverty ratio, and self-reported health status, respectively. [d]*P*-values were calculated using the Chi-square test for categorical groups and *t*-test for continuous variables.

cancer, chronic obstructive pulmonary disease, hypertension, and cardiovascular disease), and general health status (excellent, very good, good, fair, or poor). To capture potential peak exposure events close to the time of blood sampling, participants also reported their water-use activities (swimming pool, hot tub, or steam room) in the past 72 h and time interval since last shower or bath. Height and weight were measured during scheduled medical examinations. BMI was calculated using weight in kilograms divided by height in meters squared.

2.4. Mortality Ascertainment. Mortality was ascertained through linkage to the National Death Index from the date of survey participation through December 31, 2015 (the end of mortality follow-up data).[38] The National Center for Health Statistics has publicly provided Linked Mortality Files related to the 1999−2012 NHANES participants with National Death Index data.[38] Our primary outcome was all-cause, total mortality. Secondary outcomes were defined using underlying causes of death following the International Classification of Diseases, 10th Revision (ICD-10) codes for heart diseases (codes I00−09, I11, I13, I20−51), cancer (codes C00−97), and any other causes. Person years of follow-up were defined as the interval from the date of blood sampling to the date of death or to the end of follow-up (December 31, 2015), whichever occurred first.

2.5. Statistical Analysis. All analyses incorporated sample weights, stratification, and clustering of the complex sampling design of NHANES to ensure nationally representative estimates.[29] Baseline characteristics of living and dead participants were compared using the *t*-test for continuous variables and Chi-square test for categorical groups. Cox proportional hazard regression models were fit to assess the hazard ratios (HRs) and 95% confidence intervals (CIs) with time-to-event as the time variable for the associations between blood THM concentrations and the risk of all-cause and cause-specific mortality. Individuals were assigned to quartiles for TCM, BDCM, Br-THM, and TTHM concentrations. Because a large proportion of measurements were lower than the LOD

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for DBCM (42.4%) and TBM (66.1%), we categorized individuals into three groups: the low-exposure group with concentrations <LOD, and the median-, and high-exposure groups that were equally divided among detectable samples.

Covariates were selected a priori based on prior NHANES findings,[17] which were further added to Cox models if their inclusion changed the age-adjusted HRs by ≥10%.[39] Multivariable models were adjusted for age (continuous), sex (male or female), BMI (<18.5, 18.5−24.9, 25.0−29.9, and ≥30.0 kg/m^2), race/ethnicity (non-Hispanic black, non-Hispanic white, Mexican American, or other), educational level (lower than high school, high school, college or above), family income-to-poverty ratio (0−1.0, 1.1−3.0, or >3.0), cigarette smoking (never, former, or current), alcohol use (never, low-to-moderate, or heavy), general health status (very good-to-excellent, good, or poor-to-fair), and peak exposure events within 72 h (yes or no). Tests for linear trend were evaluated by modeling quartiles (or categories) of THM concentrations as ordinal variables using integer values (i.e., 0−2 or 0−3). Missing data on family income-to-poverty ratio (n = 489), education level (n = 6), and self-reported general health status (n = 3) were replaced by median values.

We explored effect modification by performing analyses stratified by age at recruitment (<65 vs ≥ 65 years), BMI (<25 vs ≥ 25 kg/m^2), sex (male vs female), cigarette smoking status (never vs ever), alcohol consumption (never vs ever), survey year (1999−2006 vs 2007−2012), and fasting time (≤10 vs >10 h). Several sensitivity analyses were also conducted. First, we ran complete case analyses after excluding participants who had any missing data to assess the potential bias introduced by the replacement method by median values. Second, we excluded participants reporting cardiovascular disease or cancer at baseline whose mortality risk was less likely to be influenced by the THMs determined at recruitment. Third, we excluded participants who died within 1 year after recruitment as these deaths were not likely influenced by the THMs (or other factors) after recruitment. Fourth, we additionally included the timing of examination session (morning, afternoon, and evening) and the time interval since last shower or bath as covariates in the Cox models because they were found to influence blood THM concentrations.[40,41] Fifth, we added age squared term as a covariate in the Cox models to account for potential nonlinear association between age and mortality. Finally, as part of a sensitivity analysis, we included participants who were 20−39 years of age at recruitment to assess potential population selection bias introduced by our primary analysis to analyze adults 40 years or older. All data were analyzed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

3. RESULTS

3.1. Participant Characteristics. We totally included 6720 U.S. adults with a mean age and BMI at recruitment of 55.1 years (95% CI: 54.6−55.6) and 29.0 kg/m^2 (95% CI: 28.8−29.2), respectively (Table 1). Compared with participants who died during follow-up, adults who remained alive were more likely to be young females and nonsmokers. They also had a better educational background, family income-to-poverty ratio, and general health status, a lower prevalence of chronic diseases (diabetes, cancer, chronic obstructive pulmonary disease, hypertension, and cardiovascular disease), but higher self-reported alcohol consumption.

3.2. Distribution of Blood THM Concentrations. Table 2 shows the distribution of blood THMs, which accounted for complex survey design by applying survey sample weights. Of 6720 enrolled participants, 6365 (94.7%), 6645 (98.9%), 6550 (97.5%), and 6551 (97.5%) adults had quantified TCM, BDCM, DBCM, and TBM biomarkers, respectively. The detection rates of TCM, BDCM, DBCM, and TBM were 91.0, 74.7, 57.6, and 33.9%, respectively. Median blood concentrations of TCM, BDCM, DBCM, TBM, Br-THM, and TTHM were 8.9, 1.4, 0.67, 0.71, 3.3, and 13.9 pg/mL, respectively.

Table 2. Distribution of Blood THM Concentrations in NHANES Participants 1999−2012[a]

blood THMs (pg/mL)	N[b]	%>LOD	mean (95% CI)	median
TCM	6365	91.0	17.3 (15.5, 19.1)	8.9
BDCM	6645	74.7	2.8 (2.5, 3.1)	1.4
DBCM	6550	57.6	1.9 (1.7, 2.1)	0.67
TBM	6551	33.9	2.3 (1.8, 2.9)	0.71
Br-THMs	6366	NA	6.9 (6.2, 7.6)	3.3
TTHMs	6040	NA	23.9 (21.7, 26.1)	13.9

[a]Abbreviations: LOD, limit of detection; THMs, trihalomethanes; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Br-THMs, sum of BDCM, DBCM, and TBM; TTHMs, sum of TCM and Br-THMs; NA, not applicable. [b]The number of samples for THMs is different because invalid measurements are not reported in the NHANES Laboratory data files.

3.3. Blood THMs and Mortality. During 50 372 person years of follow-up (median follow-up, 7.1 years; the maximum follow-up, 16.8 years), 815 deaths occurred, including 207 from cancer, 148 from heart disease, and 460 from other causes. After adjusting for covariates, we found a positive trend of higher total all-cause mortality risk across increasing quartile concentrations of blood TCM and TTHMs (both p for trend = 0.02). Compared with adults in the lowest quartile, participants in the highest quartile of TCM and TTHMs had HRs of 1.35 (95% CI: 1.05−1.74) and 1.37 (1.05−1.79) for total all-cause mortality, respectively (Table 3). Additionally, we found a higher risk of all-cause mortality among participants in the third quartile of BDCM (HR = 1.33; 95% CI: 1.04−1.71) and those in the highest-exposure categories of TBM (HR = 1.32; 95% CI: 0.98−1.81) compared with participants in the lowest-exposure categories, though there was only weak evidence of dose−response relationship (p for trend = 0.29 and 0.13, respectively). When cause-specific mortality was assessed (Table 4), a positive dose−response relationship was found between blood DBCM and TBM and cancer mortality risk (HR = 1.65; 1.07−2.55; and HR = 1.91; 1.19−3.08, comparing the highest- vs lowest-exposure categories) and between blood TCM and TTHMs and risk of other causes (noncancer/nonheart disease) mortality (HR = 1.61; 1.11−2.33; and HR = 1.55; 1.06−2.27, comparing the highest- vs lowest-exposure quartiles). Besides, we found a higher risk of cancer mortality among participants in the third quartiles of BDCM and TTHMs (HR = 1.84; 1.07−3.17; and HR = 1.67; 1.02−2.72, respectively) and those in the highest quartile of Br-THMs (HR = 1.66; 0.94−2.91), compared to participants in the lowest quartiles. Blood THMs were unrelated to the risk of mortality due to heart disease.

3.4. Subgroup and Sensitivity Analyses. There was no evidence of interaction for age, sex, BMI, smoking status, alcohol use, survey year, and fasting time (Table S1). In sensitivity analyses, the associations of TCM and TTHMs with

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Table 3. Hazard Ratios (95% CIs) of All-Cause Mortality According to Blood THM Concentrations (NHANES, 1999−2012)[a]

THMs (pg/mL)	*n*/person years[b]	HR (95% CI) model 1[c]	model 2[d]	model 3[e]
TCM				
Q1 (≤4.19)	187/11 053	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (4.20−8.90)	194/11 330	1.24(1.01, 1.53)	1.31(1.07, 1.61)	1.31(1.07, 1.61)
Q3 (8.91−18.0)	201/12 040	1.37 (1.11, 1.68)	1.40 (1.14, 1.72)	1.41 (1.14, 1.73)
Q4 (>18.0)	183/12 755	1.33 (1.03, 1.71)	1.34 (1.04, 1.73)	1.35 (1.05, 1.74)
P-trend		0.03	0.02	0.02
BDCM				
Q1 (≤ 0.44)	220/12 453	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (0.45−1.49)	201/12 077	1.20 (0.96, 1.51)	1.22 (0.99, 1.52)	1.23 (0.99, 1.52)
Q3 (1.50−3.50)	215/12 793	1.26 (0.99, 1.60)	1.33 (1.03, 1.71)	1.33 (1.04, 1.71)
Q4 (>3.50)	164/12 458	1.02 (0.80, 1.31)	1.08 (0.84, 1.40)	1.08 (0.84, 1.40)
P-trend		0.58	0.29	0.29
DBCM				
T1 (≤0.44)	381/21 751	1.00 (reference)	1.00 (reference)	1.00 (reference)
T2 (0.45−1.78)	225/14 039	1.08 (0.89, 1.31)	1.13 (0.92, 1.38)	1.13 (0.92, 1.38)
T3 (>1.78)	198/13 429	1.10 (0.87, 1.41)	1.16 (0.90, 1.49)	1.16 (0.90, 1.49)
P-trend		0.37	0.20	0.20
TBM				
T1 (≤1.06)	574/33 065	1.00 (reference)	1.00 (reference)	1.00 (reference)
T2 (1.07−2.12)	107/7 678	0.92 (0.72, 1.18)	0.94 (0.73, 1.22)	0.94 (0.73, 1.22)
T3 (>2.12)	116/8 037	1.24 (0.92, 1.67)	1.33 (0.98, 1.80)	1.32 (0.98, 1.81)
P-trend		0.28	0.14	0.13
Br-THMs				
Q1 (≤1.94)	225/11 416	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (1.95−3.48)	190/11 913	1.01 (0.79, 1.29)	1.05 (0.83, 1.33)	1.06 (0.83, 1.34)
Q3 (3.49−7.10)	201/11 997	1.02 (0.79, 1.31)	1.08 (0.83, 1.41)	1.08 (0.83, 1.41)
Q4 (>7.10)	162/12 125	0.97 (0.73 to 1.28)	1.04 (0.78, 1.39)	1.04 (0.78, 1.39)
P-trend		0.85	0.73	0.72
TTHMs				
Q1 (≤7.36)	178/10 418	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (7.37−14.14)	205/10 727	1.47 (1.16, 1.87)	1.53 (1.20, 1.94)	1.53 (1.20, 1.94)
Q3 (14.15−26.39)	177/11 322	1.44 (1.11, 1.87)	1.48 (1.12, 1.94)	1.48 (1.13, 1.95)
Q4 (>26.39)	173/12 121	1.29 (0.99, 1.70)	1.36 (1.04, 1.78)	1.37 (1.05, 1.79)
P-trend		0.06	0.03	0.02

[a]Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; THMs, trihalomethanes; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Br-THMs, sum of BDCM, DBCM, and TBM; TTHMs, sum of TCM and Br-THMs. [b]The number of deaths and person years are absolute, unweighted values. [c]Model 1 was adjusted for age, sex, cigarette smoking, and self-reported general health. [d]Model 2 was additionally adjusted for race/ethnicity, education level, family income-to-poverty ratio level, BMI, and alcohol drinking. [e]Model 3 was further adjusted for water-use activity within 72 h.

all-cause mortality did not materially change when we excluded participants who had any missing data or self-reported prevalent cardiovascular disease or cancer at recruitment, when we excluded deaths occurring within the first year of follow-up, and when we additionally included age squared term or the timing of examination session and the time interval since last shower or bath as covariates in the Cox models (Table S2). Our findings were also robust when we further included participants who were 20−39 years of age at recruitment (Table S3); these results were consistent with the more restricted subsample of only adults 40 years and older in our primary analysis.

4. DISCUSSION

The median blood TCM and BDCM concentrations in our present study were similar to that of the overall NHANES population aged >12 years recruited in 2001−2012 (8.88 vs 8.60 and 1.40 vs 1.40 pg/mL, respectively).[42] Among 6720 U.S. adults aged 40 years and older at recruitment, we found that higher blood concentrations of TCM, BDCM, and TTHMs at enrollment were associated with a greater risk of all-cause mortality during follow-up. Individuals in the highest-exposure categories of TCM, TBM, and TTHMs had 35, 32, and 37% higher risk of all-cause mortality, respectively, compared with adults in the lowest-exposure categories. Besides, individuals in the third quartile of BDCM had a 33% higher total all-cause mortality risk than adults in the lowest quartile. When cause-specific mortality was evaluated, we found a greater risk of cancer mortality among adults with higher blood BDCM, DBCM, TBM, Br-THM, and TTHM concentrations at enrollment, while blood TCM and TTHMs were associated with a greater risk of noncancer/nonheart disease mortality.

Accumulating evidence points to an association of THM exposure with cancer morbidity and mortality in diverse settings.[43−45] In support of our findings, exposure to higher levels of THMs in drinking water has been associated with a greater risk of death due to all cancers,[15] colon,[16] bladder,[46,47]

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Table 4. Hazard Ratios (95% CIs) of Cause-Specific Mortality According to Blood THM Concentrations (NHANES, 1999−2012)[a,b]

	heart disease		cancer		other cause	
THMs (pg/mL)	HR (95% CI)	*n*/person years[c]	HR (95% CI)	*n*/person years[c]	HR (95% CI)	*n*/person years[c]
TCM						
Q1 (≤4.19)	1.00 (reference)	45/11 053	1.00 (reference)	50/11 053	1.00 (reference)	92/11 053
Q2 (4.20−8.90)	1.04 (0.54, 1.99)	32/11 330	1.17 (0.71, 1.92)	44/11 330	1.50 (1.11, 2.04)	118/11 330
Q3 (8.91−18.0)	1.26 (0.72, 2.14)	38/12 040	1.41 (0.92, 2.16)	47/12 040	1.45 (1.07, 1.97)	116/12 040
Q4 (>18.0)	1.00 (0.51, 1.95)	28/12 755	1.15 (0.70, 1.89)	50/12 755	1.61 (1.11, 2.33)	105/12 755
P-trend	0.80		0.43		0.02	
BDCM						
Q1 (≤ 0.44)	1.00 (reference)	45/12 453	1.00 (reference)	49/12 453	1.00 (reference)	126/12 453
Q2 (0.45−1.49)	1.25 (0.73, 2.14)	41/12 077	1.29 (0.73, 2.26)	50/12 077	1.22 (0.89, 1.67)	110/12 077
Q3 (1.50−3.50)	1.41 (0.86, 2.33)	44/12 793	1.84 (1.07, 3.17)	62/12 793	1.07 (0.74, 1.56)	109/12 793
Q4 (>3.50)	0.55 (0.23, 1.35)	16/12 458	1.43 (0.80, 2.54)	41/12 458	1.11 (0.82, 1.51)	107/12 458
P-trend	0.38		0.09		0.64	
DBCM						
T1 (≤0.44)	1.00 (reference)	80/21 751	1.00 (reference)	88/21 751	1.00 (reference)	213/21 751
T2 (0.45−1.78)	1.19 (0.74, 1.92)	42/14 039	1.40 (0.90, 2.17)	61/14 039	1.01 (0.78, 1.30)	122/14 039
T3 (>1.78)	0.72 (0.42, 1.23)	25/13 429	1.65 (1.07, 2.55)	56/13 429	1.10 (0.81, 1.49)	117/13 429
P-trend	0.33		0.02		0.58	
TBM						
T1 (≤1.06)	1.00 (reference)	108/33 065	1.00 (reference)	138/33 065	1.00 (reference)	328/33 065
T2 (1.07−2.12)	0.98 (0.50, 1.90)	16/7678	1.11 (0.71, 1.72)	27/7678	0.85 (0.60, 1.21)	64/7678
T3 (>2.12)	1.29 (0.63, 2.64)	21/8037	1.91 (1.19, 3.08)	37/8037	1.04 (0.71, 1.51)	58/8037
P-trend	0.56		0.01		0.88	
Br-THMs						
Q1 (≤1.94)	1.00 (reference)	45/11 416	1.00 (reference)	49/11 416	1.0	131/11 416
Q2 (1.95−3.48)	1.14 (0.65, 1.97)	45/11 913	1.55 (0.94, 2.56)	52/11 913	0.85 (0.59, 1.22)	93/11 913
Q3 (3.49−7.10)	1.30 (0.78, 2.16)	38/11 997	1.16 (0.69, 1.98)	50/11 997	0.99 (0.70, 1.38)	113/11 997
Q4 (>7.10)	0.51 (0.24, 1.10)	15/12 125	1.66 (0.94, 2.91)	44/12 125	0.96 (0.68, 1.35)	103/12 125
P-trend	0.16		0.15		0.96	
TTHMs						
Q1 (≤7.36)	1.00 (reference)	44/10 418	1.00 (reference)	44/10 418	1.00 (reference)	90/10 418
Q2 (7.37−14.14)	0.99 (0.57, 1.72)	32/10 727	1.79 (1.09, 2.93)	51/10 727	1.65 (1.16, 2.35)	122/10 727
Q3 (14.15−26.39)	1.56 (0.97, 2.51)	38/11 322	1.67 (1.02, 2.72)	41/11 322	1.38 (0.93, 2.05)	98/11 322
Q4 (>26.39)	0.88 (0.45, 1.75)	25/12 121	1.41 (0.82, 2.42)	44/12 121	1.55 (1.06, 2.27)	104/12 121
P-trend	0.75		0.27		0.05	

[a]Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; THMs, trihalomethanes; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Br-THMs, sum of BDCM, DBCM, and TBM; TTHMs, sum of TCM and Br-THMs. [b]Models were adjusted for age, sex, race/ethnicity, education level, family income-to-poverty ratio level, BMI, alcohol drinking, cigarette smoking, self-reported general health, and water-use activity within 72 h. [c]The number of deaths and person years are absolute, unweighted values.

and brain cancer.[46] Yet, a lack of association between THM exposure and deaths due to esophageal, rectal, and kidney cancers was also reported.[16,48−50] However, these previous studies estimated exposure to total THMs from tap water consumption as a surrogate to assign exposure to individuals, which could result in exposure misclassification due to the temporal and spatial variability of monitoring data and within- and between-individual variability in water usage and metabolism.[41,51] In an earlier NHANES analysis, Min and colleagues reported a positive association between blood DBCM, TBM, and Br-THM concentrations and cancer mortality risk among 933 adults aged 40−59 years,[17] which is in agreement with our updated analysis including a larger sample size over a longer study follow-up period. Besides, both studies reported a higher risk of cancer mortality among participants with moderate levels of blood BDCM concentrations, compared to participants in the lowest exposure levels. In our current analysis, however, we also found that moderate levels of blood TTHMs were associated with a greater risk of cancer mortality. Additionally, the hazard ratios of cancer mortality in relation to blood THM concentrations reported by Min et al. were slightly higher than our present study. The discrepancy between studies could be driven by the difference in population size. One key methodological issue of the previous NHANES analysis by Min et al. is that only 19 cancer deaths occurred during the shorter-term follow-up. As a result, Min and colleagues reported much wider 95% confidence intervals for the estimated hazard ratios of cancer mortality related to THMs than that of our present study, indicating possible insufficient statistical power to generate precise estimations. In comparison, we analyzed a total of 207 cancer deaths and our findings were less prone to false positives due to a larger number of cases.

This study, to our knowledge, is the first to explore the association between THM exposure and total, all-cause, and cardiovascular mortality. While some in vivo and in vitro evidence has supported the cardiac toxicity of THMs,[21] we did not find any convincing associations between blood THMs

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exposure and heart disease mortality, which might be due to the difference in species susceptibility and/or exposure levels tested in laboratory animals compared with those normally found in humans.[52] Instead, we found a relationship between elevated blood TCM and TTHM concentrations and a greater risk of all-cause and cancer mortality risk. Previous toxicological and epidemiological studies have associated exposure to THMs with adverse reproductive outcomes,[25] neurotoxicity,[53] liver injury,[34] respiratory impairment,[54] and diabetes.[23] These health conditions have been associated with an increased mortality risk, making potential associations between THM exposures and total mortality biologically plausible.

Although the mechanisms underlying the associations between THM exposure and mortality are not fully understood, many DBPs, including THMs, have been classified as cytotoxic, mutagenic, or genotoxic based on experimental animal studies and in vitro assays.[54−56] In an observational study conducted among 50 healthy adults, Kogevinas and colleagues reported that higher levels of individual Br-THMs in exhaled breath after swimming were associated with greater micronuclei counts in peripheral blood lymphocytes and urine mutagenicity.[57] Besides, exposure to THMs was also reported to be associated with metabolic changes such as protein-free radical generation, lipid peroxidation, and oxidative stress both in animals and humans,[58−60] which could result in liver damage, insulin resistance, and diabetes,[23,34] eventually leading to an increased risk of death.

Our study has several limitations. First, we relied on a single measurement of blood THMs at enrollment to predict death over the subsequent follow-up period, which may lead to exposure misclassification. Although a single measurement is thought to reflect steady-state levels in humans,[19] such misclassification would tend to bias effect estimates toward the null. Besides, the influence of changes in personal water-use habits and national reduction in THM levels due to the U.S. EPA's preventive policies cannot be fully ruled out.[40] As a result, Ashley and colleagues reported a significant decline in the levels of TCM in blood and tap water among the U.S. NHANES population recruited between 2001 and 2012.[42] Our stratified analysis, however, showed no evidence of effect modification by survey year (1999−2006 vs 2007−2012). Second, although we have adjusted for an extensive set of potential confounders such as demographic indicators, self-reported health conditions, lifestyle factors, and BMI, the possibility of unmeasured and residual confounding cannot be fully ruled out.[61,62] Third, from 2007 to 2012, NHANES cause-specific death categories only included heart disease and cancer. Thus, the leading causes of deaths related to blood TCM and TTHMs were unclear. Besides, the misclassification of underlying causes based on the death certificate in the U.S. cannot be fully ruled out.[63] Fourth, causality cannot be determined because of the observational nature of the study design. However, we used a nationally representative sample of U.S. adults with a large sample size and longitudinal study design and evaluated internal exposure levels (blood biomarkers of THMs), which greatly improved methodological issues in previous studies, contributing to higher robustness of our present findings.

In conclusion, we found positive associations between blood TCM, BDCM, TBM, and TTHMs and risk of all-cause mortality; between BDCM, DBCM, TBM, Br-THMs, and TTHMs and risk of cancer mortality; and between TCM and TTHMs and risk of noncancer/nonheart disease mortality among U.S. adults. Although our results should be confirmed in well-established cohort studies, they provide evidence that population exposure to THMs may contribute to overall mortality among U.S. adults.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.1c00862.

Hazard ratios (95% CIs) of all-cause mortality for participants in the highest quartiles of TCM and TTHM compared with participants in the lowest quartiles and *p*-values for linear trend across quartiles, stratified by age, sex, BMI, cigarette smoking, and alcohol use (NHANES 1999−2012) (Table S1); sensitivity analyses of the associations between blood THM concentrations and risk of all-cause mortality (NHANES 1999−2012) (Table S2); and hazard ratios (95% CIs) of all-cause and cause-specific mortality according to blood THM concentrations among 11 035 U.S. adults aged ≥20 years (NHANES, 1999−2012) (Table S3) (PDF)

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Author Contributions

Y.S. analyzed the data. Y.S. and Y.X.W. drafted the manuscript. Y.X.W. and C.M. lead the study conception, study design, and analysis plan. C.C. validated the accuracy of data analysis with a technical review. Y.S., Y.X.W., C.C., V.M., L.W., Y.Z., and C.M. interpreted the results and critically appraised the manuscript for important intellectual content.

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Notes

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