Association of blood trihalomethane concentrations with asthma in US adolescents: nationally representative cross-sectional study

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Among a representative sample of 2359 US adolescents, we found that exposure to THMs was associated with a greater risk of asthma, particularly among those who were co-exposed to tobacco smoke https://bit.ly/3mpHxgq

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Abstract

Background Population studies show that the use of swimming pools is associated with the risk of asthma and allergic diseases among children. Our objective was to explore the associations between blood trihalomethane (THM) concentrations and asthma among US adolescents, and assess to what extent the association is modified by active tobacco smoke exposure.

Methods We included 2359 adolescents aged 12–19 years with measured blood concentrations of chloroform (trichloromethane (TCM)), bromodichloromethane (BDCM), dibromochloromethane (DBCM) and bromoform (tribromomethane (TBM)) from the National Health and Nutrition Examination Survey 2005–2012. Logistic regression models were fitted to assess the odds ratios for the association of blood THM concentrations (three or four categories) with the risk of self-reported current and ever (lifetime) asthma.

Results Blood DBCM concentrations were associated with a higher risk of ever asthma among all adolescents (OR 1.54 (95% CI 1.07–2.21), comparing the extreme exposure categories). The relationship was stronger among adolescents exposed to tobacco smoke (OR 3.96 (95% CI 1.89–8.30), comparing the extreme exposure categories). We also found positive relationships between blood brominated THM concentrations (sum of BDCM, DBCM and TBM) and risk of ever asthma and between blood DBCM and brominated THM concentrations and risk of current asthma among adolescents with tobacco smoke exposure. The relative excess risk of ever asthma due to the interaction between high blood DBCM and brominated THM concentrations and tobacco smoke exposure was 1.87 (95% CI 0.30–3.43) and 0.78 (95% CI 0.07–1.49), respectively.

Conclusions Exposure to THMs is associated with a higher risk of asthma in adolescents, particularly among those exposed to tobacco smoke.

Introduction

Asthma, characterised by repeated episodes of wheezing, breathlessness, chest tightness and coughing, is the most common chronic lung disease during childhood. Globally, approximately 14% of children have asthma [1]. Growing evidence shows that asthma predisposes children and adolescents to a myriad of

long-term sequelae, such as irrecoverable loss of lung function and chronic obstructive pulmonary disease, making it chiefly important to identify potentially modifiable risk factors to improve prevention strategies. The International Study of Asthma and Allergies in Childhood has revealed that the prevalence of allergic diseases including asthma varies greatly between regions, countries and centres within a city or country, suggesting the potential role of local environmental factors [2].

Disinfection byproducts are a class of chemicals formed when disinfectants react with organic matter in source waters. Because disinfection of water is globally used to kill disease-causing microbes in the distribution system, humans are ubiquitously exposed to disinfection byproducts through ingestion, inhalation and dermal absorption during daily consumption and water-use activities. Several population studies have shown that chlorinated swimming pool attendance is associated with a higher risk of asthma and allergic diseases among children and adolescents [3–8]. However, some studies have reported conflicting results [9–11]. Most previous studies assessed disinfection byproduct exposures based on reports of swimming frequency from questionnaires or environmental monitoring data, which were prone to result in exposure misclassification because they did not account for factors that could influence individual intake and disinfection byproduct metabolism. More importantly, while the strong association of tobacco use with asthma risk is well documented [12], no study has explored whether tobacco smoke exposure modifies the association between disinfection byproducts and asthma.

Trihalomethanes (THMs) are the most common species of disinfection byproducts in chlorinated water, accounting for 66% of disinfection byproduct compounds. Blood concentrations represent integrative measures of exposure from multiple routes and are sensitive to low levels of exposure [13]. Although blood THM concentrations decrease within minutes to hours after exposure, they are believed to be relatively stable due to the high frequency of daily water-use activities and slower partitioning out of adipose tissue [14]. In this study, we explored blood THM concentrations in relation to asthma among a representative sample of civilian, noninstitutionalised US adolescents and assessed to what extent the association was modified by tobacco smoke exposure.

Methods

Study population

Data were pooled from four independent cycles (2005–2006, 2007–2008, 2009–2010 and 2011–2012) of the National Health and Nutrition Examination Survey (NHANES), a cross-sectional population-based survey designed to assess the health and nutritional status in the noninstitutionalised US population. The collection of NHANES data has been described in detail elsewhere [15]. A randomly sampled subset (one-half) of adolescents aged 12–19 years who participated in NHANES 2005–2012 was tested for blood THM concentrations (n=2976). To be included in our current study, participants had to provide at least one valid measurement of specific blood THM concentrations and had no missing data on tobacco smoke exposure (*i.e.* serum cotinine). Finally, 2359 adolescents were eligible for inclusion (figure 1). Most demographic and lifestyle characteristics were similar between included and excluded adolescents, indicating that the participants in our analytical sample were representative of the broader NHANES population (supplementary table S1). NHANES was approved by the Ethics Review Board of the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC). All participants provided informed consent before participation.

Measurement of blood THMs

Procedures for peripheral blood sampling, processing and determination have been described elsewhere [16]. In brief, blood concentrations of four specific THMs (*i.e.* chloroform (trichloromethane (TCM)), bromodichloromethane (BDCM), dibromochloromethane (DBCM) and bromoform (tribromomethane (TBM)) were measured *via* solid-phase microextraction gas chromatography and mass spectrometry. Blood brominated trihalomethanes (Br-THMs) were the total concentrations of BDCM, DBCM and TBM, and blood total trihalomethanes (TTHMs) were the summarised concentrations of TCM and Br-THMs. For samples with values lower than the limit of detection (LOD), data were replaced with LOD/$\sqrt{2}$.

Definition of asthma

Data on asthma and any related symptoms were collected by trained interviewers using a standardised questionnaire. According to the recommendation from a pooled European birth cohort study [17], lifetime or ever asthma was defined by respondents giving an affirmative response to the question, “Has a doctor or other health professional ever told you that you have asthma?”. Current asthma was defined as participants further affirmatively replying to the question “In the past 12 months have you had wheezing or whistling in your chest?”. Adolescents without physician-diagnosed asthma were treated as the comparison.

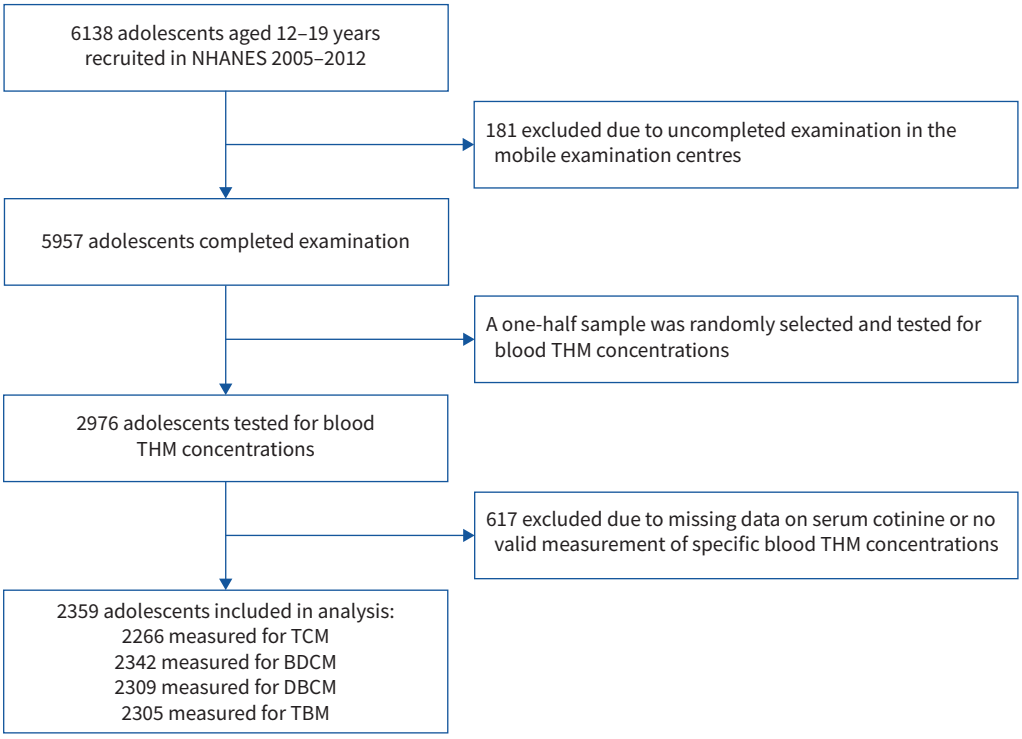

FIGURE 1 Study population flowchart. NHANES: National Health and Nutrition Examination Survey; THM: trihalomethane; TCM: trichloromethane (chloroform); BDCM: bromodichloromethane; DBCM: dibromochloromethane; TBM: tribromomethane (bromoform).

Tobacco smoke exposure ascertainment

Tobacco smoke exposure was ascertained by serum cotinine and a questionnaire regarding recent tobacco use. Serum cotinine is the leading metabolite of nicotine and can thus be used as a marker for tobacco smoke exposure [18]. Serum cotinine was measured by isotope-dilution high-performance liquid chromatography/atmospheric pressure chemical ionisation tandem mass spectrometry. For participants aged ⩾12 years, they were also asked to report if they had consumed tobacco or nicotine products (*e.g.* cigarettes, pipes, cigars, chewing tobacco, snuff, nicotine patches and nicotine gum) in the past 5 days. Adolescents were considered exposed to tobacco smoke if their serum cotinine concentrations were >10 $ng \cdot mL^{-1}$ or they had self-reported consumption of tobacco or nicotine products in the past 5 days [19].

Covariates

Information on age, sex, race/ethnicity, family history of asthma, physical activity, sampling season, current allergic symptoms (*i.e.* hay fever, rhinitis, allergy, itchy rash and wheeze in the past year), family income and water-use activities (*e.g.* swimming, showering and bathing) were collected at enrolment. Height and weight were measured and body mass index (BMI) was calculated ($kg \cdot m^{-2}$). Age-specific BMI z-scores were calculated to obtain standardised values according to the growth charts for the US developed by the Centers for Disease Control and Prevention [20]. Family income was assessed with the income to poverty ratio, which is a ratio of family income to poverty threshold specific to family size, year and state. Leisure-time physical activity was defined as the total hours of moderate-to-vigorous activity during leisure-time per week. Missing data on BMI z-scores (n=31 (1.31%)), family income to poverty ratio (n=154 (6.52%)) and physical activity (n=10 (0.4%)) were imputed with median values.

Statistical analysis

Because tobacco smoke exposure showed a strong association with asthma among adolescents from NHANES [18], the analyses were first conducted among all participants and then performed separately among adolescents with and without tobacco smoke exposure, with adjustment for complex, multistage sampling survey designs (*e.g.* sampling weights, stratification and clusters). Descriptive statistics were performed to describe participants' demographic characteristics and distribution of blood THM

concentrations according to tobacco smoke exposure. The difference in demographic characteristics between subgroups was assessed using Rao–Scott Chi-squared tests for categorical variables and t-tests for continuous variables.

Both crude (unadjusted) and adjusted logistic regression models were fit to assess the odds ratios and 95% confidence intervals for the association of blood THM concentrations with the risk of ever or current asthma. Adolescents were assigned to quartiles for TCM, Br-THMs and TTHMs, whereas three groups were created for BDCM (tertiles), DBCM (<50th, 50–75th and >75th) and TBM (<75th, 75–87.5th and >87.5th), given that a relatively relevant proportion of observations were below the LOD. Tests for linear trends were conducted by modelling categories of THM concentrations as ordinal variables using the median values within each category. Because tobacco use is strongly associated with asthma [12], we also examined the interaction between blood THM concentrations and tobacco smoke exposure on both multiplicative and additive scales. The multiplicative interaction was assessed using the likelihood ratio test by comparing the fit of models with and without the interaction term between each THM and tobacco smoke exposure. We calculated the relative excess risk due to interaction (RERI) to assess the additive interaction by substituting odds ratios for the relative risks in the RERI equation [21]. Because a higher prevalence of allergy was reported among male swimmers than females [22], we also conducted a stratified analysis to explore potential modification by sex.

Covariates were selected *a priori* and were then included in multivariable models if their inclusion changed the age-adjusted odds ratios by ⩾5%. Final logistic regression models were adjusted for age (continuous), sex (male *versus* female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican American and Other), BMI z-scores (continuous), family income to poverty ratio (0–1.0, 1.1–3.0 or >3.0), family history of asthma (yes *versus* no), swimming/hot tub/steam room use within 72 h (yes *versus* no) and survey cycles (2005–2006, 2007–2008, 2009–2010 or 2011–2012).

Several sensitivity analyses of the association between blood THMs and ever asthma were conducted. First, we excluded adolescents who had missing data on BMI z-scores or family income to poverty ratio to assess the influence of the imputation method. Second, we assessed the potential influence of peak exposures by 1) excluding adolescents who spent any time at a swimming pool/hot tub/steam room in the past 72 h, and 2) additionally including the timing of examination session (morning, afternoon and evening), sampling season (November through April *versus* May through October) and time interval since the last shower/bath (⩽2, 3–6, 7–14 and >14 h) as covariates in the adjusted models. Finally, we tested whether recent allergy and physical activity affected our findings by additionally including current allergic symptoms (yes *versus* no) and leisure-time physical activity (<3, 3–7 and >7 h) in the adjusted models. All data analyses were performed using the PROC SURVEY procedure with SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Participant characteristics

Among 2359 adolescents aged 12–19 years (mean 15.5 (95% CI 15.3–15.6) years), 441 (20.4%) were ever diagnosed with asthma and 196 (9.1%) reported current asthma (table 1). Compared with adolescents without tobacco smoke exposure, adolescents who were exposed to tobacco smoke tended to be older (mean 17.1 (95% CI 16.8–17.3) *versus* 15.2 (95% CI 15.0–15.3) years) and were more likely to be male (240 (60.6%) *versus* 962 (49.6%)), Non-Hispanic White (144 (67.3%) *versus* 497 (56.7%)) and have a family income to poverty ratio <1.0 (162 (34.9%) *versus* 572 (21.3%)) (table 1). However, they were less likely to spend any time in a swimming pool/hot tub/steam room in the past 72 h (15 (5.1%) *versus* 116 (9.7%)).

Distribution of blood THMs

TCM, BDCM, DBCM and TBM were detected in 90.0%, 71.1%, 51.5% and 27.8% of the total study population, respectively (table 2). The median blood concentrations of TCM, BDCM, DBCM, TBM, Br-THMs and TTHMs were 6.6, 1.1, 0.4, 0.7, 2.7 and 10.6 $pg \cdot mL^{-1}$, respectively. The median blood THM concentrations were similar according to tobacco smoke exposure, although the detection rate of TCM, BDCM, DBCM and TBM was slightly higher among adolescents without tobacco exposure. Participants' demographic characteristics and lifestyle factors were mostly similar across quartiles of blood TTHM concentrations, except for survey cycle, race/ethnicity, time interval since last shower/bath and swimming pool/hot tub/steam room use within 72 h (supplementary table S2).

TABLE 1 Characteristics according to tobacco smoke exposure for study participants in the National Health and Nutrition Examination Survey 2005–2012

	All (n=2359)	Tobacco smoke exposure		p-value
		Yes (n=378)	No (n=1981)	
Survey cycle				0.29
2005–2006	882 (24.6)	156 (28.0)	726 (24.0)	
2007–2008	457 (24.5)	67 (25.4)	390 (24.3)	
2009–2010	526 (22.7)	88 (23.6)	438 (22.5)	
2011–2012	494 (28.3)	67 (23.0)	427 (29.3)	
Age (years)	15.5 (15.3–15.6)	17.1 (16.8–17.3)	15.2 (15.0–15.3)	<0.0001
BMI (z-score)	0.62 (0.57–0.68)	0.57 (0.41–0.73)	0.63 (0.56–0.70)	0.52
Sex				0.001
Male	1202 (51.4)	240 (60.6)	962 (49.6)	
Female	1157 (48.6)	138 (39.4)	1019 (50.4)	
Race/ethnicity				0.002
Non-Hispanic White	641 (58.4)	144 (67.3)	497 (56.7)	
Non-Hispanic Black	684 (14.8)	112 (13.8)	572 (15.0)	
Mexican American	646 (13.5)	70 (8.3)	576 (14.6)	
Other	388 (13.2)	52 (10.6)	336 (13.7)	
Family income to poverty ratio				0.0004
0–1.0	734 (23.6)	162 (34.9)	572 (21.3)	
1.1–3.0	859 (35.6)	128 (37.8)	731 (35.1)	
>3.0	612 (40.9)	70 (27.3)	542 (43.6)	
Leisure-time physical activity (h per week)				0.07
<3	1032 (39.3)	176 (46.7)	856 (37.8)	
3–7	539 (25.1)	75 (21.6)	464 (25.8)	
>7	778 (35.6)	124 (31.7)	654 (36.4)	
Current allergic conditions				0.34
Yes	630 (27.3)	28 (8.5)	171 (10.4)	
No	1729 (72.7)	350 (91.5)	1810 (89.6)	
Examination session				0.71
Morning	1174 (50.3)	194 (51.3)	980 (50.1)	
Afternoon	777 (31.7)	124 (33.0)	653 (31.5)	
Evening	408 (18.0)	60 (15.6)	348 (18.4)	
Time interval since last shower/bath (h)				0.11
⩽2	312 (14.2)	56 (16.3)	256 (13.8)	
3–6	578 (23.2)	102 (24.9)	476 (22.9)	
7–14	584 (25.0)	105 (28.2)	479 (24.3)	
>14	885 (37.6)	115 (30.6)	770 (39.0)	
Sampling season				0.09
November–April	1222 (42.8)	176 (37.8)	1046 (43.8)	
May–October	1137 (57.2)	202 (62.2)	935 (56.2)	
Swimming pool/hot tub/steam room use within 72 h				0.02
Yes	131 (8.9)	15 (5.1)	116 (9.7)	
No	2228 (91.1)	363 (94.9)	1865 (90.3)	
Family history of asthma				0.48
Yes	455 (22.3)	80 (24.1)	375 (21.9)	
No	1904 (77.7)	298 (75.9)	1606 (78.1)	
Ever (lifetime) asthma				0.11
Yes	441 (20.4)	93 (24.6)	348 (19.6)	
Never	1918 (79.6)	285 (75.4)	1633 (80.4)	
Current asthma				0.26
Yes	196 (9.1)	45 (11.0)	151 (8.7)	
No	2163 (90.9)	333 (89.0)	1830 (91.3)	

Data are presented as n (%) or mean (95% CI), unless otherwise stated; accounting for complex, multistage sampling survey designs (*e.g.* sampling weights, stratification and clusters) to ensure nationally representative estimation. 31, 154 and 10 participants had missing information on body mass index (BMI) z-score, family income to poverty ratio and levels of leisure-time physical activity, respectively. p-value was calculated by the Rao–Scott Chi-squared test and t-test for categorical and continuous variables, respectively.

TABLE 2 Distribution of blood trihalomethane (THM) concentrations according to tobacco smoke exposure (National Health and Nutrition Examination Survey 2005–2012)

	TCM ($pg \cdot mL^{-1}$)	BDCM ($pg \cdot mL^{-1}$)	DBCM ($pg \cdot mL^{-1}$)	TBM ($pg \cdot mL^{-1}$)	Br-THMs ($pg \cdot mL^{-1}$)	TTHMs ($pg \cdot mL^{-1}$)
All (n=2359)						
n	2266	2342	2309	2305	2253	2161
% >LOD	90.0	71.1	51.5	27.8	NA	NA
GM	7.0	1.3	0.9	1.0	3.6	11.6
Median (IQR)	6.6 (3.1–14.0)	1.1 (0.4–2.9)	0.4 (0.4–1.6)	0.7 (0.7–1.0)	2.7 (1.6–5.8)	10.6 (5.6–22.2)
Tobacco smoke exposure (n=378)						
n	366	374	366	373	361	349
% >LOD	86.6	67.7	47.0	24.9	NA	NA
GM	6.8	1.3	0.9	0.9	3.5	11.6
Median (IQR)	7.0 (2.6–13.9)	1.0 (0.4–2.9)	0.4 (0.4–1.6)	0.7 (0.7–0.7)	2.6 (1.6–5.4)	10.6 (5.0–22.3)
No tobacco smoke exposure (n=1981)						
n	1900	1968	1943	1932	1892	1812
% >LOD	90.6	71.8	52.4	28.4	NA	NA
GM	7.0	1.3	0.9	1.0	3.6	11.6
Median (IQR)	6.5 (3.2–14.0)	1.1 (0.4–2.9)	0.4 (0.4–1.6)	0.7 (0.7–0.7)	2.7 (1.6–5.8)	10.6 (5.6–22.2)

TCM: trichloromethane (chloroform); BDCM: bromodichloromethane; DBCM: dibromochloromethane; TBM: tribromomethane (bromoform); Br-THMs: sum of BDCM, DBCM and TBM; TTHMs: sum of TCM and Br-THMs; LOD: limit of detection; GM: geometric mean; IQR: interquartile range; NA: not applicable.

Blood THMs and asthma

In the unadjusted models, blood THM concentrations were not associated with the risk of ever asthma among adolescents (table 3). After adjusting for tobacco smoke exposure and other confounders, however, blood DBCM and Br-THM concentrations were associated with a higher risk of ever asthma among all adolescents (OR 1.54 (95% CI 1.07–2.21) and 1.46 (95% CI 0.98–2.17), respectively, comparing the extreme exposure categories). When the analysis was stratified by tobacco smoke exposure, we observed a higher risk of ever asthma across the categories of blood DBCM and Br-THM concentrations among adolescents who had tobacco smoke exposure both in the unadjusted and adjusted logistic regression models (all $p_{trend}<0.05$). In the adjusted models for smokers, adolescents in the highest exposure category of DBCM and Br-THMs had ORs for ever asthma of 3.96 (95% CI 1.89–8.30) and 3.28 (95% CI 1.43–7.53), respectively, compared with adolescents in the lowest exposure category (table 3). These associations, however, were not observed among adolescents without tobacco smoke exposure. The multiplicative and additive interaction results suggested that the associations of blood DBCM and Br-THM concentrations with ever asthma were modified by tobacco smoke exposure (all $p_{interaction}<0.05$) (tables 3 and 4). A strong relative excess risk of ever asthma due to the interaction of high blood DBCM and Br-THM concentrations with tobacco smoke exposure was observed: 1.87 (95% CI 0.30–3.43) and 0.78 (95% CI 0.07–1.49), respectively (table 4).

Similar results were observed when the associations between blood THM concentrations and current asthma risk were explored (table 5). In multivariable models, adolescents in the highest *versus* lowest exposure category of DBCM and Br-THMs had ORs for current asthma of 3.72 (95% CI 1.40–9.89) and 3.79 (95% CI 1.22–11.79), respectively. Again, these associations between DBCM and Br-THM concentrations and current asthma were not apparent among adolescents without tobacco smoke exposure (table 5). There was no evidence of multiplicative interaction between blood DBCM and Br-THM concentrations and tobacco smoke exposure on the risk of current asthma (table 5). However, we found a strong excess risk of current asthma due to the additive interaction between high blood Br-THM concentrations and tobacco smoke exposure (RERI 1.32 (95% CI 0.01–2.64)) (table 4).

We did not find any evidence of effect modification by sex for the associations of blood DBCM and Br-THM concentrations and risk of ever or current asthma ($p_{interaction}>0.05$) (supplementary table S3). However, we found positive associations between blood TCM and TTHM concentrations and risk of current asthma only among males with tobacco smoke exposure, which were modified by sex (both $p_{interaction}<0.05$) (supplementary table S3), although the concentrations of blood THMs and serum cotinine

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TABLE 3 Odds ratios of ever asthma in relation to blood trihalomethane (THM) concentrations among US adolescents according to tobacco smoke exposure (National Health and Nutrition Examination Survey 2005–2012)

Blood THM (pg·mL^{-1})	All (n=2359)			Tobacco smoke exposure (n=378)			No tobacco smoke exposure (n=1981)			$p_{interaction}$-value for adjusted model
	n/N[#]	Unadjusted model OR (95% CI)	Adjusted model OR (95% CI)[¶]	n/N[#]	Unadjusted model OR (95% CI)	Adjusted model OR (95% CI)[+]	n/N[#]	Unadjusted model OR (95% CI)	Adjusted model OR (95% CI)[+]	
TCM										0.32
Q1 (1.48–4.11)	109/567	Reference	Reference	22/95	Reference	Reference	87/472	Reference	Reference	
Q2 (4.12–8.34)	106/566	0.73 (0.53–1.01)	0.76 (0.57–1.03)	22/86	0.89 (0.41–1.94)	0.82 (0.40–1.73)	84/480	0.71 (0.49–1.01)	0.73 (0.52–1.03)	
Q3 (8.35–16.90)	106/561	0.74 (0.50–1.09)	0.79 (0.51–1.23)	23/99	0.66 (0.27–1.59)	0.54 (0.22–1.33)	83/462	0.75 (0.51–1.11)	0.86 (0.52–1.41)	
Q4 (>16.90)	103/572	0.79 (0.53–1.19)	0.80 (0.53–1.20)	24/86	1.36 (0.52–3.55)	1.32 (0.53–3.32)	79/486	0.69 (0.47–1.02)	0.72 (0.48–1.08)	
p_{trend}-value[§]		0.45	0.48		0.46	0.43		0.17	0.26	
BDCM										0.05
T1 (0.44–0.75)	159/778	Reference	Reference	30/136	Reference	Reference	129/642	Reference	Reference	
T2 (0.76–2.50)	148/784	0.88 (0.61–1.28)	0.83 (0.57–1.21)	26/120	1.16 (0.55–2.44)	0.99 (0.40–2.41)	122/664	0.84 (0.56–1.24)	0.78 (0.51–1.19)	
T3 (>2.50)	132/780	0.94 (0.69–1.29)	0.94 (0.69–1.29)	37/118	1.74 (0.86–3.55)	1.66 (0.77–3.57)	95/662	0.68 (0.48–0.94)	0.82 (0.59–1.14)	
p_{trend}-value[§]		0.25	0.95		0.12	0.14		0.02	0.35	
DBCM										0.03
<50th (0.44–0.65)	221/1155	Reference	Reference	34/198	Reference	Reference	187/957	Reference	Reference	
50–75th (0.66–1.87)	105/578	0.88 (0.59–1.31)	1.00 (0.65–1.54)	27/91	1.65 (0.80–3.41)	1.61 (0.77–3.36)	78/487	0.78 (0.50–1.22)	0.90 (0.54–1.49)	
>75th (>1.87)	107/576	1.26 (0.89–1.79)	1.54 (1.07–2.21)	29/77	3.34 (1.54–7.24)	3.96 (1.89–8.30)	78/499	1.01 (0.71–1.44)	1.28 (0.85–1.93)	
p_{trend}-value[§]		0.15	0.01		0.003	<0.001		0.79	0.15	
TBM										0.99
<75th (0.71–1.13)	324/1730	Reference	Reference	70/291	Reference	Reference	254/1439	Reference	Reference	
75–87.5th (1.14–2.10)	58/287	1.35 (0.86–2.12)	1.43 (0.92–2.24)	13/52	1.30 (0.49–3.48)	1.69 (0.70–4.09)	45/235	1.35 (0.82–2.21)	1.44 (0.85–2.44)	
>87.5th (>2.10)	48/288	1.03 (0.63–1.71)	1.23 (0.71–2.15)	9/30	1.29 (0.44–3.79)	1.39 (0.48–4.00)	39/258	1.01 (0.61–1.67)	1.25 (0.72–2.17)	
p_{trend}-value[§]		0.78	0.38		0.54	0.34		0.89	0.36	
Br-THMs										0.02
Q1 (1.58–1.78)	105/563	Reference	Reference		Reference	Reference	87/462	Reference	Reference	
Q2 (1.79–3.15)	116/563	1.12 (0.74–1.72)	1.04 (0.68–1.58)	18/101	1.44 (0.67–3.09)	1.39 (0.57–3.38)	95/474	1.07 (0.67–1.72)	0.91 (0.54–1.53)	
Q3 (3.16–6.69)	100/564	0.87 (0.60–1.27)	0.92 (0.62–1.35)	21/89	1.31 (0.48–3.59)	1.21 (0.41–3.60)	78/471	0.79 (0.54–1.16)	0.86 (0.55–1.36)	
Q4 (>6.69)	101/563	1.23 (0.83–1.85)	1.46 (0.98–2.17)	22/93	3.08 (1.38–6.84)	3.28 (1.43–7.53)	72/485	0.99 (0.66–1.51)	1.19 (0.77–1.82)	
p_{trend}-value[§]		0.34	0.04	29/78	0.005	0.003		0.87	0.25	
TTHMs										0.20
Q1 (3.07–6.99)	108/540	Reference	Reference	21/85	Reference	Reference	87/455	Reference	Reference	
Q2 (7.00–12.97)	99/541	0.57 (0.38–0.84)	0.58 (0.38–0.88)	22/91	0.67 (0.31–1.47)	0.52 (0.25–1.10)	77/449	0.55 (0.36–0.83)	0.57 (0.37–0.90)	
Q3 (12.98–25.63)	99/540	0.69 (0.45–1.05)	0.76 (0.49–1.18)	19/92	0.57 (0.22–1.44)	0.49 (0.20–1.19)	80/449	0.72 (0.47–1.10)	0.87 (0.54–1.40)	
Q4 (>25.63)	99/540	0.86 (0.58–1.29)	0.92 (0.59–1.42)	26/81	1.66 (0.72–3.83)	1.42 (0.65–3.12)	73/459	0.73 (0.50–1.06)	0.83 (0.54–1.29)	
p_{trend}-value[§]		0.91	0.80		0.13	0.14		0.36	0.85	

TCM: trichloromethane (chloroform); Q: quartile; BDCM: bromodichloromethane; T: tertile; DBCM: dibromochloromethane; TBM: tribromomethane (bromoform); Br-THMs: sum of BDCM, DBCM and TBM; TTHMs: sum of TCM and Br-THMs. [#]: proportions of adolescents with ever diagnosed asthma are absolute, unweighted values; [¶]: adjusted for age, sex, race/ethnicity, body mass index (BMI) z-score, family income to poverty ratio, family history of asthma, swimming pool/hot tub/steam room use within 72 h, survey cycle and tobacco smoke exposure; [+]: adjusted for age, sex, race/ethnicity, BMI z-score, family income to poverty ratio, family history of asthma, swimming pool/hot tub/steam room use within 72 h and survey cycle; [§]: tests for linear trend were conducted by modelling categories of THM concentrations as ordinal variables using the median values within each category.

TABLE 4 Additive scale interactions between blood dibromochloromethane (DBCM) and brominated trihalomethanes (Br-THMs; sum of bromodichloromethane, dibromochloromethane and tribromomethane (bromoform)) concentrations and tobacco smoke exposure and the risk of asthma[#]

Blood THM	Tobacco smoke exposure[¶]	Ever asthma		Current asthma	
		n	OR (95% CI)	n	OR (95% CI)
DBCM					
Low DBCM (<75th)	No	1444	1.00 (reference)	1292	1.00 (reference)
	Yes	289	1.20 (0.85–1.70)	259	1.44 (0.90–2.31)
High DBCM (⩾75th)	No	499	0.98 (0.73–1.31)	457	1.05 (0.70–1.59)
	Yes	77	3.04 (1.80–5.13)	61	3.51 (1.73–7.12)
RERI (95% CI)			1.87 (0.30–3.43)*		2.01 (−0.42–4.44)
Br-THMs					
Low Br-THMs (<50th)	No	817	1.00 (reference)	715	1.00 (reference)
	Yes	166	1.08 (0.69–1.69)	145	1.15 (0.59–2.27)
High Br-THMs (⩾50th)	No	1075	0.81 (0.63–1.04)	990	1.11 (0.77–1.59)
	Yes	195	1.67 (1.13–2.48)	170	2.59 (1.52–4.39)
RERI (95% CI)			0.78 (0.07–1.49)*		1.32 (0.01–2.64)*

RERI: relative excess risk due to interaction. [#]: all models were adjusted for age, sex, race/ethnicity, body mass index z-score, family income to poverty ratio, family history of asthma, swimming pool/hot tub/steam room use within 72 h and survey cycle; [¶]: participants were considered exposed to tobacco smoke if their serum cotinine concentrations were >10 $ng \cdot mL^{-1}$ or they had self-reported consumption of tobacco or nicotine products in the past 5 days. *: $p<0.05$.

were similar among males and females (supplementary figures S1 and S2). The elevated risk of ever asthma comparing the extreme exposure categories of blood DBCM and Br-THM concentrations among adolescents exposed to tobacco smoke persisted when we excluded adolescents who had missing data on BMI z-scores or family income to poverty ratio (supplementary table S4), when we additionally included specific covariates related to THM exposures, leisure-time physical activity or allergic symptoms in the adjusted models (supplementary table S5 and S6) and when we excluded adolescents who spent any time at a swimming pool/hot tub/steam room in the past 72 h (supplementary table S7).

Discussion

This cross-sectional analysis of a representative sample of adolescents from the US population showed that higher blood DBCM and Br-THM concentrations were associated with a greater risk of ever or current asthma among adolescents exposed to tobacco smoke. These associations, however, were not observed in adolescents without tobacco smoke exposure. The joint effects of high blood DBCM and Br-THM concentrations and tobacco smoke exposure on ever or current asthma were greater than the summed effects due to each individual exposure. We also found some evidence of modification by sex for the positive associations between blood TCM and TTHM concentrations and risk of current asthma, which was observed only among males with tobacco smoke exposure.

Previous population studies have shown that early-life exposure to chlorinated swimming pool environments was associated with a higher risk of asthma, especially among young adolescents and those with an atopic predisposition [3–8, 23]. Furthermore, chlorinated swimming pool attendance has been associated with an increased prevalence of allergic diseases (*e.g.* conjunctivitis, rhinitis and laryngitis), bronchial hyperreactivity and respiratory damage [23, 24]. However, conflicting results are also reported [9–11]. Prior research mostly assessed disinfection byproduct exposures based on reports of swimming frequency from self-reported questionnaires, which is prone to exposure misclassification due to the multiple exposure routes and sources and inter- and intra-individual physiological differences in absorption and metabolism of disinfection byproducts. Internal exposure biomarkers reflect integrative measures of exposure to disinfection byproducts from all routes and sources, providing a more accurate exposure assessment [13]. In an early study conducted among 133 indoor swimming pool workers, Fantuzzi *et al.* [25] reported that employees with THM alveolar air values >21 $\mu g \cdot m^{-3}$ experienced higher risks of dyspnoea, asthma, red eyes and blocked nose than participants with lower exposure levels.

Most mechanistic studies suggest that THMs may increase asthma risk by inducing perturbations of the immune system. In animal studies, Munson *et al.* [26] reported depressed humoral and cellular immunity

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TABLE 5 Odds ratios of current asthma in relation to blood trihalomethane (THM) concentrations among US adolescents according to tobacco smoke exposure (National Health and Nutrition Examination Survey 2005–2012)[#]

Blood THM (pg·mL^{-1})	All (n=2114)			Tobacco smoke exposure (n=330)			No tobacco smoke exposure (n=1784)			$p_{interaction}$-value for adjusted model
	n/N[¶]	Unadjusted model OR (95% CI)	Adjusted model OR (95% CI)[+]	n/N[¶]	Unadjusted model OR (95% CI)	Adjusted model OR (95% CI)[§]	n/N[¶]	Unadjusted model OR (95% CI)	Adjusted model OR (95% CI)[§]	
TCM										0.32
Q1 (1.48–4.11)	45/503	Reference	Reference	7/80	Reference	Reference	38/423	Reference	Reference	
Q2 (4.12–8.34)	40/500	0.67 (0.40–1.12)	0.66 (0.39–1.13)	11/75	1.28 (0.34–4.85)	1.07 (0.31–13.75)	29/425	0.58 (0.32–1.07)	0.56 (0.30–1.08)	
Q3 (8.35–16.90)	56/511	0.92 (0.58–1.46)	0.96 (0.57–1.63)	14/90	1.54 (0.43–5.54)	1.20 (0.35–4.15)	42/421	0.81 (0.50–1.32)	0.89 (0.49–1.61)	
Q4 (>16.90)	46/515	0.81 (0.47–1.40)	0.78 (0.44–1.41)	12/74	2.09 (0.52–8.43)	1.67 (0.53–5.25)	34/441	0.65 (0.35–1.19)	0.62 (0.33–1.19)	
p_{trend}-value[##]		0.73	0.68		0.23	0.29		0.34	0.33	
BDCM										0.05
T1 (0.44–0.75)	63/682	Reference	Reference	9/115	Reference	Reference	54/567	Reference	Reference	
T2 (0.76–2.50)	66/702	0.99 (0.59–1.65)	0.99 (0.60–1.64)	16/110	1.94 (0.74–5.03)	1.39 (0.54–3.59)	50/592	0.87 (0.51–1.48)	0.86 (0.49–1.51)	
T3 (>2.50)	66/714	0.95 (0.57–1.59)	1.15 (0.67–1.96)	20/101	3.01 (1.02–8.82)	2.58 (0.96–6.93)	46/613	0.72 (0.43–1.21)	0.92 (0.54–1.57)	
p_{trend}-value[##]		0.85	0.57		0.05	0.06		0.22	0.83	
DBCM										0.03
< 50th (0.44–0.65)	93/1027	Reference	Reference	15/179	Reference	Reference	78/848	Reference	Reference	
50–75th (0.66–1.87)	51/524	1.00 (0.61–1.65)	1.26 (0.74–2.16)	16/80	2.51 (1.01–6.24)	2.28 (0.93–5.59)	35/444	0.81 (0.45–1.45)	1.06 (0.56–2.00)	
>75th (>1.87)	49/518	1.26 (0.72–2.19)	1.63 (0.90–2.98)	13/61	2.51 (0.98–6.45)	3.72 (1.40–9.89)	36/457	1.10 (0.62–1.96)	1.46 (0.79–2.68)	
p_{trend}-value[##]		0.40	0.12		0.06	0.01		0.66	0.21	
TBM										0.99
< 75th (0.71–1.13)	138/1544	Reference	Reference	34/255	Reference	Reference	104/1289	Reference	Reference	
75–87.5th (1.14–2.10)	26/255	1.12 (0.55–2.26)	1.16 (0.59–2.28)	5/44	0.33 (0.11–0.95)	0.43 (0.14–1.30)	21/211	1.39 (0.74–2.60)	1.37 (0.67,2.70)	
>87.5th (>2.10)	27/267	1.38 (0.67–2.83)	1.63 (0.75–3.52)	5/26	0.96 (0.25–3.72)	1.12 (0.28–4.57)	22/241	1.51 (0.73–3.12)	1.87 (0.87–4.01)	
p_{trend}-value[##]		0.37	0.21		0.66	0.92		0.25	0.10	
Br-THMs										0.02
Q1 (1.58–1.78)	41/499	Reference	Reference	7/90	Reference	Reference	34/409	Reference	Reference	
Q2 (1.79–3.15)	48/495	1.04 (0.56–1.94)	0.98 (0.53–1.82)	9/77	1.66 (0.46–5.92)	1.24 (0.33–4.67)	39/418	0.94 (0.52–1.71)	0.81 (0.43–1.54)	
Q3 (3.16–6.69)	51/515	1.08 (0.57–2.07)	1.28 (0.65–2.51)	13/84	1.52 (0.47–4.88)	1.15 (0.35–3.76)	38/431	1.01 (0.53–1.94)	1.24 (0.61–2.56)	
Q4 (>6.69)	49/511	1.36 (0.73–2.53)	1.64 (0.87–3.11)	15/64	3.68 (1.10–12.34)	3.79 (1.22–11.79)	34/447	1.07 (0.56–2.05)	1.30 (0.68–2.46)	
p_{trend}-value[##]		0.28	0.08		0.02	0.01		0.75	0.26	
TTHMs										0.20
Q1 (3.07–6.99)	40/472	Reference	Reference	6/70	Reference	Reference	34/402	Reference	Reference	
Q2 (7.00–12.97)	44/485	0.57 (0.32–1.02)	0.60 (0.32–1.10)	10/79	0.90 (0.25–3.31)	0.62 (0.16–2.45)	34/406	0.53 (0.29–0.96)	0.56 (0.29–1.08)	
Q3 (12.98–25.63)	51/493	0.91 (0.50–1.65)	0.98 (0.51–1.86)	14/87	1.64 (0.44–6.08)	1.46 (0.45–4.72)	37/406	0.77 (0.42–1.43)	0.89 (0.44–1.80)	
Q4 (>25.63)	45/486	0.98 (0.55–1.74)	1.00 (0.54–1.84)	13/68	2.49 (0.69–9.04)	1.91 (0.63–5.77)	32/418	0.79 (0.43–1.47)	0.84 (0.44–1.61)	
p_{trend}-value[##]		0.65	0.62		0.06	0.10		0.79	0.96	

TCM: trichloromethane (chloroform); Q: quartile; BDCM: bromodichloromethane; T: tertile; DBCM: dibromochloromethane; TBM: tribromomethane (bromoform); Br-THMs: sum of BDCM, DBCM and TBM; TTHMs: sum of TCM and Br-THMs. [#]: participants who ever received a diagnosis of asthma but with no wheezing or whistling in the past year were excluded from this analysis (n=245); [¶]: proportions of adolescents with ever diagnosed asthma are absolute, unweighted values; [+]: adjusted for age, sex, race/ethnicity, body mass index (BMI) z-score, family income to poverty ratio, family history of asthma, swimming pool/hot tub/steam room use within 72 h, survey cycle, and tobacco smoke exposure; [§]: adjusted for age, sex, race/ethnicity, BMI z-score, family income to poverty ratio, family history of asthma, swimming pool/hot tub/steam room use within 72 h, and survey cycle; [##]: tests for linear trend were conducted by modelling categories of THM concentrations as ordinal variables using the median values within each category.

in mice after administration of BDCM or DBCM. Auttachoatet *et al.* [27] observed decreased numbers of blood circulating neutrophils in female B6C3F1 mice when TCM exposure occurred *via* drinking water. Exposure to TCM by inhalation at 20 ppm was also reported to produce a greater number of inflammatory and goblet cells in the lungs and increased blood levels of IgE in mice [28]. A recent population study showed that THM levels in exhaled breath after swimming in a chlorinated pool were associated with acute changes in serum immune markers [29]. Other proposed mechanisms for disinfection byproduct exposure related to asthma and respiratory damage include oxidative stress and hyperpermeability of the lung epithelium [28]. In support of these hypotheses, Varraso *et al.* [30] revealed that exposure to THMs was associated with higher levels of oxidative stress markers in 21 male swimmers; Font-Ribera *et al.* [28] studied 50 healthy and nonsmoker adults, reporting that THM concentrations in exhaled breath after swimming in a chlorinated pool were positively associated with serum club cell secretory protein 16 (CC16), a marker of lung epithelium permeability and integrity.

To the best of our knowledge, this present study is the first to assess the THM–asthma association among adolescents. We found positive associations between blood BDCM and DBCM concentrations and risk of ever or current asthma among adolescents who were exposed to tobacco smoke exposure. The strong additive interaction between high blood BDCM and DBCM concentrations and tobacco smoke exposure suggests that tobacco use might interact synergistically with THM exposure to further accelerate the development of asthma. This is not surprising given the well-documented association between tobacco use and asthma risk [12], as well as shared mechanisms of tobacco smoke and THMs [31]. Substantial evidence from animal models and clinical studies has shown that the imbalance between oxidants and antioxidants resulting from exposure to tobacco smoke is associated with oxidative stress, increased mucosal inflammation and increased expression of inflammatory cytokines, which eventually promote the development of asthma and respiratory diseases [32]. Co-exposure to THMs and tobacco smoke may also exert their synergistic effects through shared metabolic pathways. For instance, exposure to tobacco smoke increases the activity of enzymes that metabolise cigarette toxins (*e.g.* cytochrome P450) and reduces the activity of enzymes that detoxify these compounds (*e.g.* glutathione *S*-transferase enzymes) [33], which are also involved in the metabolism and activation of THMs [34]. Interestingly, we found positive associations between blood TCM and TTHMs and the risk of current asthma among males with tobacco smoke exposure, indicating some evidence of effect modification by sex given the similar levels of blood THM and cotinine in males and females. In support of these findings, previous studies have revealed a higher prevalence of allergy among male swimmers than females [22]. A stronger association of THM exposure with other health outcomes, such as neonatal neurobehavioral development and child cognition, was also reported in boys compared with girls [35, 36]. However, more studies are needed to explore the underlying mechanisms of any sex-specific associations and multiple testing concerns cannot be ruled out.

The drinking water concentrations of TTHMs (median 25.3 $\mu g \cdot L^{-1}$) in the NHANES population were among the medium environmental exposure levels measured in previous studies from the UK (mean 26.5 $\mu g \cdot L^{-1}$), Spain (median 23.5 $\mu g \cdot L^{-1}$), Italy (median 1.5 $\mu g \cdot L^{-1}$), Greece (mean 29.8 $\mu g \cdot L^{-1}$) and China (median 10.53 $\mu g \cdot L^{-1}$) [37, 38]. In this study, the excess risk of asthma due to high blood DBCM and Br-THM concentrations and tobacco smoke exposure was higher than the summed risk associated with each individual factor, suggesting that the previously well-established associations of tobacco smoke exposure with asthma could be further exacerbated by high blood BDCM and DBCM concentrations. Our novel findings strengthen the growing evidence that local environmental factors play an important role in the development/exacerbation of asthma and emphasise the importance of preventing adolescents' asthma by reducing exposure to both THMs and tobacco smoke. The Disinfectants and Disinfection Byproducts Rule issued by the US Environmental Protection Agency in 1998 and 2006 has resulted in continued lower blood THM concentrations in the NHANES population from 2001 to 2012 [39], supporting the effectiveness of setting maximum contaminant levels in household water as a policy for reducing exposure to THMs and ultimately preventing THM-related health effects. Given that few countries have measured blood THM concentrations in the general population, an improved and continued worldwide surveillance of THM levels in drinking water and humans is needed.

The major strength of this study is its nationally representative and large sample of US adolescents. In addition, we used direct measurements of internal exposure biomarkers for THMs and tobacco smoke exposure, which reduced exposure misclassification. Our study also has several limitations. First, despite the strong biological plausibility of THM exposure on asthma and allergic diseases, the exposure biomarkers were collected after asthma incidence occurred, which precluded inferences of causality due to the potential for reverse causation. However, we are not aware of any plausible mechanism through which asthma might affect THM exposure or excretion. In support of this point, we found that participants' water-use activities (swimming pool/hot tub/steam room use) within 72 h were similar according to current

asthma status (supplementary table S8). This suggests that asthma history did not influence exposure conditions and thus minimises the potential for reverse causation. Second, although blood concentrations are reliable biomarkers of THM exposure and are believed to reflect steady-state exposure levels due to the high frequency of daily water-use activities and slower partitioning out of adipose tissue [14], exposure misclassification cannot be fully excluded given that the measured THM concentrations may vary over time and may not provide accurate estimates of the etiologically relevant exposure that precedes the outcome. Nevertheless, such nondifferential misclassification would tend to bias effect estimates towards the null. Third, despite our control for multiple potential confounders, the possibility of residual uncontrolled confounding (*e.g.* tobacco polycyclic aromatic hydrocarbons and metabolic genotypes) cannot be ruled out. Fourth, the detection rate of blood DBCM and TBM concentrations was relatively low (51.5% and 27.8%, respectively), which may result in biased risk estimation. Fifth, causality cannot be inferred due to the observational nature of the cross-sectional study design. Finally, physician-diagnosed asthma and wheezing symptoms were self-reported, which were subject to potential errors in reporting by the study participants, although previous studies have demonstrated the reliability of self-reported asthma [40].

The results of this cross-sectional analysis among a representative sample of US adolescents suggest that exposure to THMs is associated with a greater risk of asthma, particularly among those who are co-exposed to tobacco smoke. Our results refine and extend previous evidence showing that swimming pool attendance is associated with a higher risk of developing asthma and allergic diseases, and emphasise the importance of preventing adolescents' asthma by reducing exposure to both THMs and tobacco smoke.

Author contributions: Y. Sun analysed the data. Y. Sun and Y-X. Wang drafted the manuscript. Y-X. Wang and C. Messerlian led the study conception, study design, analysis plan and interpretation of findings. P-F. Xia validated the accuracy of data analysis with a technical review. Y. Sun, P-F. Xia, J. Xie, V. Mustieles, Y. Zhang, Y-X. Wang and C. Messerlian interpreted the results and critically appraised the manuscript for important intellectual content.

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