EUROPEAN RESPIRATORY journal
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original research article

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Please cite this article as: Sun Y, Xia P-F, Xie J, *et al.* Association of blood trihalomethane concentrations with asthma in U.S. adolescents: nationally representative cross-sectional study. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.01440-2021).

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

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Twitter: Among a representative sample of 2,359 U.S. 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.

ABSTRACT

Background: Population studies show that the use of swimming pools is associated with the risk of asthma and allergic diseases among children.

Objective: To explore the associations between blood trihalomethane (THM) concentrations and asthma among U.S. adolescents and assess to what extent the association is modified by active tobacco smoke exposure.

Methods: We included 2,359 adolescents aged 12-19 years with measured blood concentrations of chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM) from the National Health and Nutrition Examination Surveys 2005-2012. Logistic regression models were fitted to assess the odds ratios (ORs) for the association of THM concentrations (three or four categories) with the risk of self-reported ***current*** and ***ever*** (lifetime) asthma.

Results: Blood DBCM concentration was associated with a greater risk of ***ever*** asthma among all adolescents (OR=1.54; 95% confidence intervals: 1.07, 2.21, comparing the extreme exposure categories). The relation was stronger among adolescents exposed to tobacco smoke (OR=3.96; 1.89, 8.30, comparing the extreme exposure categories). We also found positive relationships between brominated THMs (sum of BDCM, DBCM, and TBM) and risk of ***ever*** asthma and between DBCM and brominated THMs 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 THMs and tobacco smoke exposure was 1.87 (0.30, 3.43) and 0.78 (0.07, 1.49), respectively.

Conclusions: Exposure to THMs is associated with a greater risk of asthma in adolescents,

particularly among those exposed to tobacco smoke.

Keywords: asthma; trihalomethane; disinfection by-products; epidemiology; adolescent

INTRODUCTION

Asthma, characterized 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 centers within a city or country, suggesting the potential role of local environmental factors [2].

Disinfection by-products (DBPs) 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 DBPs 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 DBP exposures based on reports of swimming frequency from questionnaires or environmental monitoring data, which are prone to result in exposure misclassification because they do not account for factors that could influence individual intake and DBP 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 DBPs and asthma.

Trihalomethanes (THMs) are the most common species of DBPs in chlorinated water, accounting for 66% of DBP compounds. Blood concentrations represent integrative measures of exposure from multiple routes and are sensitive to low levels of exposure [13]. Although blood THMs 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, non-institutionalized U.S. 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 non-institutionalized U.S. 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 the NHANES 2005–2012 were tested for blood THM concentrations (n =2,976). 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, 2,359 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). The 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 of peripheral blood sampling, processing, and determination have been described elsewhere [16]. In brief, blood concentrations of 4 specific THMs [i.e. chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (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 summarized 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 the standardized questionnaire. According to the recommendation from the 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.

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 thus can be used as a marker for tobacco smoke exposure [18]. Serum cotinine was measured by an isotope-dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass. For participants aged 12 years and older, 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/mL 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 enrollment. Height and weight were measured and body mass index

(BMI) was calculated as weight (kg) divided by height squared (m^2). The age-specific BMI *z*-scores were calculated to obtain standardization values according to the growth charts for the U.S. 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-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 firstly 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-square tests for categorical variables and *t*-tests for continuous variables.

Both crude and adjusted logistic regression models were fit to assess the odds ratios (ORs) and 95% confidence intervals (CIs) for the association of blood THM concentrations with the

risk of ever or current asthma. Adolescents were assigned to quartiles for TCM, Br-THM, and TTHM, whereas three groups were created for BDCM (tertiles), DBCM (< 50^{th}, 50-75^{th}, > 75^{th}), and TBM (< 75^{th}, 75-87.5^{th}, > 87.5^{th}), given that a relatively relevant proportion of observations were below the LOD. Tests for linear trends were conducted by modeling categories of THM concentrations as ordinal variables using the median values within each category. Because tobacco use is strongly associated with asthma [12], we examined the interaction between THMs and tobacco smoke exposure on both the 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 or sex. We calculated the relative excess risk due to interaction (RERI) to assess the additive interaction by substituting ORs for the relative risks (RRs) 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 the potential modification by sex.

Covariates were selected *a priori* and were then included in multivariable models if their inclusion changed the age-adjusted ORs by ≥5%. Final logistic regression models were adjusted for age (continuous), sex (male vs. 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 vs. no), swimming/hot tub/sauna use within 72 hours (yes vs. 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 a) excluding adolescents who spent any time at a swimming pool, a hot tub, or a steam room in the past 72 hours; and b) additionally including the timing of examination session (morning, afternoon, and evening), sampling season (November through April vs. May through October), and time interval since the last shower or bath (≤2, 3-6, 7-14, >14 hours) 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 vs. no) and leisure-time physical activity (<3, 3-7, and >7 hours) in the adjusted models. All data analyses were performed using the PROC SURVEY procedure with SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Participant characteristics

Among 2,359 adolescents aged 12-19 years (mean [95% CI]: 15.5 [15.3, 15.6]), 441 (20.4%) were ever diagnosed with asthma and 196 (9.1%) reported current asthma (table 1). Compared to adolescents without tobacco smoke exposure, adolescents who were exposed to tobacco smoke tended to be older (mean [95% CI]: 17.1 [16.8, 17.3] vs. 15.2 [15.0, 15.3]) and were more likely to be male [N (%): 240 (60.6%) vs. 962 (49.6%)], non-Hispanic White [N [%]: 144 (67.3%) vs. 497 (56.7%)], and have a family income-poverty ratio lower than 1.0 [N

(%): 162 (34.9%) vs. 572 (21.3%)] (Table 1). However, they were less likely to spend any time in a swimming pool, hot tub, or steam room in the past 72 hours [N (%): 15 (5.1%) vs. 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 (table 2). The median blood concentrations of TCM, BDCM, DBCM, TBM, Br-THM, and TTHMs were 6.6, 1.1, 0.4, 0.7, 2.7, and 10.6 pg/mL, respectively. The median blood THM concentrations were similar according to tobacco smoke exposure, though 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 or bath, and swimming pool/hot tub/ steam room use within 72 hours (supplementary table S2).

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 concentration was 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). 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-THMs

among adolescents who had tobacco smoke exposure both in the unadjusted and adjusted logistic regression models (all p for 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 additive and multiplicative interaction results suggested that the associations of blood DBCM and Br-THMs with ***ever*** asthma were modified by tobacco smoke exposure (table 3 and table 4; all p for interaction <0.05). A significant relative excess risk of ***ever*** asthma due to the interaction of high blood DBCM and Br-THMs with tobacco smoke exposure was observed: 1.87 (0.30, 3.43) and 0.78 (0.07, 1.49), respectively (table 4).

Similar results were observed when the associations between blood THMs and ***current*** asthma risk were explored (table 5). In multivariable models, adolescents in the highest vs. 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-THMs and ***current*** asthma did not achieve statistical significance among adolescents without tobacco smoke exposure (table 5). There was no evidence of multiplicative interaction between blood DBCM and Br-THMs and tobacco smoke exposure on the risk of ***current*** asthma (table 5). However, we found a significant excess risk of ***current*** asthma due to the additive interaction between high blood Br-THMs and tobacco smoke exposure (RERI=1.32; 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-THMs and risk of ***ever*** or ***current*** asthma (p for interaction >0.05; supplementary table S3). However, we found positive associations between blood TCM and TTHMs and risk of ***current*** asthma only among males with tobacco smoke exposure, which were modified by sex (both p for interaction <0.05; supplementary table S3), though the concentrations of blood THMs and serum cotinine were similar among males and females (supplementary figure S1 and S2). The elevated risk of ***ever*** asthma comparing the extreme exposure categories of blood DBCM and Br-THMs among adolescents who are exposed to tobacco smoke persisted when we excluded adolescents who had missing data on BMI z-scores or family income-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, a hot tub, or a steam room in the past 72 hours (supplementary table S7).

DISCUSSION

This cross-sectional analysis of a representative sample of adolescents from the U.S. population showed that higher blood DBCM and Br-THM concentrations were associated with a greater risk of ***ever*** or ***current*** asthma among adolescents who are 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 and tobacco smoke exposure

on ***ever*** or ***current*** asthma were significantly 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 TTHMs 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 DBP 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 DBPs. Internal exposure biomarkers reflect integrative measures of exposure to DBPs from all routes and sources, providing a more accurate exposure assessment [13]. In an early study conducted among 133 indoor swimming pool workers, Fantuzzi and colleagues reported that employees with THM alveolar air values higher than 21 $\mu g/m^3$ experienced higher risks of dyspnea, asthma, red eyes, and blocked nose than participants with lower exposure levels [25].

Most mechanistic studies suggest that THMs may increase asthma risk by inducing

perturbations of the immune system. In animal studies, Munson and colleagues reported depressed humoral and cellular immunity in mice after administration of BDCM or DBCM [26]. Auttachoatet and colleagues observed decreased numbers of blood circulating neutrophils in female B6C3F1 mice when TCM exposure occurred *via* drinking water [27]. 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 DBP exposures related to asthma and respiratory damage include oxidative stress and hyperpermeability of the lung epithelium [28]. In support of these hypotheses, Varraso and colleagues revealed that exposure to THMs was associated with higher levels of oxidative stress markers in 21 male swimmers [30]; Font-Ribera and colleagues studied 50 healthy and non-smoker adults, reporting that THM concentrations in exhaled breath after swimming in a chlorinated pool were positively associated with serum Clara cell secretory protein 16 (CC16), a marker of lung epithelium permeability and integrity [28].

This present study, to our knowledge, is the first to assess the THMs–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 significant additive interaction between high blood BDCM and DBCM 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 metabolize 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 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 μg/L) in the NHANES

population were among the medium environmental exposure levels measured in previous studies from the United Kingdom (mean: 26.5 μg/L), Spain (median: 23.5 μg/L), Italy (median: 1.5 μg/L), Greece (mean: 29.8 μg/L), and China (median: 10.53 μg/L) [37, 38]. In this study, the excess risk of asthma due to high blood DBCM and Br-THM 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. Our novel findings strengthen the growing evidence that local environmental factors play an important role in the development/exacerbation of asthma and emphasize the importance of preventing adolescents' asthma by reducing exposure to both THMs and tobacco smoke. The Disinfectants and Disinfection Byproducts Rule issued by the U.S. 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 level 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 THMs levels in drinking water and humans is needed.

The major strength of this study is its nationally representative and large sample of U.S. adolescents. Besides, 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, and steam room use) within 72 hours were similar according to current asthma status (supplementary table S8). This suggests that asthma history did not influence exposure conditions and thus minimizes 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 excluded given that the measured THM concentrations may vary over time and may not provide accurate estimates of the etiologically relevant exposures that preceded the outcome. Nevertheless, such non-differential 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 is 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, though previous studies have demonstrated the reliability of self-reported asthma [40].

The results of this cross-sectional analysis among a representative sample of U.S. 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 emphasize the importance of preventing adolescents' asthma by reducing exposure to both THMs and tobacco smoke.

Author Contributions: Yang Sun analyzed the data. Yang Sun and Yi-Xin Wang drafted the manuscript. Yi-Xin Wang and Carmen Messerlian lead the study conception, study design, analysis plan, and interpretation of findings. Peng-Fei Xia validated the accuracy of data analysis with a technical review. Yang Sun, Peng-Fei Xia, Jing Xie, Vicente Mustieles, Yu Zhang, Yi-Xin Wang, Carmen Messerlian interpreted the results and critically appraised the manuscript for important intellectual content.

Conflict of interest: None declared.

Funding: This study was supported by the National Natural Science Foundation of China [No. 81903281]. C.M. is supported by the National Institute of Environmental Health Sciences of the National Institutes of Health under Award Number R01ES031657.

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Figure Legend

Figure 1. Study Population Flowchart.
Abbreviations: THM, trihalomethane; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform.

Table 1. Characteristics according to tobacco smoke exposure for study participants in NHANES 2005-2012 [mean (95% CI) or N (%)].

Characteristic [a]	All (N=2,359)	Tobacco smoke exposure		P-value [b]
		Yes (n=378)	No (n=1,981)	
Survey cycle				
2005-2006	882 (24.6)	156 (28.0)	726 (24.0)	
2007-2008	457 (24.5)	67 (25.4)	390 (24.3)	0.29
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				
Male	1,202 (51.4)	240 (60.6)	962 (49.6)	0.001
Female	1,157 (48.6)	138 (39.4)	1,019 (50.4)	
Race/ethnicity				
Non-Hispanic White	641 (58.4)	144 (67.3)	497 (56.7)	
Non-Hispanic Black	684 (14.8)	112 (13.8)	572 (15.0)	0.002
Mexican American	646 (13.5)	70 (8.3)	576 (14.6)	
Other	388 (13.2)	52 (10.6)	336 (13.7)	
Family income-poverty ratio				
0-1.0	734 (23.6)	162 (34.9)	572 (21.3)	0.0004
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 (hours per week)				
< 3	1,032 (39.3)	176 (46.7)	856 (37.8)	0.07
3-7	539 (25.1)	75 (21.6)	464 (25.8)	
>7	778 (35.6)	124 (31.7)	654 (36.4)	
Current allergic conditions				
Yes	630 (27.3)	28 (8.5)	171 (10.4)	0.34
No	1,729 (72.7)	350 (91.5)	1,810 (89.6)	
Examination session				
Morning	1,174 (50.3)	194 (51.3)	980 (50.1)	0.71
Afternoon	777 (31.7)	124 (33.0)	653 (31.5)	
Evening	408 (18.0)	60 (15.6)	348 (18.4)	
Time interval since the last shower or bath (hour)				
≤ 2	312 (14.2)	56 (16.3)	256 (13.8)	0.11
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				
November through April	1,222 (42.8)	176 (37.8)	1,046 (43.8)	0.09
May through October	1,137 (57.2)	202 (62.2)	935 (56.2)	
Swimming pool/hot tub/ steam room use within 72h				0.02
Yes	131 (8.9)	15 (5.1)	116 (9.7)	
No	2,228 (91.1)	363 (94.9)	1,865 (90.3)	
Family history of asthma				0.48
Yes	455 (22.3)	80 (24.1)	375 (21.9)	
No	1,904 (77.7)	298 (75.9)	1,606 (78.1)	
Ever (lifetime) asthma				
Yes	441 (20.4)	93 (24.6)	348 (19.6)	0.11
Never	1,918 (79.6)	285 (75.4)	1,633 (80.4)	
Current asthma				0.26

Yes	196 (9.1)	45 (11.0)	151 (8.7)
No	2,163 (90.9)	333 (89.0)	1,830 (91.3)

Mean (95% CI) and N (%) were accounted for complex, multistage sampling survey designs (e.g., sampling weights, stratification, and clusters) to ensure nationally representative estimation.

[a]A total of 31, 154, and 10 participants had missing information on BMI Z - score, family income-poverty ratio, and levels of leisure-time physical activity, respectively.

[b] P-value was calculated by Rao-Scott chi-square test and t-test for categorical and continuous variables, respectively.

Table 2 Distribution of blood THM concentrations (pg/ml) according to tobacco smoke exposure (NHANES, 2005-2012).

	TCM	BDCM	DBCM	TBM	Br-THMs	TTHMs
All (N = 2,359)						
n	2,266	2,342	2,309	2,305	2,253	2,161
% > 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 = 1,981)						
n	1,900	1,968	1,943	1,932	1,892	1,812
% > 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)

Abbreviations: THM, trihalomethane; 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; LOD, limit of detection; GM, geometric; IQR, interquartile range; NA, not applicable

Table 3. ORs (95% CIs) of **ever** asthma in relation to blood THM concentrations among U.S. adolescents according to tobacco smoke exposure (NHANES, 2005-2012).

Blood THMs (pg/ml)	**All (N=2,359)**			**Tobacco smoke exposure (n = 378)**			**No tobacco smoke exposure (n = 1,981)**			**P for interaction for** adjusted model
	n/N[b]	Unadjusted model OR (95% CI)	Adjusted model OR (95% CI)[c]	n/N[b]	Unadjusted model OR (95% CI)	Adjusted model OR (95% CI)[d]	n/N[b]	Unadjusted model OR (95% CI)	Adjusted model OR (95% CI)[d]	
TCM										
Q1 (1.48-4.11)	109/567	Ref.	Ref.	22/95	Ref.	Ref.	87/472	Ref.	Ref.	
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)	0.32
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 for trend[a]		0.45	0.48		0.46	0.43		0.17	0.26	
BDCM										
T1 (0.44-0.75)	159/778	Ref.	Ref.	30/136	Ref.	Ref.	129/642	Ref.	Ref.	
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)	0.05
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 for trend[a]		0.25	0.95		0.12	0.14		0.02	0.35	
DBCM										
< 50th (0.44-0.65)	221/1,155	Ref.	Ref.	34/198	Ref.	Ref.	187/957	Ref.	Ref.	
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)	0.03
> 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 for trend[a]		0.15	0.01		0.003	< 0.001		0.79	0.15	
TBM										
< 75th (0.71-1.13)	324/1,730	Ref.	Ref.	70/291	Ref.	Ref.	254/1,439	Ref.	Ref.	
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)	0.99
> 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 for trend[a]		0.78	0.38		0.54	0.34		0.89	0.36	
Br-THMs										
Q1 (1.58-1.78)	105/563	Ref.	Ref.		Ref.	Ref.	87/462	Ref.	Ref.	
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)	0.02
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 for trend[a]		0.34	0.04	29/78	0.005	0.003		0.87	0.25	
TTHMs										0.20

Q1 (3.07-6.99)	108/540	Ref.	Ref.	21/85	Ref.	Ref.	87/455	Ref.	Ref.	
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 for trend[a]		0.91	0.80		0.13	0.14		0.36	0.85	

Abbreviations: THM, trihalomethane; 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.

[a] Tests for linear trend were conducted by modeling categories of THM concentrations as ordinal variables using the median values within each category.

[b] The proportion of adolescents with ever diagnosed asthma are absolute, unweighted values.

[c] Adjusted for age, sex, race/ethnicity, BMI Z-score, family income-poverty ratio, family history of asthma, swimming pool/hot tub/ steam room use within 72h, survey cycle, and tobacco smoke exposure.

[d] Adjusted for age, sex, race/ethnicity, BMI Z-score, family income-poverty ratio, family history of asthma, swimming pool/hot tub/ steam room use within 72h, and survey cycle.

Table 4. Additive scale interactions between blood DBCM and Br-THM concentrations and tobacco smoke exposure and the risk of asthma.[a]

Blood THMs	Tobacco smoke exposure[b]	*Ever asthma*		*Current asthma*	
		n	ORs (95% CIs)	n	ORs (95% CIs)
DBCM					
Low DBCM (<75th)	No	1,444	1.0 (ref.)	1,292	1.0 (ref.)
	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	1.0 (ref.)	715	1.0 (ref.)
	Yes	166	1.08 (0.69, 1.69)	145	1.15 (0.59, 2.27)
High Br-THMs (≥50th)	No	1,075	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)*

Abbreviations: Abbreviations: THM, trihalomethane; 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; RERI, the relative excess risk due to interaction.

[a]All models were adjusted for age, sex, race/ethnicity, BMI *Z*-score, family income- poverty ratio, family history of asthma, swimming pool/hot tub/ steam room use within 72h, and survey cycle.

[b] Participants were considered exposed to tobacco smoke if their serum cotinine concentrations were >10 ng/mL or they had self-reported consumption of tobacco or nicotine products in the past 5 days.

*P<0.05.

Table 5. ORs (95% CIs) of current asthma in relation to blood THM concentrations among U.S. adolescents according to tobacco smoke exposure (NHANES, 2005-2012).[a]

Blood THMs (pg/ml)	All (N=2,114)			Tobacco smoke exposure (n = 330)			No tobacco smoke exposure (n = 1,784)			P for interaction for adjusted model
	n/N[c]	Crude model OR (95% CI)	Adjusted model OR (95% CI)[d]	n/N[c]	Crude model OR (95% CI)	Adjusted model OR (95% CI)[e]	n/N[c]	Crude model OR (95% CI)	Adjusted model OR (95% CI)[e]	
TCM										0.32
Q1 (1.48-4.11)	45/503	Ref.	Ref.	7/80	Ref.	Ref.	38/423	Ref.	Ref.	
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 for trend[b]		0.73	0.68		0.23	0.29		0.34	0.33	
BDCM										0.05
T1 (0.44-0.75)	63/682	Ref.	Ref.	9/115	Ref.	Ref.	54/567	Ref.	Ref.	
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 for trend[b]		0.85	0.57		0.05	0.06		0.22	0.83	
DBCM										0.03
< 50th (0.44-0.65)	93/1,027	Ref.	Ref.	15/179	Ref.	Ref.	78/848	Ref.	Ref.	
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 for trend[b]		0.40	0.12		0.06	0.01		0.66	0.21	
TBM										0.99
< 75th (0.71-1.13)	138/1,544	Ref.	Ref.	34/255	Ref.	Ref.	104/1,289	Ref.	Ref.	
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 for trend[b]		0.37	0.21		0.66	0.92		0.25	0.10	
Br-THMs										0.02
Q1 (1.58-1.78)	41/499	Ref.	Ref.	7/90	Ref.	Ref.	34/409	Ref.	Ref.	
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 for trend[b]		0.28	0.08		0.02	0.01		0.75	0.26	
TTHMs										0.20
Q1 (3.07-6.99)	40/472	Ref.	Ref.	6/70	Ref.	Ref.	34/402	Ref.	Ref.	
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 for trend[b]		0.65	0.62		0.06	0.10		0.79	0.96	

Abbreviations: THM, trihalomethane; 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

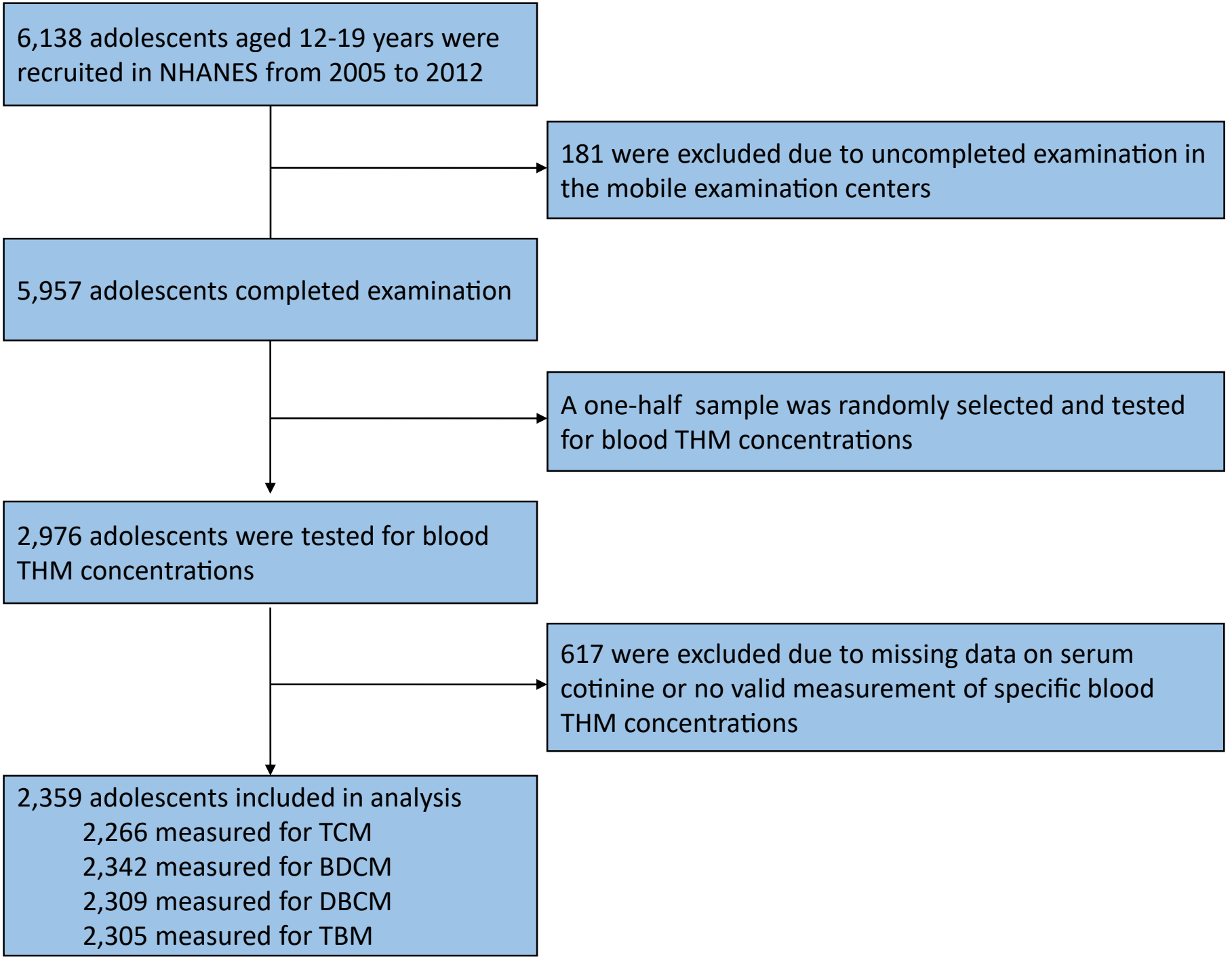
[a] Participants who ever received a diagnosis of asthma but no wheezing or whistling in the past year were excluded from this analysis (n = 245).

[b] Tests for linear trend were conducted by modeling categories of THM concentrations as ordinal variables using the median values within each category.

[c] The proportion of adolescents with ever diagnosed asthma are absolute, unweighted values.

[d] Adjusted for age, sex, race/ethnicity, BMI Z-score, family income-poverty ratio, family history of asthma, swimming pool/hot tub/ steam room use within 72h, survey cycle, and tobacco smoke exposure.

[e] Adjusted for age, sex, race/ethnicity, BMI Z-score, family income-poverty ratio, family history of asthma, swimming pool/hot tub/ steam room use within 72h, and survey cycle.


6,138 adolescents aged 12-19 years were recruited in NHANES from 2005 to 2012
181 were excluded due to uncompleted examination in the mobile examination centers
5,957 adolescents completed examination
A one-half sample was randomly selected and tested for blood THM concentrations
2,976 adolescents were tested for blood THM concentrations
617 were excluded due to missing data on serum cotinine or no valid measurement of specific blood THM concentrations
2,359 adolescents included in analysis
2,266 measured for TCM
2,342 measured for BDCM
2,309 measured for DBCM
2,305 measured for TBM

Online Data Supplement

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

Yang Sun, Peng-Fei Xia, Jing Xie, Vicente Mustieles, Yu Zhang, Yi-Xin Wang, Carmen Messerlian

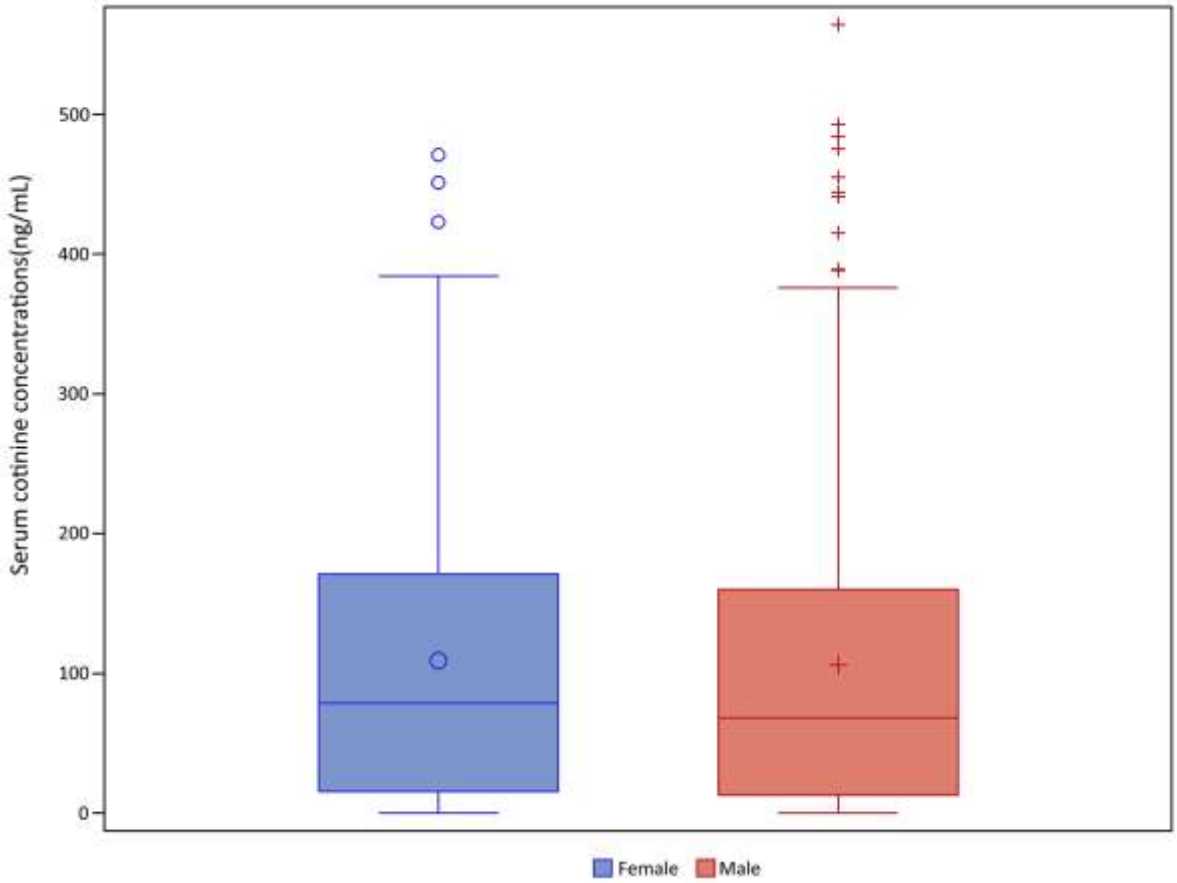


Figure S1. Distribution of serum cotinine concentrations (ng/mL) according to sex among participants with tobacco smoke exposure (NHANES, 2005-2012). The displayed values are the 10th (bottom whisker), 25th percentile (bottom of the box), median (line in box), 75th percentile (top of the box), and 90th (top whisker) of the concentrations. *P* for the Wilcoxon Rank-Sum Test > 0.05.

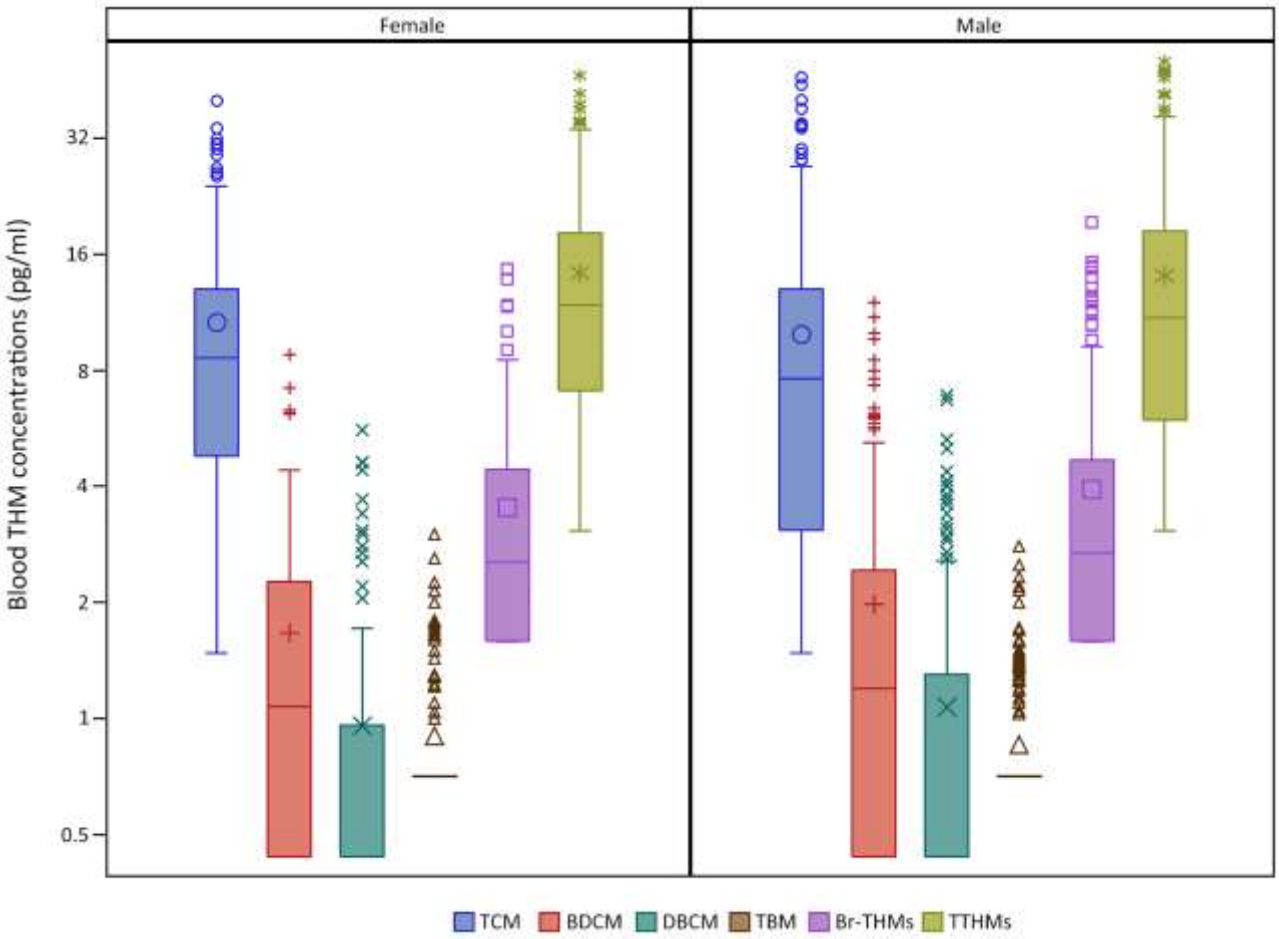


Figure S2. Distribution of blood THM concentrations (pg/ml) according to sex among participants with tobacco smoke exposure (NHANES, 2005-2012). The displayed values are the 10th (bottom whisker), 25th percentile (bottom of the box), median (line in box), 75th percentile (top of the box), and 90th (top whisker) of the concentrations. *P* for the Wilcoxon Rank-Sum Test all > 0.05. Abbreviations: THM, trihalomethane; 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.

Table S1. Characteristics of included adolescents and those excluded for study participants in NHANES 2005-2012 [mean (95% CI) or N (%)].[a]

Characteristic	Included participants (n=2,359)	Excluded participants (n=3,779)	P-value[b]
Survey cycle			
2005-2006	882 (24.7)	1,406 (25.1)	
2007-2008	457 (24.3)	781 (25.5)	0.89
2009-2010	526 (25.2)	813 (24.4)	
2011-2012	494 (25.7)	779 (25.0)	
Age, years	15.5 (15.4, 15.6)	15.4 (15.3, 15.5)	0.21
BMI Z - score	0.62 (0.57, 0.67)	0.51 (0.44, 0.57)	0.002
Sex			
Male	1,202 (49.9)	1,940 (51.6)	0.29
Female	1,157 (50.1)	1,839 (48.4)	
Race/ethnicity			
Non-Hispanic White	641 (58.6)	1,053 (59.5)	
Non-Hispanic Black	684 (14.9)	1,107 (15.0)	0.44
Mexican American	646 (13.5)	969 (12.1)	
Other	388 (13.0)	650 (13.4)	
Family income-poverty ratio			
0-1.0	734 (23.4)	1,051 (21.6)	0.13
1.1-3.0	859 (35.6)	1,461 (39.3)	
>3.0	612 (41.0)	930 (39.1)	
Leisure-time physical activity (hours per week)			
< 3	1,032 (39.6)	1,477 (39.8)	0.80
3-7	539 (25.3)	817 (24.2)	
>7	778 (35.0)	1,185 (36.0)	
Current allergic conditions			
Yes	630 (27.0)	952 (25.0)	0.31
No	1,729 (73.0)	2,827 (75.0)	
Examination session			
Morning	1,174 (50.4)	1,695 (47.6)	0.71
Afternoon	777 (31.7)	1,203 (32.2)	
Evening	408 (17.9)	700 (20.2)	
Sampling season			
November through April	1,222 (42.9)	1,819 (44.2)	0.50
May through October	1,137 (50.1)	1,779 (55.8)	
Family history of asthma			
Yes	455 (21.9)	710 (22.1)	0.89
No	1,904 (78.1)	3,069 (77.9)	
Ever (lifetime) asthma			
Yes	441 (20.3)	722 (19.6)	0.69
Never	1,918 (79.7)	3,057 (80.4)	
Current asthma			
Yes	196 (9.1)	272 (7.7)	0.20
No	2,163 (90.9)	3,507 (92.3)	

Mean (95% CI) and N (%) were accounted for complex, multistage sampling survey designs (e.g., sampling weights, stratification, and clusters) to ensure nationally representative estimation.

[a] A total of 31, 491, and 310 participants had missing information on BMI Z - score, family income-poverty ratio, and levels of leisure-time physical activity, respectively; data on water-use activities was only collected among participants who were measured for blood volatile organic compounds.

[b] P-value was calculated by Rao-Scott chi-square test and t-test for categorical and continuous variables.

Table S2. Characteristics of study participants in NHANES 2005-2012 according to quartiles of blood TTHM concentrations [mean (95% CI) or N (%)].

Characteristic[a]	**Blood TTHM**				
	Quartile 1 (n=540)	Quartile 2 (n=540)	Quartile 3 (n=541)	Quartile4 (n=540)	P[b]
Survey cycle					
2005-2006	138 (17.4)	202 (23.3)	234 (31.3)	219 (27.7)	
2007-2008	133 (28.0)	99 (21.1)	91 (22.7)	90 (23.5)	< 0.001
2009-2010	117 (17.5)	123 (23.9)	121 (25.9)	147 (32.1)	
2011-2012	152 (37.1)	116 (31.7)	95 (20.1)	84 (16.7)	
Age, years	15.5 (15.3, 15.8)	15.4 (15.2, 15.7)	15.5 (15.2, 15.8)	15.4 (15.2, 15.7)	0.94
BMI Z - score	0.55 (0.44, 0.67)	0.66 (0.51, 0.81)	0.64 (0.52, 0.77)	0.62 (0.50, 0.75)	0.61
Sex					
Male	290 (50.5)	262 (49.2)	264 (48.7)	273 (55.4)	0.42
Female	250 (49.5)	278 (50.8)	277 (51.3)	267 (44.6)	
Race/ethnicity					
Non-Hispanic White	205 (68.3)	138 (57.6)	126 (52.0)	123 (50.5)	
Non-Hispanic Black	112 (9.5)	171 (16.3)	177 (18.8)	186 (20.2)	< 0.001
Mexican American	138 (11.8)	136 (12.6)	151 (14.7)	143 (14.2)	
Other	85 (10.4)	95 (13.5)	87 (14.5)	88 (15.1)	
Family income-poverty ratio					
0-1.0	146 (19.5)	177 (25.2)	173 (24.8)	187 (27.8)	0.15
1.1-3.0	199 (34.5)	198 (36.0)	191 (33.2)	187 (37.0)	
>3.0	163 (46.0)	132 (38.8)	138 (42.0)	125 (35.2)	
Leisure-time physical activity level (hours per week)					
< 3	242 (40.9)	241 (38.7)	230 (36.0)	254 (43.4)	0.79
3-7	132 (24.6)	115 (24.7)	126 (27.6)	121 (23.9)	
>7	164 (34.4)	182 (36.6)	183 (36.3)	172 (32.7)	
Current allergic conditions					
Yes	140 (29.3)	141 (23.3)	156 (27.6)	137 (27.4)	0.46
No	400 (70.7)	399 (76.7)	385 (72.4)	403 (72.6)	
Examination session					0.33

Morning	256 (50.1)	248 (47.4)	258 (49.7)	319 (58.2)	
Afternoon	181 (31.8)	185 (34.1)	187 (32.8)	155 (28.7)	
Evening	103 (18.1)	107 (18.5)	96 (17.5)	66 (13.1)	
Time interval since last shower or bath (hour)					
≤ 2	51 (11.7)	45 (12.2)	89 (17.7)	111 (20.0)	< 0.001
3-6	90 (17.0)	128 (22.5)	127 (23.0)	189 (36.1)	
7-14	153 (30.6)	144 (24.7)	137 (23.6)	102 (17.5)	
> 14	246 (40.7)	223 (40.6)	188 (35.7)	138 (26.4)	
Sampling season					
November 1 through April 30	251 (36.1)	245 (55.7)	267 (40.4)	291 (47.1)	0.15
May 1 through October 31	289 (63.9)	295 (44.3)	274 (59.6)	249 (52.9)	
Swimming pool/hot tub/ steam room use within 72h					
Yes	18 (5.6)	32 (10.7)	25 (8.7)	43 (12.8)	0.04
No	522 (94.4)	508 (89.3)	516 (91.3)	497 (87.2)	

Abbreviations: 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.

All estimates were accounted for complex survey designs.

[a] A total of 30, 150, and 9 participants had missing information on BMI Z - score, family income-poverty ratio, and Leisure-time physical activity level, respectively.

[b] P-value was calculated by Rao-Scott chi-square test and t-test for categorical and continuous variables, respectively.

Table S3. Adjusted ORs (95% CIs) of **ever** asthma and **current** asthma in relation to blood THM concentrations among U.S. adolescents with tobacco smoke exposure (n = 378), stratified by sex (NHANES, 2005-2012).[a]

Blood THMs (pg/ml)	Ever asthma			Current asthma[c]		
	Male (n = 240)	Female (n = 138)	*P* for interaction	Male (n = 212)	Female (n = 118)	*P* for interaction
TCM						
Q1 (1.48-4.11)	Ref.	Ref.		Ref.	Ref.	
Q2 (4.12-8.34)	0.73 (0.27, 1.93)	0.43 (0.11, 1.78)	0.11	1.90 (0.20, 18.07)	0.47 (0.04, 6.12)	0.01
Q3 (8.35-16.90)	0.62 (0.20, 1.93)	0.12 (0.02, 0.80)		3.52 (0.43, 28.65)	0.05 (0.001, 1.93)	
Q4 (> 16.90)	1.89 (0.74, 4.84)	0.37 (0.11, 1.32)		6.23 (1.25, 31.09)	0.13 (0.006, 2.66)	
P for trend[b]	0.15	0.27		0.002	0.19	
BDCM						
T1 (0.44-0.75)	Ref.	Ref.		Ref.	Ref.	
T2 (0.76-2.50)	0.83 (0.23, 3.02)	1.04 (0.47, 2.32)	0.55	1.18 (0.19, 7.49)	4.12 (1.46, 11.65)	0.08
T3 (> 2.50)	1.82 (0.75, 4.47)	0.86 (0.25, 2.98)		4.75 (1.29, 17.49)	1.52 (0.18, 12.88)	
P for trend[b]	0.10	0.80		0.008	0.98	
DBCM						
< 50th (0.44-0.65)	Ref.	Ref.		Ref.	Ref.	
50-75th (0.66-1.87)	1.34 (0.52, 3.45)	1.62 (0.54, 4.85)	0.10	1.93 (0.59, 6.28)	5.93 (1.61, 21.85)	0.11
> 75th (>1.87)	5.96 (2.79, 12.73)	1.90 (0.53, 6.81)		7.57 (2.21, 25.89)	2.11 (0.22, 20.19)	
P for trend[b]	< 0.001	0.39		0.001	0.74	
TBM						
< 75th (0.71-1.13)	Ref.	Ref.		Ref.	Ref.	
75-87.5th (1.14-2.10)	2.65 (1.05, 6.68)	1.06 (0.20, 5.66)	0.87	0.60 (0.15, 2.46)	1.25 (0.12, 12.67)	0.83
> 87.5th (> 2.10)	1.12 (0.23, 5.55)	2.28 (0.53, 9.79)		1.29 (0.28, 5.93)	1.36 (0.12, 15.43)	
P for trend[b]	0.82	0.29		0.76	0.78	
Br-THMs						
Q1 (1.58-1.78)	Ref.	Ref.		Ref.	Ref.	
Q2 (1.79-3.15)	1.22 (0.39, 3.79)	1.15 (0.30, 4.37)	0.22	2.42 (0.55, 10.92)	0.96 (0.27, 3.48)	0.11
Q3 (3.16-6.69)	0.84 (0.21, 3.30)	0.91 (0.21, 3.60)		1.33 (0.54, 3.28)	1.75 (0.39, 7.74)	
Q4 (> 6.69)	4.25 (1.69, 10.72)	1.72 (0.39, 7.56)		9.63 (4.00, 23.23)	2.16 (0.28, 16.88)	
P for trend[b]	< 0.001	0.43		0.002	0.48	
TTHMs						
Q1 (3.07-6.99)	Ref.	Ref.		Ref.	Ref.	
Q2 (7.00-12.97)	0.46 (0.17, 1.23)	0.40 (0.16, 1.00)	0.10	0.86 (0.15, 4.85)	0.55 (0.11, 2.75)	0.02
Q3 (12.98-25.63)	0.45 (0.16, 1.27)	0.21 (0.03, 1.32)		3.31 (1.23, 8.92)	0.36 (0.03, 5.09)	
Q4 (> 25.63)	2.53 (1.20, 5.34)	0.45 (0.12, 1.66)		6.72 (3.52, 12.80)	0.27 (0.04, 2.10)	
P for trend[b]	0.005	0.38		<0.001	0.27	

[a] All models adjusted for age, race/ethnicity, BMI *Z*-score, family income-poverty ratio, family history of asthma, swimming pool/hot tub/ steam room use within 72h, and survey cycle.

[b] Tests for linear trend were conducted by modeling categories of THM concentrations as ordinal variables using the median values within each category.

[c] Participants who ever received a diagnosis of asthma but no wheezing or whistling in the past year were excluded in the model for current asthma (n = 48).

Table S4. Sensitivity analyses of the associations between **ever** asthma and blood THM concentrations among U.S. adolescents according to tobacco smoke exposure, excluding participants with missing data on BMI z-scores or family income-poverty ratio (NHANES, 2005-2012).[a,b]

Blood THMs (pg/ml)	All[d] (N=2,176)	Tobacco smoke exposure (n = 351)	No tobacco smoke exposure (n = 1,825)	*P* for interaction
TCM				
Q1 (1.48-4.11)	Ref.	Ref.	Ref.	
Q2 (4.12-8.34)	0.76 (0.55, 1.03)	0.90 (0.41, 1.98)	0.71 (0.50, 1.02)	0.32
Q3 (8.35-16.90)	0.77 (0.50, 1.20)	0.59 (0.23, 1.49)	0.82 (0.49, 1.36)	
Q4 (> 16.90)	0.80 (0.53, 1.19)	1.36 (0.51, 3.63)	0.71 (0.47, 1.07)	
P for trend[c]	0.47	0.43	0.25	
BDCM				
T1 (0.44-0.75)	Ref.	Ref.	Ref.	
T2 (0.76-2.50)	0.79 (0.54, 1.17)	1.13 (0.47, 2.71)	0.72 (0.46, 1.12)	0.03
T3 (> 2.50)	0.93 (0.67, 1.27)	1.89 (0.85, 4.19)	0.79 (0.57, 1.09)	
P for trend[c]	0.90	0.10	0.27	
DBCM				
< 50th (0.44-0.65)	Ref.	Ref.	Ref.	
50-75th (0.66-1.87)	1.03 (0.67, 1.57)	1.67 (0.76, 3.66)	0.93 (0.56, 1.56)	0.03
> 75th (> 1.87)	1.54 (1.08, 2.18)	4.31 (2.00, 9.29)	1.27 (0.85, 1.90)	
P for trend[c]	0.01	< 0.001	0.18	
TBM				
< 75th (0.71-1.13)	Ref.	Ref.	Ref.	
75-87.5th (1.14-2.10)	1.45 (0.93, 2.26)	1.58 (0.64, 3.90)	1.49 (0.88, 2.52)	0.98
> 87.5th (> 2.10)	1.12 (0.61, 2.03)	1.38 (0.46, 4.11)	1.13 (0.63, 2.04)	
P for trend[c]	0.59	0.40	0.59	
Br-THMs				
Q1 (1.58-1.78)	Ref.	Ref.	Ref.	
Q2 (1.79-3.15)	1.01 (0.65, 1.54)	1.44 (0.57, 3.65)	0.87 (0.51, 1.49)	0.02
Q3 (3.16-6.69)	0.86 (0.58, 1.28)	1.27 (0.40, 3.99)	0.80 (0.51, 1.27)	
Q4 (> 6.69)	1.39 (0.94, 2.07)	3.57 (1.52, 8.41)	1.10 (0.71, 1.70)	
P for trend[c]	0.07	0.003	0.41	
TTHMs				
Q1 (3.07-6.99)	Ref.	Ref.	Ref.	
Q2 (7.00-12.97)	0.56 (0.37, 0.85)	0.58 (0.27, 2.52)	0.54 (0.34, 0.86)	0.14
Q3 (12.98-25.63)	0.72 (0.46, 1.13)	0.56 (0.22, 1.38)	0.80 (0.49, 1.31)	
Q4 (> 25.63)	0.89 (0.57, 1.39)	1.58 (0.72, 3.48)	0.79 (0.50, 1.23)	
P for trend[c]	0.89	0.09	0.70	

[a] All models adjusted for age, sex, race/ethnicity, BMI *Z*-score, family income-poverty ratio, family history of asthma, swimming pool/hot tub/ steam room use within 72h, and survey cycle.
[b] Participants with missing data on BMI z-scores or family income-poverty ratio (n =185) were excluded.
[c] Tests for linear trend were conducted by modeling categories of THM concentrations as ordinal variables using the median values within each category.
[d] Models were additionally adjusted for tobacco smoke exposure.

Table S5. Sensitivity analyses of the associations between **ever** asthma and blood THM concentrations among U.S. adolescents according to tobacco smoke exposure with additional adjustment for specific covariates related to THM exposures (NHANES, 2005-2012).[a]

Blood THMs (pg/ml)	All[c] (N=2,359)	Tobacco smoke exposure (n = 378)	No tobacco smoke exposure (n = 1,981)	*P* for interaction
TCM				
Q1 (1.48-4.11)	Ref.	Ref.	Ref.	
Q2 (4.12-8.34)	0.74 (0.55, 1.01)	0.80 (0.37, 1.70)	0.71 (0.49, 1.02)	0.29
Q3 (8.35-16.90)	0.79 (0.51, 1.22)	0.52 (0.22, 1.25)	0.86 (0.53, 1.41)	
Q4 (> 16.90)	0.77 (0.51, 1.22)	1.16 (0.48, 2.81)	0.70 (0.46, 1.07)	
P for trend[b]	0.40	0.58	0.24	
BDCM				
T1 (0.44-0.75)	Ref.	Ref.	Ref.	
T2 (0.76-2.50)	0.80 (0.56, 1.16)	0.84 (0.38, 1.89)	0.74 (0.49, 1.13)	0.05
T3 (> 2.50)	0.89 (0.64, 1.23)	1.54 (0.68, 3.49)	0.77 (0.54, 1.09)	
P for trend[b]	0.65	0.23	0.23	
DBCM				
< 50th (0.44-0.65)	Ref.	Ref.	Ref.	
50-75th (0.66-1.87)	0.96 (0.61, 1.51)	1.61 (0.73, 3.56)	0.85 (0.51, 1.42)	0.03
> 75th (> 1.87)	1.47 (1.02, 2.12)	3.86 (1.75, 8.49)	1.20 (0.78, 1.84)	
P for trend[b]	0.02	0.001	0.29	
TBM				
< 75th (0.71-1.13)	Ref.	Ref.	Ref.	
75-87.5th (1.14-2.10)	1.38 (0.87, 2.19)	1.49 (0.63, 3.53)	1.37 (0.79, 2.37)	0.99
> 87.5th (> 2.10)	1.16 (0.66, 2.04)	1.26 (0.43, 3.69)	1.18 (0.68, 2.05)	
P for trend[b]	0.53	0.51	0.51	
Br-THMs				
Q1 (1.58-1.78)	Ref.	Ref.	Ref.	
Q2 (1.79-3.15)	1.02 (0.67, 1.56)	1.19 (0.48, 2.96)	0.90 (0.54, 1.50)	0.02
Q3 (3.16-6.69)	0.87 (0.58, 1.31)	0.98 (0.36, 2.65)	0.81 (0.51, 1.29)	
Q4 (> 6.69)	1.37 (0.91, 2.08)	3.10 (1.30, 2.65)	1.10 (0.69, 1.75)	
P for trend[b]	0.08	0.008	0.24	
TTHMs				
Q1 (3.07-6.99)	Ref.	Ref.	Ref.	
Q2 (7.00-12.97)	0.57 (0.38, 0.86)	0.46 (0.21, 1.03)	0.56 (0.36, 0.87)	0.19
Q3 (12.98-25.63)	0.74 (0.48, 1.15)	0.46 (0.19, 1.13)	0.85 (0.53, 1.36)	
Q4 (> 25.63)	0.85 (0.54, 1.35)	1.13 (0.51, 2.50)	0.78 (0.49, 1.23)	
P for trend[b]	0.97	0.32	0.68	

[a] All models adjusted for age, sex, race/ethnicity, BMI *Z*-score, family income-poverty ratio, family history of asthma, examination session, sampling season, and the time interval since last shower or bath, swimming pool/hot tub/ steam room use within 72h, and survey cycle.

[b] Tests for linear trend were conducted by modeling categories of THM concentrations as ordinal variables using the median values within each category.

[c] Models were additionally adjusted for tobacco smoke exposure.

Table S6. Sensitivity analyses of the associations between **ever** asthma and blood THM concentrations among U.S. adolescents according to tobacco smoke exposure with additional adjustment for levels of leisure-time physical activity and allergic symptoms (NHANES, 2005-2012).[a]

Blood THMs (pg/ml)	All[c] (N=2,359)	Tobacco smoke exposure (n = 378)	No tobacco smoke exposure (n = 1,981)	*P* for interaction
TCM				
Q1 (1.48-4.11)	Ref.	Ref.	Ref.	
Q2 (4.12-8.34)	0.84 (0.62, 1.13)	0.95 (0.44, 2.06)	0.78 (0.55, 1.12)	0.17
Q3 (8.35-16.90)	0.80 (0.49, 1.30)	0.54 (0.23, 1.25)	0.86 (0.48, 1.53)	
Q4 (> 16.90)	0.86 (0.57, 1.31)	1.48 (0.63, 3.49)	0.75 (0.48, 1.17)	
P for trend[b]	0.63	0.30	0.34	
BDCM				
T1 (0.44-0.75)	Ref.	Ref.	Ref.	
T2 (0.76-2.50)	0.93 (0.62, 1.38)	1.05 (0.41, 2.70)	0.87 (0.56, 1.37)	0.06
T3 (> 2.50)	1.03 (0.72, 1.47)	1.82 (0.77, 4.31)	0.89 (0.59, 1.33)	
P for trend[b]	0.77	0.12	0.63	
DBCM				
< 50th (0.44-0.65)	Ref.	Ref.	Ref.	
50-75th (0.66-1.87)	1.00 (0.65, 1.53)	1.57 (0.75, 3.31)	0.90 (0.55, 1.47)	0.04
> 75th (> 1.87)	1.74 (1.18, 2.56)	4.92 (1.98, 12.17)	1.41 (0.90, 2.20)	
P for trend[b]	0.004	0.001	0.09	
TBM				
< 75th (0.71-1.13)	Ref.	Ref.	Ref.	
75-87.5th (1.14-2.10)	1.50 (0.88, 2.55)	1.65 (0.68, 4.02)	1.49 (0.81, 2.72)	0.64
> 87.5th (> 2.10)	1.27 (0.76, 2.14)	1.61 (0.55, 4.75)	1.24 (0.74, 2.09)	
P for trend[b]	0.27	0.25	0.35	
Br-THMs				
Q1 (1.58-1.78)	Ref.	Ref.	Ref.	
Q2 (1.79-3.15)	1.07 (0.67, 1.69)	1.43 (0.59, 3.46)	0.95 (0.54, 1.66)	0.03
Q3 (3.16-6.69)	1.01 (0.68, 1.49)	1.30 (0.40, 4.19)	0.93 (0.61, 1.43)	
Q4 (> 6.69)	1.57 (1.03, 2.38)	3.57 (1.37, 9.32)	1.24 (0.77, 1.99)	
P for trend[b]	0.02	0.006	0.25	
TTHMs				
Q1 (3.07-6.99)	Ref.	Ref.	Ref.	
Q2 (7.00-12.97)	0.64 (0.43, 0.95)	0.62 (0.30, 1.27)	0.63 (0.42, 0.96)	0.12
Q3 (12.98-25.63)	0.78 (0.48, 1.28)	0.49 (0.20, 1.20)	0.91 (0.52, 1.59)	
Q4 (> 25.63)	0.96 (0.62, 1.47)	1.55 (0.67, 3.61)	0.83 (0.53, 1.30)	
P for trend[b]	0.72	0.14	0.77	

[a] All models adjusted for age, sex, race/ethnicity, BMI *Z*-score, family income-poverty ratio, family history of asthma, levels of leisure-time physical activity, current allergic symptoms, and survey cycle.
[b] Tests for linear trend were conducted by modeling categories of THM concentrations as ordinal variables using the median values within each category.
[c] Models were additionally adjusted for tobacco smoke exposure.

Table S7. Sensitivity analyses of the associations between **ever** asthma and blood THM concentrations among U.S. adolescents according to tobacco smoke exposure, excluding participants who spent any time at a swimming pool, a hot tub, or a steam room in the past 72 hours (NHANES, 2005-2012).[a]

Blood THMs (pg/ml)	All[c] (N=2,228)	Tobacco smoke exposure (n = 363)	No tobacco smoke exposure (n = 1,865)	*P* for interaction
TCM				
Q1 (1.48-4.11)	Ref.	Ref.	Ref.	
Q2 (4.12-8.34)	0.80 (0.57, 1.12)	0.87 (0.42, 1.80)	0.77 (0.51, 1.15)	0.44
Q3 (8.35-16.90)	0.81 (0.52, 1.26)	0.52 (0.21, 1.30)	0.88 (0.53, 1.45)	
Q4 (> 16.90)	0.73 (0.48, 1.11)	1.16 (0.44, 3.11)	0.66 (0.43, 1.02)	
P for trend[b]	0.22	0.67	0.13	
BDCM				
T1 (0.44-0.75)	Ref.	Ref.	Ref.	
T2 (0.76-2.50)	0.87 (0.59, 1.30)	0.94 (0.42, 2.11)	0.99 (0.61, 1.61)	0.11
T3 (> 2.50)	0.92 (0.66, 1.28)	1.44 (0.65, 3.21)	0.86 (0.57, 1.28)	
P for trend[b]	0.74	0.30	0.33	
DBCM				
< 50th (0.44-0.65)	Ref.	Ref.	Ref.	
50-75th (0.66-1.87)	1.02 (0.67, 1.55)	1.51 (0.72, 3.18)	0.94 (0.57, 1.55)	0.05
> 75th (> 1.87)	1.51 (1.05, 2.18)	3.76 (1.76, 8.05)	1.15 (0.76, 1.75)	
P for trend[b]	0.02	0.002	0.17	
TBM				
< 75th (0.71-1.13)	Ref.	Ref.	Ref.	
75-87.5th (1.14-2.10)	1.47 (0.93, 2.33)	1.74 (0.75, 4.05)	1.11 (0.70, 1.75)	0.50
> 87.5th (> 2.10)	1.35 (0.76, 2.40)	1.12 (0.31, 4.07)	1.65 (0.97, 2.79)	
P for trend[b]	0.23	0.60	0.15	
Br-THMs				
Q1 (1.58-1.78)	Ref.	Ref.	Ref.	
Q2 (1.79-3.15)	1.05 (0.70, 1.58)	1.47 (0.63, 3.43)	0.93 (0.56, 1.53)	0.14
Q3 (3.16-6.69)	0.93 (0.62, 1.37)	1.16 (0.42, 3.22)	0.88 (0.55, 1.40)	
Q4 (> 6.69)	1.39 (0.93, 2.09)	2.68 (1.12, 6.44)	1.20 (0.78, 1.86)	
P for trend[b]	0.09	0.03	0.25	
TTHMs				
Q1 (3.07-6.99)	Ref.	Ref.	Ref.	
Q2 (7.00-12.97)	0.58 (0.38, 0.87)	0.53 (0.27, 1.07)	0.58 (0.37, 0.90)	0.55
Q3 (12.98-25.63)	0.75 (0.48, 1.16)	0.47 (0.19, 1.19)	0.87 (0.54, 1.38)	
Q4 (> 25.63)	0.80 (0.51, 1.26)	1.11 (0.45, 2.68)	0.77 (0.49, 1.21)	
P for trend[b]	0.70	0.53	0.58	

[a] All models adjusted for age, sex, race/ethnicity, BMI *Z*-score, family income-poverty ratio, family history of asthma, and survey cycle.

[b] Tests for linear trend were conducted by modeling categories of THM concentrations as ordinal variables using the median values within each category.

[c] Models were additionally adjusted for tobacco smoke exposure.

Table S8. Water-use activities of study participants in NHANES 2005-2012 according to asthma history [N (%).

Swimming pool/hot tub/ steam room use within 72h	Current asthma (n = 196)	No asthma (n=1,918)	P-value[a]
Yes	10 (6.1)	109 (9.4)	0.29
No	186 (93.9)	1,809 (90.6)	

[a] P-value was calculated by the Rao-Scott chi-square test.