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Blood trihalomethane concentrations and allergic sensitization: A nationwide cross-sectional study

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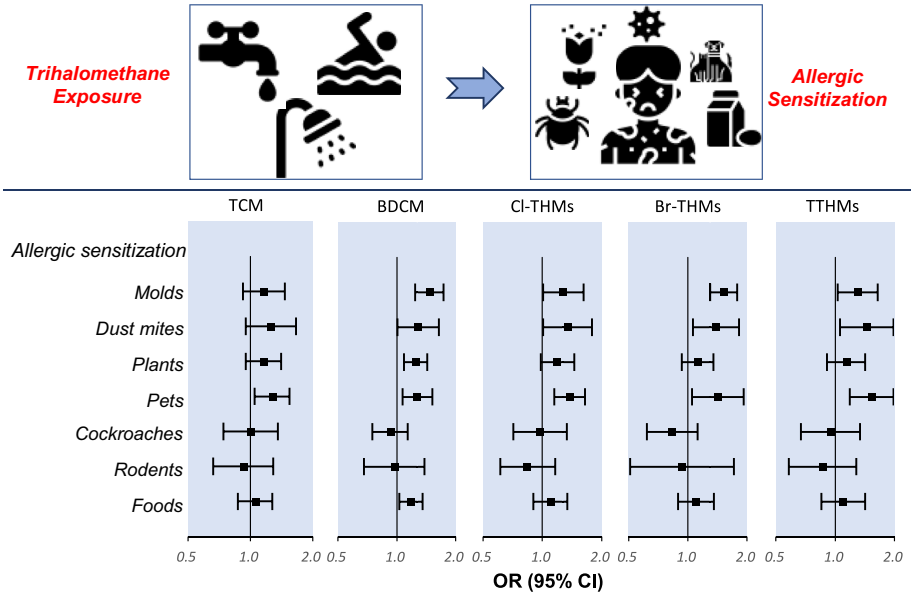
HIGHLIGHTS

- We included 932 U.S. adolescents and 2187 adults from NHANES 2005–2006.
- The associations of blood THMs with19 IgE allergen-specific antibodies were assessed.
- THMs were related to mold, dust mite, plant, pet, and food sensitization in adolescents.
- These associations were partly independent of current allergic symptoms.
- Reducing THM exposure may be helpful for preventing allergic diseases.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Exposure to disinfection by-products has been associated with several allergic diseases, but its association with allergen-specific immunoglobulin E (IgE) antibodies remains inconclusive.
Methods: We included 932 U.S. adolescents and 2187 adults from the National Health and Nutrition Examination Survey 2005–2006 who had quantified blood THM concentrations [chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM)] and 19 allergen-specific IgE antibodies. The odds ratios

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NHANES
Water pollution

(ORs) of allergen-specific sensitization per 2.7-fold increment in blood THM concentrations were estimated by multivariable logistic regression models.
Results: Blood THM concentrations were unrelated to any allergen-specific sensitization in adults. Among adolescents, however, we found positive associations between blood TCM and chlorinated THMs (Cl-THMs: sum of TCM, BDCM, and DBCM) concentrations and the odds of pet sensitization [OR = 1.28 (95 % CI: 1.05, 1.55) and 1.38 (1.15, 1.65), respectively, per each 2.7-fold increment], between blood BDCM concentrations and the odds of mold [OR = 1.47 (1.24, 1.74)], plant [OR = 1.25 (1.09, 1.43)], pet [OR = 1.27 (1.07, 1.52)], and food sensitization [OR = 1.18 (1.03, 1.36)], and between blood brominated THM (Br-THMs: sum of BDCM, DBCM, and TBM) and total THM (TTHMs: sum of 4 THMs) concentrations and the odds of mold [OR = 1.52 (1.30 1.78) and 1.30 (1.03, 1.65), respectively], dust mite [OR = 1.39 (1.06, 1.82) and 1.45 (1.06, 1.98), respectively], and pet sensitization [OR = 1.42 (1.05, 1.92) and 1.54 (1.19, 1.98), respectively].
Conclusion: Higher blood concentrations of THMs were associated with a greater risk of allergic sensitization among U.S. adolescents but not in adults.

1. Introduction

Allergic diseases such as asthma, allergic rhinitis, and eczema are among the most common chronic ill-health conditions (Kay, 2001a; Kay, 2001b). These diseases have dramatically increased in prevalence over the past decades (Krishna et al., 2020; Platts-Mills, 2015), which adds a considerable burden to health care costs. The International Study of Asthma and Allergies (ISAAC), a multicountry cross-sectional survey, also showed global changes in the prevalence of asthma, rhinoconjunctivitis, and eczema among 498,083 children between 2002–03 and 1992–98, with increases being more common than decreases (Asher et al., 2006). Meanwhile, the ISAAC demonstrated highly varying prevalences of these allergic diseases between regions, countries, and centers in the same country among nearly 1.2 million children from 233 centers in 98 countries (Mallol et al., 2013). The increasing prevalence over a relatively short period coupled with the evidence of geospatial variability in estimates points to a key role of local environmental factors (Murrison et al., 2019; Burbank et al., 2017). Therefore, identifying modifiable risk factors such as local environmental pollutants is urgently needed to improve prevention strategies.

Disinfection by-products (DBPs) are a group of pollutants formed when disinfectants (e.g., chlorine and chlorine dioxide) react with natural organic materials in raw water (Sun et al., 2020). DBPs are a complex mixture of hundreds of chemicals, among which trihalomethanes (THMs) are the most abundant species. All humans are virtually exposed to DBPs in daily water-use activities (e.g., drinking and showering). Evidence has emerged that DBPs are positively associated with allergic diseases among children and adults, including asthma, allergic rhinitis, and dermal symptoms (e.g., eczema, rash, and generalized itching) (Couto et al., 2021; Sun et al., 2022; Kanikowska et al., 2018). Several studies conducted among school-aged adolescents have also reported an association between chlorinated swimming pool attendance and aeroallergen-specific immunoglobulin E (IgE) antibodies in serum (Bernard et al., 2008; Voisin et al., 2014; Jacobs et al., 2012), which is the cornerstones of the diagnostic evaluation in suspected allergic diseases (Bernstein et al., 2008; Ansotegui et al., 2020). To date, only one study has comprehensively explored the associations between DBP exposure and allergen-specific IgE among 853 adolescents from the National Health and Nutrition Examination Surveys (NHANES) 2005–2006 when data on serum 19 allergen-specific IgEs were determined (Min et al., 2016). In this study, THM concentrations in tap water were associated with a greater risk of sensitization to house dust mite allergen. However, the use of tap-water monitoring data is prone to exposure misclassification bias because it ignores spatial and temporal variability of tap-water THM concentrations and within- and between-person differences in water-use activities and THM metabolism (Grellier et al., 2015). Blood THM concentrations represent more integrative measures from multiple exposure routes and sources, which are sensitive to low levels of exposure and are believed to reflect steady-state exposure due to frequent daily water-use activities and slow partitioning out of adipose tissues (Blount et al., 2011a). Additionally, no study has explored the association of THM exposure with allergen-specific IgE among adults, whose immune system may differ from adolescents. Therefore, we comprehensively investigated whether THM concentrations in blood were associated with 19 allergen-specific IgE antibodies in serum in a nationwide sample of United States (U.S.) adolescents and adults from NHANES 2005–2006.

2. Methods

2.1. Study population

NHANES is a nationwide cross-sectional survey designed to assess the health and nutritional status of the non-institutional U.S. population in 2-year increments (NCHS, 2017). We included participants from the NHANES 2005–2006 survey because serum IgE was only determined in this survey cycle (Salo et al., 2014). We further limited eligibility to a randomly sampled one-half of the participants aged 12 years and over who were qualified for the measurement of blood concentrations of volatile organic chemicals, including THMs. In the present analysis, we included 932 adolescents (ages 12–19 years) and 2187 adults (ages ≥ 20 years) with measurements of at least one specific blood THMs. NHANES has been approved by the research ethics review board of the National Center for Health Statistics and all participants have provided informed consent (NCHS, 2020).

2.2. Blood THM measurements

Procedures of peripheral blood sampling, storing, determination, and quality control (QC) have been described in detail in our previous studies (Sun et al., 2021a; Sun et al., 2021b). Briefly, whole blood samples were collected by venipuncture in THM-free glass vacutainers containing potassium oxalate and sodium fluoride. Because THMs are highly volatile, all samples were kept at 4 °C during storage and shipment and were analyzed within 2 to 3 weeks of collection. Blood concentrations of chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM) were measured by solid-phase microextraction gas chromatography and mass spectrometry. Values lower than the limit of detection (LOD) were replaced with LOD/√2 (NCHS, 2011). We calculated blood concentrations of chlorinated THMs (Cl-THMs) by summing the concentrations of TCM, BDCM, and DBCM; brominated THMs (Br-THMs) by summing the concentrations of BDCM, DBCM, and TBM; and total THMs (TTHMs) by summing the concentrations of all 4 THMs (Sun et al., 2021a).

2.3. Definition of allergic sensitization and allergic symptom

Procedures of specimen collection, storage, and determination for 19 specific IgE allergens in serum have been described in detail on the NHANES website (NCHS, 2006). Briefly, the specific allergen of interest, covalently coupled to ImmunoCap cellulose carrier, reacted with the specific IgE in serum samples. After washing and incubating with a developing agent, the resulting fluorescence was measured using the Pharmacia

Diagnostics ImmunoCAP 1000 System (Kalamazoo, Michigan). The NHANES implemented a comprehensive data QC program, including blind QC, bench QC, and external QC, to warrant the accuracy, precision, and trueness of laboratory determinations (NCHS, 2006). The reportable range for undiluted samples ranged from <0.35 to 100 kU/L. To avoid the similarities in biological and statistical properties of 19 specific allergens (Min and Min, 2015a; Min and Min, 2015b), we classified them into the following 7 categories: a) molds (*Alternaria* and *Aspergillus*); b) dust mites (*D. farinae* and *D. pteronyssinus*); c) plants (ragweed, ryegrass, Bermuda grass, white oak, birch, and Russian thistle); d) pets (dog and cat); e) cockroach; f) rodents (mouse and rat); and g) foods (egg, milk, peanut, and shrimp). Sensitization to an allergen category was defined as having at least one specific IgE concentration equal to or higher than 0.35 kU/L within the category. Information on allergic symptoms was obtained from household interviews. Participants who reported any episodes of hay fever, rhinitis, allergy, and itchy rash in the past 12 months were identified as having current allergic symptoms.

2.4. Covariates

Demographic information, lifestyle factors, and water-use activities were collected through standardized questionnaires (Sun et al., 2021b). Family income was classified as the ratio of family income to the poverty line. We calculated the total hours of self-reported moderate-to-vigorous intensity activities during leisure time (Armstrong et al., 2018). Participants who engaged in <7 h per week of moderate-to-vigorous intensity activity were considered to be physically inactive (CDC, 2021a). Height and weight were measured by trained staff and used to calculate body mass index (BMI) for adults (overweight/obesity was defined as ≥ 25 kg/m^2). For adolescents, we calculated the age- and sex-specific BMI Z-scores according to growth charts for U.S. children (CDC, 2019); we defined overweight or obesity as BMI $\geq$ 85th percentile of the reference population (CDC, 2019; CDC, 2021b). Serum cotinine was measured to determine nicotine concentrations (CDC, 2008). Participants who consumed tobacco or nicotine products in the past 5 days or had serum cotinine concentrations >10 ng/mL were considered exposed to tobacco smoke (Sun et al., 2022). Dietary data were obtained from two 24-hour dietary recall interviews, which were used to calculate the total Healthy Eating Index (HEI–2015) score to reflect participants' overall dietary quality (Shan et al., 2019).

2.5. Statistical analysis

All analyses accounted for complex, multistage sampling survey designs to achieve nationally representative estimates, using the PROC SURVEY procedure with SAS version 9.4 (SAS Institute Inc., Cary, NC). We conducted all statistical analyses separately for adolescents and adults because of differences in covariate structure and outcome prevalence. Descriptive statistics were performed to obtain participant demographic characteristics, lifestyle factors, water-use activities, allergic sensitization prevalence, and the distribution of blood THM concentrations. DBCM and TBM were not included in subsequent analyses because of low detection rates (both < 50 %) (Sun et al., 2022). We used logistic regression models to assess the odds ratios (ORs) and 95 % confidence intervals (CIs) for the associations of blood TCM, BDCM, Cl-THM, Br-THM, and TTHM concentrations with 7 allergen-specific sensitizations. Covariates were selected a priori based on previous NHANES findings (Min et al., 2016), which included age, sex, race/ethnicity, BMI or BMI Z-scores, family income-poverty ratio, serum cotinine concentrations, leisure-time physical activity level, swimming pool/hot tub/steam room use within 3 days, and HEI-2015 score. Missing data (n < 5 %) on BMI, income-poverty ratio, HEI-2015 score, and physical activity were imputed with median values. To address the multiple testing issue, we applied the false discovery rate (FDR)-based multiple comparison procedures to adjust for original *p*-values (Benjamini and Hochberg, 2000).

To explore whether our findings were related to self-reported allergic symptoms, we expanded our logistic regression models for allergen-specific sensitizations to four-strata multinomial models (no sensitization and no symptom, symptom only, sensitization only, and both sensitization and symptom). A *p*-value for the OR difference across the four strata was calculated by a contrast statement in multinomial models (Hoppin et al., 2013). Stratified analyses were conducted to assess the effect modification by tobacco smoke exposure (yes vs. no), BMI (underweight or normal weight vs. overweight or obese), physical activity (moderate-to-vigorous intensity activities < 7 vs. ≥7 h/week), and HEI-2015 score (≤50th vs. >50th). Multiplicative statistical interaction was tested by conducting likelihood ratio tests (Sun et al., 2022). To simplify the interpretation of the findings, we examined the influence of self-reported allergic symptoms and effect modification only for blood TTHMs concentrations in relation to allergic sensitization that was statistically significant after FDR adjustment.

To reduce the influence of peak exposures, we a) excluded participants who used swimming pools, hot tubs, or steam rooms within 3 days (42 adolescents and 77 adults), and b) additionally adjusted for the time interval since the last shower or bath, the timing of examination session, and sampling season in the multivariable models.

3. Results

The mean (95 % CI) age of 932 adolescents and 2187 adults were 15.4 (15.2, 15.6) and 46.8 (45.2, 48.5) years, respectively (Table 1). There were approximately equal proportions of males and females, and the majority of subjects were non-Hispanic Whites (63.2 % for adolescents and 71.6 % for adults) and nonsmokers (75.7 % for adolescents and 69.3 % for adults). Only 42 (8.1 %) adolescents and 77 (5.1 %) adults reported that they spent time in a swimming pool, hot tub, or steam room within 3 days. Up to 15.3 % (154) adolescents and 10.4 % (241) adults were sensitized to molds, 27.7 % (285) and 20.5 % (485) to dust mites, 33.4 % (324) and 27.9 % (621) to plants, 20.1 % (179) and 14.9 % (324) to pets, 13.9 % (170) and 10.5 % (302) to cockroaches, 1.0 % (20) and 1.8 % (42) to rodents, and 22.4 % (224) and 14.8 % (368) to foods.

The detection rates of TCM and BDCM were >70 % both in adolescents and adults (Table 2). The median blood concentrations of TCM, BDCM, DBCM, TBM, Cl-THMs, Br-THMs, and TTHMs among adolescents were 9.0, 0.99, 0.44, 0.71, 12.2, 2.3, and 13.3 pg/mL, respectively, which were similar to that of adults (10.0, 1.3, 0.44, 0.71, 13.5, 2.9, and 14.9 pg/mL, respectively).

The results of the associations between blood THM concentrations and risk of allergic sensitization were largely similar in the crude and adjusted logistic regression models (Fig. 1 and Table S1). In the adjusted models, we found positive associations between blood TCM and Cl-THM concentrations and the odds of pet sensitization [OR = 1.28 (95 % CI: 1.05, 1.55) and 1.38 (1.15, 1.65), respectively, per each 2.7-fold increment], between blood BDCM concentrations and the odds of mold [OR = 1.47 (1.24, 1.74)], plant [OR = 1.25 (1.09, 1.43)], pet [OR = 1.27 (1.07, 1.52)], and food sensitization [OR = 1.18 (1.03, 1.36)], and between blood Br-THM and TTHM concentrations and the odds of mold [OR = 1.52 (1.30 1.78) and 1.30 (1.03, 1.65), respectively], dust mite [OR = 1.39 (1.06, 1.82) and 1.45 (1.06, 1.98), respectively], and pet sensitization [OR = 1.42 (1.05, 1.92) and 1.54 (1.19, 1.98), respectively] (all FDR-adjusted *p* values < 0.05) (Fig. 1).

The results from multinomial logistic regression models of associations between TTHM concentrations and mold, dust mite, and pet sensitization suggest differences in the OR of sensitization among adolescents with and without allergic symptoms (all p for difference < 0.05). Adolescents with allergic symptoms were more likely to have dust sensitization associated with blood TTHM concentrations (Table 3). However, the highest risk of mold and pet sensitization in relation to blood TTHM concentrations was found among adolescents who had allergic sensitization alone (Table 3). The associations of blood TTHM concentrations with dust mite and pet sensitization were not modified by tobacco smoke exposure, BMI, physical activity, and dietary quality (Fig. 2). However, we found a slightly stronger association between blood TTHM concentrations and mold sensitization among adolescents who had tobacco smoke exposure and a less healthy diet (Fig. 2).

Table 1
Characteristics of study participants in NHANES 2005–2006.[a]

Characteristic	Mean (95 % CI) or N (%)	
	Adolescents (n = 932)[c]	Adults (n = 2187)[d]
Age (years)	15.4 (15.2, 15.6)	46.8 (45.2, 48.5)
BMI[b]	0.61 (0.52, 0.71)	28.5 (28.0, 29.0)
Sex		
Male	452 (52.6)	1033 (48.5)
Female	480 (47.4)	1154 (51.5)
Race/ethnicity		
Non-Hispanic White	227 (63.2)	1078 (71.6)
Non-Hispanic Black	321 (14.9)	495 (11.1)
Mexican American	316 (11.8)	451 (8.0)
Other	68 (10.1)	163 (9.3)
Family income-poverty ratio		
0–1.0	309 (21.5)	375 (10.8)
1.1–3.0	336 (36.7)	847 (36.0)
>3.0	245 (41.8)	877 (53.2)
Serum cotinine (ng/mL)		
Nonsmoking (<1.0)	687 (75.7)	1528 (69.3)
Environmental tobacco smoke exposure (1.0–9.9)	115 (10.6)	97 (3.6)
Active smoking (≥10)	127 (13.7)	562 (27.1)
Swimming pool/hot tub/steam room use within 3 days		
Yes	42 (8.1)	77 (5.1)
No	890 (91.9)	2110 (94.9)
Examination session		
Morning	460 (48.0)	1054 (47.3)
Afternoon	305 (33.2)	795 (34.8)
Evening	167 (18.8)	338 (17.9)
Time interval since the last shower or bath (h)		
≤2	93 (10.1)	231 (12.3)
3–6	220 (22.9)	701 (34.0)
7–14	280 (28.2)	552 (24.6)
>14	339 (38.8)	703 (29.1)
Sampling season		
November 1 through April 30	508 (44.2)	980 (40.4)
May 1 through October 31	424 (55.8)	1207 (59.6)
Total Healthy Eating Index-2015 score	45.3 (44.1, 46.4)	52.5 (51.5, 53.5)
Leisure-time physical activity level (hours per week)		
<3	388 (37.1)	1522 (65.3)
3–7	191 (23.8)	351 (18.6)
>7	331 (39.1)	314 (16.1)
Specific allergic sensitization prevalence		
Molds (Alternaria and Aspergillus)	154 (15.3)	241 (10.4)
Dust mites (D. farinae and D. pteronyssinus)	285 (27.7)	485 (20.5)
Plants (ragweed, ryegrass, Bermuda grass, white oak, birch, and Russian thistle)	324 (33.4)	621 (27.9)
Pets (dog and cat)	179 (20.1)	324 (14.9)
Cockroaches	170 (13.9)	302 (10.5)
Rodents (mouse and rat)	20 (1.0)	42 (1.8)
Foods (egg, milk, peanut, and shrimp)	224 (22.4)	368 (14.8)

[a] All estimates were accounted for complex survey designs.
[b] Adolescent BMI is expressed as age- and sex-specific BMI Z-score.
[c] 6, 42, 38, and 22 adolescents had missing information on BMI z – score, family income-poverty ratio, total Healthy Eating Index-2015 score, and leisure-time physical activity level, respectively.
[d] 28, 88, and 96 adults had missing information on BMI, family income-poverty ratio, and total Healthy Eating Index-2015 score, respectively.

We did not find any evidence of associations between blood THM concentrations and any allergic sensitization among adults (Fig. 1 and Table S1). Therefore, we did not further examine the influence of self-reported allergic symptoms and effect modification by lifestyle factors among adults. Sensitivity analyses showed similar associations between blood THM concentrations and allergen-specific sensitization when we excluded participants who used swimming pools, hot tubs, or steam rooms within 3 days (Table S2) and when we additionally adjusted for covariates related to DBP exposure (e.g., sampling time and season) in the multivariable models (Table S3).

Table 2
Distribution of blood THM concentrations (pg/mL) of study participants in NHANES 2005–2006.

Characteristic	n	Detection rate (%)	GM	25th	50th	75th	95th
Adolescents (n = 932)							
TCM (pg/mL)	906	94.7	9.2	4.8	9.0	17.0	46.0
BDCM (pg/mL)	925	71.5	1.2	0.44	0.99	2.8	8.0
DBCM (pg/mL)	918	48.6	0.83	0.44	0.44	1.3	6.5
TBM (pg/mL)	885	32.7	1.0	0.71	0.71	1.2	4.8
Cl-THMS (pg/mL)	886	NA	12.4	6.1	12.2	23.0	59.0
Br-THMs (pg/mL)	865	NA	3.3	1.6	2.3	5.1	18.2
TTHMs (pg/mL)	839	NA	13.9	7.2	13.3	25.1	68.8
Adults (n = 2187)							
TCM (pg/mL)	2156	94.9	10.3	5.2	10.0	19.0	53.7
BDCM (pg/mL)	2165	71.8	1.5	0.44	1.3	3.1	10.0
DBCM (pg/mL)	2155	48.1	0.88	0.44	0.44	1.4	7.9
TBM (pg/mL)	2083	31.8	1.0	0.71	0.71	1.2	5.2
Cl-THMs (pg/mL)	2102	NA	13.7	7.0	13.5	25.9	64.7
Br-THMs (pg/mL)	2029	NA	3.7	1.6	2.9	6.1	23.0
TTHMs (pg/mL)	1998	NA	15.5	8.1	14.9	28.8	68.2

Abbreviations: THMs, trihalomethanes; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Br-THMs, the sum of BDCM, DBCM, and TBM; Cl-THMs, the sum of TCM, BDCM, and DBCM; TTHMs, the sum of TCM and Br-THMs; GM, geometric mean; NA, not applicable.

4. Discussion

Among a nationally representative sample of the U.S. population, blood THM concentrations were unrelated to allergen-specific sensitization among 2187 adults. Among 932 U.S. adolescents, however, positive associations were observed between blood TCM and Cl-THM concentrations and pet sensitization, between blood BDCM concentrations and mold, plant, pet, and food sensitization, and between blood Br-THM and TTHM concentrations and mold, dust mite, and pet sensitization. These associations were partly independent of current allergic symptoms and appeared to be stronger among adolescents who smoked or had a low-quality diet.

The mechanisms underlying the associations observed among adolescents are poorly known, but could partly be related to the cytotoxicity of THMs. Allergic sensitization occurs when allergens cross epithelial barriers of airways, the skin, and the gastrointestinal tract react with antigen-presenting cells and, thus, tight junctions occluding the paracellular routes play a critical role in preventing the penetration of ingested or inhaled allergens (Bernard, 2007). Exposure to THMs has been shown to induce airway inflammatory and oxidative response, epithelial hyperpermeability, and susceptibility to respiratory bacterial infection in mice (de Oliveira et al., 2015; Selgrade and Gilmour, 2010), which may facilitate the transepithelial passage of allergens. In population studies, swimming pool attendance has been positively associated with airway inflammation (Cavaleiro Rufo et al., 2018; Kotsiou et al., 2019), oxidative stress (Varraso et al., 2002), hyperpermeabilities of the lung epithelium (Font-Ribera et al., 2010), smooth muscle constriction (Cavaleiro Rufo et al., 2018), and perturbations of the immune system (Vlaanderen et al., 2017). Moreover, Font-Ribera and colleagues reported a positive association between DBCM concentrations in exhaled breath after swimming and serum marker of lung epithelium permeability and epithelial barrier integrity (i.e., Clara cell protein) in 48 healthy adult volunteers (Font-Ribera et al., 2010).

Our findings of positive associations between blood BDCM, Br-THM, and TTHM concentrations and dust mite sensitization support previous population evidence showing that chlorinated swimming pool attendance during infancy or early childhood is positively associated with house dust mite sensitization among adolescents (Bernard et al., 2008; Voisin et al., 2014; Jacobs et al., 2012). Our results are also consistent with the findings in an earlier NHANES analysis reporting a positive association between tap-water THM concentrations and the risk of sensitization to house dust mite allergen (Min et al., 2016). However, we also found positive associations

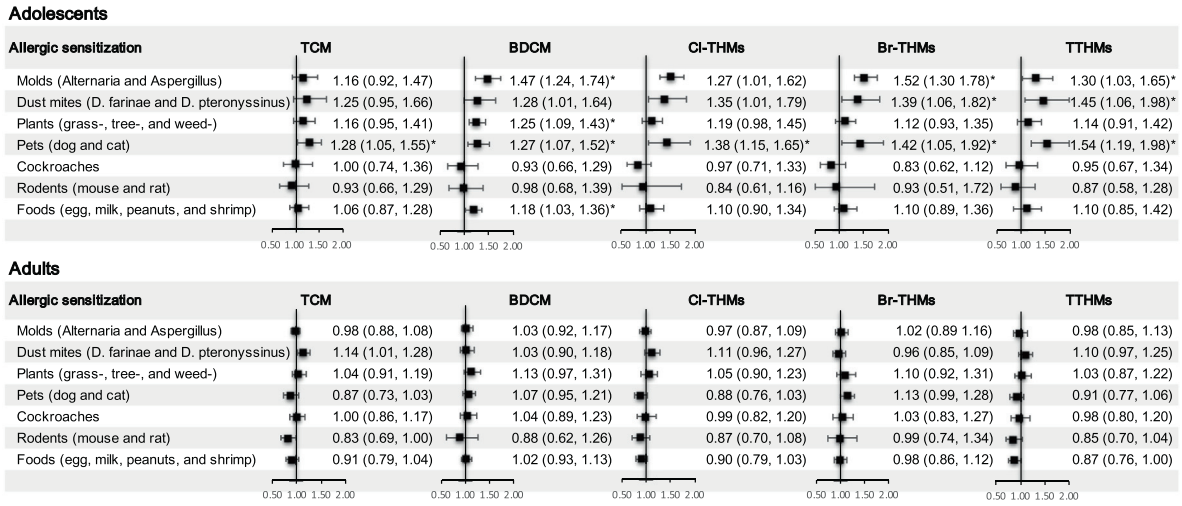

Fig. 1. Adjusted odds ratios (OR) and 95 % confidence intervals (95 % CI) for allergen-specific sensitization in relation to blood THM concentrations (pg/mL) among 932 adolescents aged 12–19 years and 2187 adults aged 20 years and over in NHANES 2005–2006.
Abbreviations: THM, trihalomethane; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Cl-THMs, the sum of TCM, BDCM, and DBCM; Br-THMs, the sum of BDCM, DBCM, and TBM; TTHMs, the sum of TCM and Br-THMs.
All models adjusted for age (continuous, years), sex (male vs. female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican American, and other), BMI or BMI z-scores (continuous), family income-poverty ratio (0–1.0, 1.1–3.0, or >3.0), serum cotinine concentrations (<1, 1–9.9, ≥10 ng/mL), leisure-time physical activity level (moderate-to-vigorous intensity activities < 3, 3–7, or >7 h per week), swimming pool/hot tub/steam room use within 3 days (yes vs. no), and HEI-2015 score (continuous). THMs were ln-transformed in models.
*FDR-adjusted *p*-value < 0.05.

between blood THM concentrations and mold, plant, pet, and food sensitization. The difference in exposure estimation of study participants may partly explain the discrepancy between studies. One key methodological issue of this previous NHANES study is the use of tap-water THM concentrations, which may have resulted in considerable exposure misclassification because such a method has a poor resolution of spatial and temporal variability of tap-water THM concentrations and ignores within- and between-person differences in water-use activities and physiological traits that can affect the absorption, distribution, and metabolism of THMs (Grellier et al., 2015).

Our study refines and extends previous evidence. We found that adolescents with allergic symptoms were more likely to have dust sensitization associated with blood TTHM concentrations, suggesting an interplay of dust sensitization and allergic symptoms in response to TTHMs. The highest risk of mold and pet sensitization in relation to blood TTHM concentrations, however, was found among adolescents who had allergic sensitization alone, suggesting that these associations were independent of allergic symptoms. Additionally, we found a stronger association between blood TTHM concentrations and mold sensitization among adolescents who had tobacco smoke and a less healthy diet, which is biologically plausible

Table 3
Odds ratios (OR) and 95 % confidence intervals (95 % CI) for mold, dust mite, and pet sensitization in relation to blood TTHM concentrations (pg/mL), stratified by allergic symptoms among 839 adolescents aged 12–19 years in NHANES 2005–2006.[a]

Outcome	n	Crude model		Adjusted model[†]	
		OR (95 % CI)	$p_{difference}$[b]	OR (95 % CI)	$p_{difference}$[b]
Molds (Alternaria and Aspergillus)					
No sensitization and no symptom	503	1.00	0.07	1.00	0.02
Symptom only	199	0.99 (0.77, 1.27)		1.01 (0.78, 1.30)	
Sensitization only	64	1.30 (0.99, 1.72)		1.37 (1.02, 1.83)*	
Both sensitization and symptom	73	1.20 (0.82, 1.75)		1.29 (0.89, 1.87)	
Dust mites (D. farinae and D. pteronyssinus)					
No sensitization and no symptom	426	1.00	0.02	1.00	0.03
Symptom only	157	0.94 (0.75, 1.18)		0.95 (0.75, 1.20)	
Sensitization only	141	1.46 (0.97, 2.19)		1.40 (0.87, 2.24)	
Both sensitization and symptom	115	1.40 (0.99, 1.99)		1.46 (1.03, 2.08)*	
Pets (dog and cat)					
No sensitization and no symptom	496	1.00	<0.001	1.00	<0.001
Symptom only	180	1.08 (0.80, 1.46)		1.11 (0.82, 1.49)	
Sensitization only	71	2.20 (1.68, 2.87)**		2.27 (1.67, 3.07)**	
Both sensitization and symptom	92	1.21 (0.92, 1.60)		1.30 (0.94, 1.81)	

Abbreviations: TTHM, total trihalomethane.
[a] All models adjusted for age (continuous, years), sex (male vs. female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican American, and other), BMI or BMI z-scores (continuous), family income-poverty ratio (0–1.0, 1.1–3.0, or >3.0), serum cotinine concentrations (< 1, 1–9.9, ≥10 ng/mL), leisure-time physical activity level (moderate-to-vigorous intensity activities < 3, 3–7, or >7 h per week), swimming pool/hot tub/steam room use within 3 days (yes vs. no), and HEI-2015 score (continuous). TTHMs were ln-transformed.
[b] *p*-Value for the difference of ORs was calculated by contrast statement in Multinomial Logistic Regression Model.
* $p < 0.05$.
** $p < 0.01$.

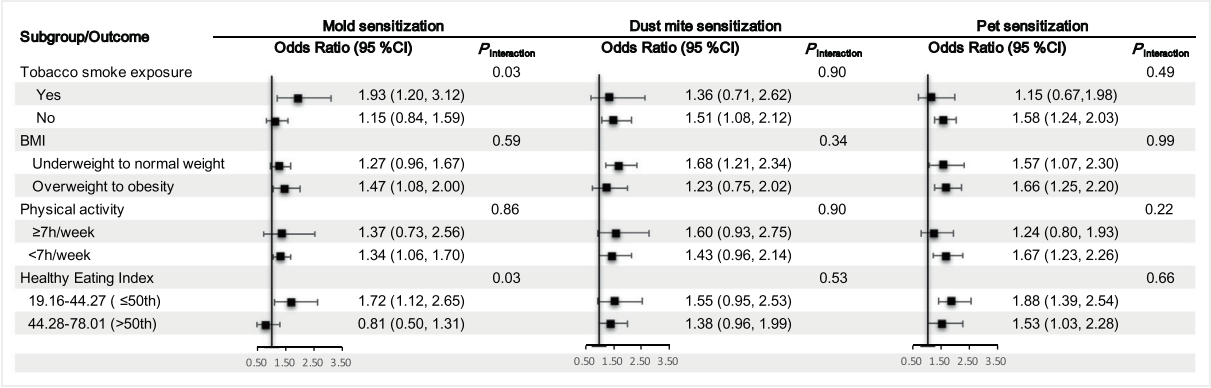

Fig. 2. Odds ratios (OR) and 95 % confidence intervals (95 % CI) for mold, dust mite, and pet sensitization in relation to blood TTHM concentrations (pg/mL), stratified by subgroups among 839 adolescents aged 12–19 years in NHANES 2005–2006. Abbreviations: TTHM, total trihalomethanes. All models adjusted for age (continuous, years), sex (male vs. female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican American, and other), BMI or BMI z-scores (continuous), family income-poverty ratio (0–1.0, 1.1–3.0, or >3.0), serum cotinine concentrations (<1, 1–9.9, ≥10 ng/mL), leisure-time physical activity level (moderate-to-vigorous intensity activities < 3, 3–7, or >7 h per week), swimming pool/hot tub/steam room use within 3 days (yes vs. no), and HEI-2015 score (continuous), except for the stratified variables. TTHMs were ln-transformed.

given that smoking and an unhealthy diet could compromise the epithelial barriers of the respiratory tract and gastrointestinal tract, respectively (Aghapour et al., 2018; Rohr et al., 2020), which may facilitate the penetration of allergens. Finally, our study is the first to investigate the associations between DBP exposure and allergic sensitization among adults. Inconsistent with the findings among adolescents, blood THM concentrations were unrelated to allergen-specific sensitization among adults. This is not surprising because young adolescents are generally more susceptible to inhalant or ingested allergens due to their immature respiratory and digestive systems. A lack of associations among adults may also reflect age-related changes in the immune system (Mediaty and Neuber, 2005). In support of this notion, the prevalence of sensitization and IgE levels were lower in adults than adolescents in our present study population (Salo et al., 2014).

The key strengths of our present study include a large nationwide sample of general adolescents and adults, the quantitative evaluation of 19 IgE-mediated sensitizations following strict quality protocols, and detailed data on various key variables related to water-use activities and allergic symptoms. Besides, we used blood THM concentrations as exposure markers, which reflect integrative measures of exposure from all routes and, thus, can more accurately assess exposure status. While exposure misclassification cannot be fully ruled out due to the measurements of blood THM concentrations at a single time point (Wang et al., 2019), they are believed to reflect steady-state exposure (Blount et al., 2011b). Our results were robust in a series of sensitivity analyses assessing the influence of peak exposures. Our study also has certain limitations. First, as with any other cross-sectional observational study, we cannot rule out reverse causality issues. Second, our findings may also be influenced by unmeasured or uncontrolled covariates (e.g., xenometabolic genotypes) and coexposure to other types of DBPs (e.g., haloacetic acids, and nitrogen- and bromine-DBPs), although we have accounted for the most important known confounders and effect modifiers (Wang et al., 2019; Ashley et al., 2020). Third, while NHANES tested for a large number of allergens, some participants may have been sensitized to other less common allergens.

5. Conclusions

The results from this large nationwide cross-sectional analysis showed that blood THM concentrations were unrelated to any allergen-specific IgE in serum among adults. However, we found that blood THM concentrations were positively associated with the odds of mold, dust mite, plant, pet, and food sensitization among adolescents. Our novel findings strengthen the evidence of potential associations between THM exposure and allergic diseases and highlight the importance of reducing THM exposure in preventing allergic diseases. The United States Environmental Protection Agency revised regulations on DBPs in 1998 to further restrict THM levels in household water. As such, a dramatic decline in blood and tap-water concentrations of THMs has been reported from biennial NHANES data between 2001 and 2012 (Ashley et al., 2020). However, more efforts are needed to maintain THM levels as low as practical to meet the World Health Organization's Guidelines for drinking-water quality (WHO G, 2011). Meanwhile, it is prudent for adolescents with allergic sensitization to be further protected from THM exposure by spending less time in water-use activities such as bathing, showering, swimming, and sauna use. These activities are strongly associated with higher blood THM concentrations in the NHANES population (Ashley et al., 2020).

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CRediT authorship contribution statement

Yang Sun: Conceptualization, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Yi-Xin Wang:** Conceptualization, Funding acquisition, Investigation, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Vicente Mustieles:** Investigation, Writing – review & editing. **Zhilei Shan:** Investigation, Writing – review & editing. **Yu Zhang:** Investigation, Writing – review & editing. **Carmen Messerlian:** Conceptualization, Funding acquisition, Investigation, Supervision, Writing – review & editing.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Carmen Messerlian reports financial support was provided by National Institutes of Health. Yi-Xin Wang reports financial support was provided by National Natural Science Foundation of China.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.162100.

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