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Association between exposure to brominated flame retardants (BFRs) and blood lipid profiles in American adults: a cross-sectional study

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Abstract

Background Exposure to brominated flame retardants (BFRs) has been linked to alterations in human metabolism and disease processes. However, the relationship between BFR exposure and blood lipid levels remains unclear. This study aimed to investigate the potential association between BFR exposure and blood lipid profiles in American adults.

Methods A cross-sectional study was conducted using data from the National Health and Nutrition Examination Survey (NHANES) 2005–2016. Serum concentrations of twelve BFRs, PBB153 and eleven polybrominated diphenyl ethers (PBDEs), were quantified using isotope dilution gas chromatography/high-resolution mass spectrometry (GC/HRMS). Blood lipid levels, including total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) were measured enzymatically. The Friedewald equation was used to determine low-density lipoprotein cholesterol (LDL-C): [LDL-C] = [TC] – [HDL-C] – [TG/5]. Remnant cholesterol (RC) was calculated using the formula: [RC] = [TC] – [HDL-C] – [LDL-C]. Multivariable regression analyses were applied to examine the associations between individual BFRs and TC, HDL-C, LDL-C, and RC. The overall associations of BFR mixtures with blood lipids were evaluated using quantile g-computation (QGC) analyses and weighted quantile sum (WQS) regression. In order to identify potential gender-specific differences, stratified mixture analyses were performed by gender.

Results A total of 3,154 eligible participants were included. Nine BFRs with a detection rate greater than 70% were included in the analysis. Individually, PBB153, PBDE209, PBDE153, and PBDE28 were positively associated with TC and RC after adjusted all covariates. Furthermore, PBB153, PBDE209, and PBDE153 were positively associated with LDL-C. No association was found between individual BFR and HDL-C. WQS and QGC analyses confirmed that BFR mixtures were positively associated with TC, LDL-C, and RC.

Conclusion This study demonstrates that BFR exposure is associated with increased levels of TC, LDL-C, and RC, indicating an elevated risk of dyslipidemia and cardiovascular diseases.

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Introduction

Dyslipidemia has a substantial financial impact worldwide and is a risk factor for atherosclerotic cardiovascular disease (ASCVD), the world's leading cause of death [1, 2]. High-density lipoprotein (HDL), the smallest lipoprotein in circulation, consists of proteins and lipids organized into distinct subspecies. It contains a hydrophobic core of neutral lipids surrounded by a monolayer of amphipathic lipids, and serves various physiological functions [3, 4]. Numerous studies conducted over the decades have consistently shown an inverse relationship between high-density lipoprotein cholesterol (HDL-C) levels and the risk of coronary heart disease (CHD) [5–7]. Additionally, low HDL-C levels linked to a range of non-cardiovascular conditions, including cancer, infectious diseases, and autoimmune disorders [8–10]. Conversely, it is well-established that reducing low-density lipoprotein cholesterol (LDL-C) levels lowers the incidence of CHD, with elevated LDL-C recognized as an independent risk factor for CHD [11].

Remnant cholesterol (RC) is an emerging lipoprotein marker that has shown promise in predicting the risk of ischemic stroke, ASCVD, and mortality [12–14]. RC is composed of triglyceride-rich lipoproteins, including chylomicron remnants, intermediate-density lipoprotein cholesterol (IDL-C), and very low-density lipoprotein cholesterol (VLDL-C). It can be computed by deducting LDL-C and HDL-C from total cholesterol (TC) using lipid profile data [15, 16]. A nationwide cohort study revealed that individuals with RC levels of 27.7 mg/dL or higher had increased hazard ratios (HRs) for all-cause mortality (HR = 1.03), ischemic stroke mortality (HR = 1.22), ischemic heart disease mortality (HR = 1.19), and cardiovascular disease mortality (HR = 1.17) compared to those with RC levels below 17.9 mg/dL [17].

Over recent decades, the widespread use of chemical flame retardants has played a key role in reducing fire-related incidents [18]. There are many different types of flame retardants, including the inorganic flame retardants, halogenated organic, phosphorus-containing, and nitrogen-containing [19]. Brominated flame retardants (BFRs) has occupied the main position due to their superior performance and low cost [20]. While traditional BFRs like polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs) have enhanced fire safety, their environmental persistence and bioaccumulative potential have raised substantial health concerns [21–23]. Exposure to BFRs—whether through inhalation, dermal contact, or ingestion—has been linked to various adverse health outcomes [24]. Previous studies have suggested associations between BFR exposure and several negative health effects, including neurotoxicity, metabolic disorders, periodontitis, chronic kidney disease, hypertension, and osteoporosis [25–29]. Additionally, prenatal exposure to BFRs has been associated with neurodevelopmental and metabolic disturbances [30, 31].

Although studies on the health effects of BFR exposure are increasing, the relationship with lipid levels remains unclear. Some studies have found that BFR exposure may be associated with decreased lipid levels. For example, PBDE209 and other PBDE congeners were inversely associated with concentrations of TC and LDL-C in studies from areas producing BFRs in China [32]. However, some studies have reported positive correlation results, such as PBDE99, PBDE47, and PBDE28 being positively associated with TC levels in pregnant US women [33, 34]. In these studies, the study population was limited to specific populations, such as residents of areas where BFRs are produced or pregnant women. The sample sizes were also limited, which may have resulted in insufficient generalizability of the results.

Environmental pollutants usually exist as mixtures, and their combined toxicity may have synergistic or antagonistic effects [35, 36]. Interactions between environmental pollutants can have significant effects on health, so assessing the mixing effects of pollutants is essential for a comprehensive assessment of their health risks. To comprehensively examine the association between single and mixed BFR exposure and lipid levels, a cross-sectional study was conducted using data from the large, representative population of the National Health and Nutrition Examination Survey (NHANES) and systematically adjusted for multiple confounding variables, including demographic characteristics and health status, to improve the robustness of the results.

Methods

Study population

This study extracted data spanning six NHANES cycles. A total of 34,180 adult participants (≥20 years) were initially considered from the 2005 to 2016 NHANES cohorts. The following are the exclusion criteria on participants: (1) missing data on serum BFRs (N = 24,296); (2) missing data on blood lipids (N = 5,230); (3) participants taking statins within 30 days prior to the examination (including rosuvastatin, fluvastatin, atorvastatin, pitavastatin, pravastatin, lovastatin, and simvastatin, N = 826), pregnant women (N = 75), participants with cancer (N = 282), participants missing data on body mass index (BMI) (N = 39), ratio of family income to poverty (PIR) (N = 271), education level (N = 2), smoking status (N = 3), diabetes (N = 2). In conclusion, the study included 3,154 participants who met the eligibility criteria (Fig. 1).

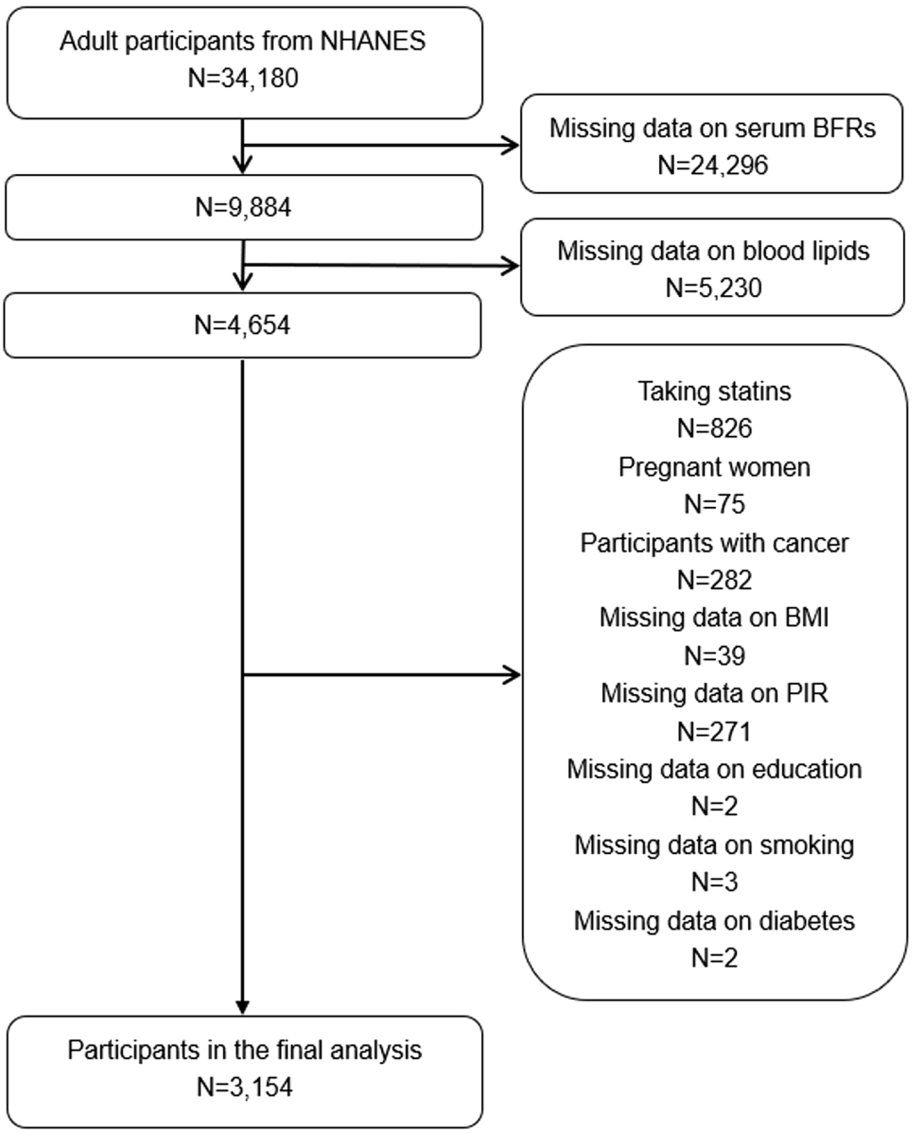

Fig. 1 Flowchart of inclusion criteria for NHANES study participants (2005–2016)

Serum brominated flame retardants

The serum BFRs were quantified using isotope dilution gas chromatography/high-resolution mass spectrometry (GC/HRMS) following the protocol outlined by Sjodin et al. [37]. Serum samples underwent automated liquid-liquid extraction and chromatographic purification to remove contaminants. Isotope-labeled internal standards were added to ensure accurate quantification. PBDEs were separated by gas chromatography and quantified using high-resolution mass spectrometry in selective ion monitoring mode. Please refer to the Supplementary file for detailed information. (Description of laboratory methodology) Although the analytical method was consistent across NHANES cycles, slight variations in the limit of detection (LOD) occurred due to updates in instrumentation and calibration. Serum BFR concentrations below the lower limit of detection (LLOD) were imputed as the LLOD value divided by the square root of 2, following NHANES guidelines. To address these differences, the highest LOD for each BFR across all cycles was used as the reference threshold. Details of the proportion of samples below the LOD across NHANES cycles are provided in supplement file. (Table S1).

In order to guarantee the precision of the analytical outcomes, only BFRs with a total detection rate higher than 70% were included in this study. PBDE183, PBDE66, and PBDE17 were excluded from further consideration due to their relatively low detection rates of 46.0%, 14.0%,

and 5.5% respectively. Ultimately, eight PBDEs including Decabromodiphenyl ether (PBDE209, LOD: 71.4%), 2, 2′, 4, 4′, 5, 6′-Hexabromodiphenyl ether (PBDE154, LOD: 76.1%), 2, 2′, 4, 4′, 5, 5′-Hexabromodiphenyl ether (PBDE153, LOD: 100%), 2, 2′, 4, 4′, 6-Pentabromodiphenyl ether (PBDE100, LOD: 100%), 2, 2′, 4, 4′, 5-Pentabromodiphenyl ether (PBDE99, LOD: 100%), 2, 2′, 3, 4, 4′-Tentabromodiphenyl ether (PBDE85, LOD: 74.9%), 2, 2′, 4, 4′-Tetrabromodiphenyl ether (PBDE47, LOD: 100%), and 2, 4, 4′-Tribromodiphenyl ether (PBDE28, LOD: 97.3%) and 2, 2′, 4, 4′, 5, 5′-Hexabromobiphenyl (PBB-153, LOD: 98.4%) were included in the further analyses.

Blood lipid profiles

HDL-C (mg/dL) was measured using a method in which non-HDL cholesterol forms water-soluble complexes with magnesium/dextran sulfate, followed by the enzymatic conversion of HDL cholesterol esters into HDL cholesterol, which was then quantified photometrically. TC (mg/dL) was assessed using an enzymatic assay that converts esterified cholesterol into free cholesterol, producing hydrogen peroxide, which reacts with 4-aminophenazone to form a measurable product at 505 nm. The Friedewald equation was used to determine LDL-C (mg/dL): [LDL-C] = [TC] − [HDL-C] − [TG/5] [38]. According to guidelines, RC (mg/dL) was derived using the formula: [RC] = [TC] − [HDL-C] − [LDL-C] [39].

Covariates

On the basis of previous studies, a range of covariates were included in the analyses [32, 40]. Demographic covariates included gender (male, female), age (< 50 years, > 50 years), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), education level (under high school, high school, and college graduate), and PIR (< 1, 1–3, and > 3). Other covariates including BMI (< 25, 25–30, and > 30 kg/m^2), smoking status (yes, no), diabetes (yes, no, and borderline), and research cycle (2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, and 2015–2016).

Statistical analyses

Continuous and categorical variables were described by mean ± standard deviation (SD) and number (%), respectively. The chi-square test and t-test were employed for the purpose of evaluating the continuous and categorical variables of participants according to gender. The continuous variables were transformed using natural logarithms in order to fit a normal distribution. MEC weights were applied in the analyses to conform to the complex, multistage sampling design [41].

Spearman correlation analysis was used to assess the relationships between nine serum BFRs. Pairwise correlation coefficients range from −1 to 1, indicating the strength and direction of the associations. The results were visualized in a heatmap, with color intensity reflecting the magnitude of the correlations.

Weighted multivariable regression analyses were used to evaluate the association between serum BFRs and TC, HDL-C, LDL-C, and RC resulting in beta values and a 95% CI. Three models were constructed in the analyses: model 1: non-adjusted; model 2: adjusted for gender, age, race, education level, PIR, smoking status, and research cycle; and model 3: adjusted for all covariates. Restricted Cubic Spline (RCS) regression was utilized to investigate the nonlinear relationship between serum BFRs and blood lipids [42]. The median concentration of BFRs was selected as the reference point, and four knots were positioned at the 5th, 35th, 65th, and 95th percentiles of the BFR distribution. In order to identify potential gender-specific differences, stratified mixture analyses were performed by gender.

The overall association between multiple BFRs and blood lipids was assessed using two models including Quantile G-computation (QGC) analyses and weighted quantile sum (WQS) regression [43, 44]. WQS regression and QGC analyses are advanced statistical techniques employed to evaluate the combined effects of multiple environmental exposures. In the WQS model, the BFRs were divided into quartiles (q = 4), meaning the observed effect corresponds to an increment from one quartile to the next. The dataset was partitioned into a training (60%) and validation (40%) subsets. To estimate the weights of the BFRs, 1,000 bootstrap iterations were performed. In the QGC model, exposures were divided into deciles (q = 10), with the estimates representing the effect of a one-decile increase in the exposure mixture. A generalized linear model was employed to estimate the joint effect, and bootstrap resampling was performed to calculate confidence intervals for the joint effect estimates.

Statistical analyses were performed using the R software 4.3.2 and EmpowerStats. *P*-value less than 0.05 was defined as statistical significance.

Results

Baseline characteristics

This study encompassed 3,154 participants (48.32% male and 51.68% female) with an average age of 44.91 ± 16.29 years. The baseline characteristics of participants by gender are summarized in Table 1. Women had a higher proportion of individuals aged ≥ 50 years. Regarding BMI, women were more likely to have a BMI ≥ 30, whereas men had a higher proportion with BMI in the 25–30 range. Men also exhibited higher levels

Table 1 Baseline characteristics of participants from NHANES 2005–2016

Variables	Total	Male	Female	*P*-value
N	3154	1524	1630	
Age (years)				**<0.001**
<50	2100 (66.58%)	1083 (71.08%)	1017 (62.39%)	
≥50	1054 (33.42%)	441 (28.92%)	613 (37.61%)	
BMI (kg/m^2)				**<0.001**
<25	1007 (31.93%)	426 (27.94%)	581 (35.62%)	
25–30	1081 (34.27%)	627 (41.16%)	454 (27.83%)	
≥30	1066 (33.80%)	471 (30.90%)	595 (36.55%)	
PIR				0.055
<1	482 (15.28%)	233 (15.31%)	259 (15.87%)	
1–3	1165 (36.94%)	595 (39.06%)	570 (34.96%)	
≥3	1497 (47.78%)	696 (45.63%)	801 (49.17%)	
Race				**0.002**
Mexican American	307 (9.73%)	175 (11.46%)	132 (8.12%)	
Other Hispanic	200 (6.34%)	105 (6.88%)	95 (5.82%)	
Non-Hispanic White	2048 (64.93%)	958 (62.86%)	1090 (66.85%)	
Non-Hispanic Black	379 (12.02%)	169 (11.10%)	210 (12.88%)	
Other Race	220 (6.98%)	117 (7.71%)	103 (6.33%)	
Education				**<0.001**
Under high school	535 (16.96%)	307 (20.17%)	228 (13.99%)	
High school	705 (22.35%)	378 (24.79%)	327 (20.08%)	
College graduate	1914 (60.69%)	839 (55.04%)	1075 (65.93%)	
Smoking status				**<0.001**
Yes	1366 (43.31%)	748 (49.08%)	618 (37.90%)	
No	1788 (56.69%)	776 (50.92%)	1012 (62.10%)	
Diabetes				**0.010**
Yes	142 (4.50%)	74 (4.88%)	68 (4.20%)	
No	2976 (94.36%)	1441 (94.57%)	1535 (94.17%)	
Borderline	36 (1.14%)	9 (0.55%)	27 (1.63%)	
Research cycle				0.400
2005-2006	520 (16.48%)	261 (17.11%)	259 (15.91%)	
2007-2008	556 (17.62%)	269 (17.65%)	287 (17.58%)	
2009-2010	513 (16.27%)	240 (15.76%)	273 (16.74%)	
2011-2012	531 (16.84%)	275 (18.03%)	256 (15.76%)	
2013-2014	513 (16.27%)	237 (15.59%)	276 (16.89%)	
2015-2016	521 (16.52%)	242 (15.86%)	279 (17.11%)	
Blood lipids (mg/dL)				
TC	5.26 ± 0.20	5.24 ± 0.20	5.27 ± 0.21	**<0.001**
HDL-C	3.96 ± 0.28	3.86 ± 0.26	4.05 ± 0.26	**<0.001**
LDL-C	4.73 ± 0.31	4.73 ± 0.30	4.72 ± 0.31	0.206
RC	3.01 ± 0.54	3.09 ± 0.54	2.93 ± 0.52	**<0.001**
BFRs (pg/g)				
PBB153	2.65 ± 1.08	2.87 ± 1.09	2.45 ± 1.02	**<0.001**
PBDE28	1.91 ± 0.62	1.95 ± 0.62	1.88 ± 0.62	**0.002**
PBDE47	4.79 ± 0.69	4.87 ± 0.68	4.72 ± 0.69	**<0.001**
PBDE85	0.91 ± 0.76	0.98 ± 0.74	0.85 ± 0.77	**<0.001**
PBDE99	3.16 ± 0.80	3.26 ± 0.77	3.07 ± 0.82	**<0.001**
PBDE100	3.22 ± 0.70	3.29 ± 0.71	3.15 ± 0.68	**<0.001**
PBDE153	4.07 ± 0.69	4.24 ± 0.68	3.91 ± 0.66	**<0.001**
PBDE154	0.82 ± 0.75	0.89 ± 0.76	0.76 ± 0.73	<0.001
PBDE209	2.76 ± 0.53	2.89 ± 0.52	2.65 ± 0.52	<0.001

Values in this table were represented as mean ± SD or number (%). BFRs and blood lipids were transformed by natural logarithms. *P*-values were calculated using weighted analyses (*N*=3,154, Expanded *N*=21,837,195)

of serum BFRs, including PBB153, PBDE153, PBDE100, PBDE99, PBDE85, PBDE47 and PBDE28. Women had higher levels of TC and HDL, while men exhibited higher levels of RC (Table 1). The overall correlation between serum BFRs was positive (Fig. 2).

Association between individual serum BFR and blood lipids

The results showed that serum PBB153 (β = 0.034), PBDE209 (β = 0.021), PBDE153 (β = 0.024), and PBDE28 (β = 0.015) were positively associated with TC after adjusting for covariates. PBB153 (β = 0.039), PBDE209 (β = 0.029), and PBDE153 (β = 0.030) were positively associated with LDL-C. PBB153 (β = 0.064), PBDE209 (β = 0.046), PBDE153 (β = 0.042), and PBDE28 (β = 0.036) were positively associated with RC. However, the association between single BFR and HDL-C was not statistically significant (Table 2). Please refer to supplement file for detailed results on multivariable regression model. (Table S2).

Restricted cubic spline (RCS) curves were used to further explore the non-linear relationships between serum BFRs and blood lipid profiles. The results obtained revealed notable threshold effects for specific serum BFRs. For PBB153, threshold effects were observed for TC at approximately 3.5, LDL-C at 3.0, and RC at 3.2, beyond which the effects plateaued. Similar threshold patterns were noted for PBDE209, with TC, LDL-C, and RC showing diminishing effects at higher concentrations. Detailed results are shown in Supplemental File. (Figure S1-4).

Association between mixed serum BFRs with blood lipids

The results of WQS regression showed that mixed serum BFRs were positively associated with TC (β = 0.035), LDL-C (β = 0.031), RC (β = 0.057), and HDL-C (β = 0.020) after adjusting for all covariates. (Table 3) In addition, WQS regression suggested that PBB153 contributed most to the overall mixture effect on TC (54.4%), HDL-C (69.2%), and LDL-C (46.7%). PBDE28 contributed most on RC (38.3%) (Fig. 3A-D). Scatter plot showed that serum BFRs were positively correlated with TC, LDL-C, RC and HDL-C overall. (Figure S5).

QGC analyses suggested that mixed serum BFRs were positively associated with TC (β = 0.036), LDL-C

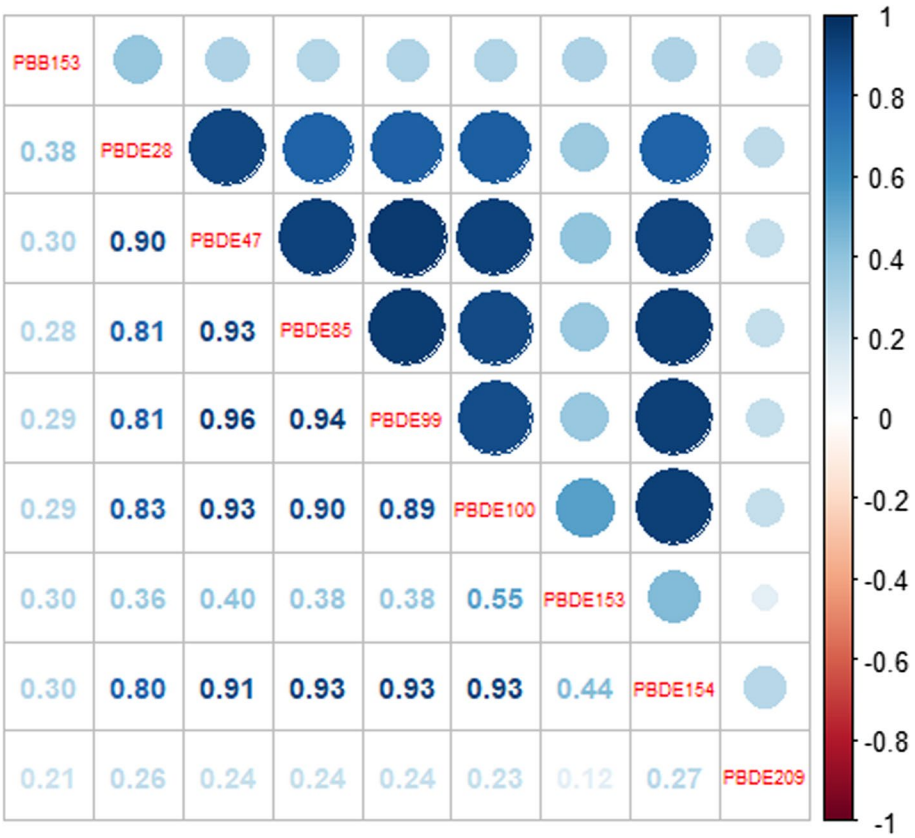

Fig. 2 Spearman correlation coefficient plot showing the relationships between serum BFRs. Correlation coefficients (range: −1 to 1) are visualized by color intensity, indicating the strength of associations

Table 2 Associations of individual BFRs with blood lipid levels in the general population

	TC	HDL-C	LDL-C	RC
BFRs	β (95% CI)*P*-value	β (95% CI)*P*-value	β (95% CI)*P*-value	β (95% CI)*P*-value
PBB153	0.034 (0.026, 0.041) **<0.001**	0.004 (-0.006, 0.013) 0.431	0.039 (0.027, 0.051) **<0.001**	0.064 (0.045, 0.084) **<0.001**
PBDE28	0.015 (0.001, 0.028) **0.031**	0.007 (-0.009, 0.023) 0.380	0.010 (-0.010, 0.030) 0.323	0.036 (0.003, 0.069) **0.033**
PBDE47	0.005 (-0.007, 0.016) 0.408	0.007 (-0.007, 0.021) 0.318	0.001 (-0.016, 0.018) 0.911	0.017 (-0.011, 0.045) 0.241
PBDE85	0.008 (-0.002, 0.018) 0.112	0.005 (-0.007, 0.017) 0.444	0.010 (-0.006, 0.025) 0.220	0.015 (-0.010, 0.040) 0.251
PBDE99	0.004 (-0.005, 0.014) 0.384	0.004 (-0.008, 0.015) 0.528	0.003 (-0.011, 0.018) 0.657	0.017 (-0.007, 0.041) 0.160
PBDE100	0.008 (-0.003, 0.019) 0.144	0.005 (-0.008, 0.018) 0.448	0.005 (-0.011, 0.022) 0.525	0.021 (-0.007, 0.048) 0.136
PBDE153	0.024 (0.013, 0.034) **<0.001**	-0.003 (-0.016, 0.010) 0.660	0.030 (0.014, 0.046) **<0.001**	0.042 (0.016, 0.068) **0.002**
PBDE154	0.006 (-0.004, 0.017) 0.238	-0.001 (-0.014, 0.011) 0.832	0.007 (-0.009, 0.023) 0.406	0.020 (-0.006, 0.047) 0.128
PBDE209	0.021 (0.007, 0.036) **0.004**	-0.007 (-0.024, 0.011) 0.446	0.029 (0.007, 0.051) **0.009**	0.046 (0.010, 0.081) **0.013**

Multivariable regression models assessing the associations between serum concentrations of individual BFRs and blood lipids in the general population. The following covariates were adjusted: gender, age, race, education level, PIR, BMI, smoking status, diabetes, and research cycle

Table 3 Association between mixed serum BFRs and blood lipids In the general population by WQS regression and QCG analyses

Model	Outcomes	WQS β (95% CI)	*P*-value
WQS	TC	0.035 (0.021, 0.049)	**< 0.001**
	LDL-C	0.031 (0.010, 0.053)	**0.005**
	RC	0.057 (0.020, 0.094)	**0.002**
	HDL-C	0.020 (0.005, 0.035)	**0.008**
QGC	TC	0.036 (0.023, 0.049)	**< 0.001**
	LDL-C	0.036 (0.017, 0.055)	**< 0.001**
	RC	0.065 (0.035, 0.094)	**< 0.001**
	HDL-C	0.015 (0, 0.030)	0.054

The following covariates were adjusted: gender, age, race, education level, PIR, BMI, smoking status, diabetes, and research cycle. *QGC* Quantile g-computation, *WQS* Weighted quantile sum

(β = 0.036), and RC (β = 0.065). However, the association between mixed BFRs and HDL-C was also not statistically significant. (Table 3) The results of the single exposure weighting in the QGC analyses were similar with the WQS regression. The results suggested that PBB153 contributed most on TC and LDL-C. PBDE28 contributed most on RC. (Figures 4A-D and 5 (A–D) illustrated the associations between joint exposure to BFRs and blood lipid levels based on QGC analyses. Taking the first decile of the BFR mixture as a reference, TC, LDL-C and RC showed a significant upward trend with increasing mixture concentration. ($P < 0.05$). The association with HDL-C was positive but not statistically significant (Fig. 5A-D).

Stratified analyses by gender

The associations between individual BFRs and blood lipids were examined using multivariable regression models. The results indicated significant positive associations between certain BFRs (e.g., PBB153) and TC, LDL-C, and RC in both males and females after adjusted covariates. However, the magnitude of these associations varied by gender and BFR type. Detailed results are provided in supplemental file. (Table S3 and S4) The stratified mixture analyses revealed significant associations between mixed serum BFRs and blood lipid outcomes in both males and females. For males, WQS and QGC models consistently showed positive associations with TC and RC, while associations with HDL-C were not statistically significant. Mixed serum BFRs were positively associated with TC, LDL-C, and HDL-C in females (Table 4). There were some differences between the results of the stratified mixed analysis and the results of the overall participants.

Discussion

This study explored the association between exposure to BFRs and blood lipid profiles in American adults using NHANES data. The results showed that individual PBB153, PBDE209, PBDE153, and PBDE28 were positively associated with TC and RC after adjusted all covariates. In addition, PBB153, PBDE209, and PBDE153 were positively associated with LDL-C, while no significant association was found between any individual BFR and HDL-C. Further analysis using WQS regression and QGC analyses confirmed that BFR mixtures were positively associated with TC, LDL-C, and RC. The main results of the stratified analyses were consistent with those in the overall population. The findings suggest that BFR exposure may lead to increased levels of TC, LDL-C, and RC, indicating a potential link to dyslipidemia and increased risk of cardiovascular diseases.

The findings of some previous studies contrast with our results. For instance, a study of 172 participants from Laizhou Bay, China, a major flame retardant production area, found that serum levels of various PBDE congeners—including PBDE209, PBDE154, PBDE100, PBDE99, and total PBDEs—were marginally to significantly

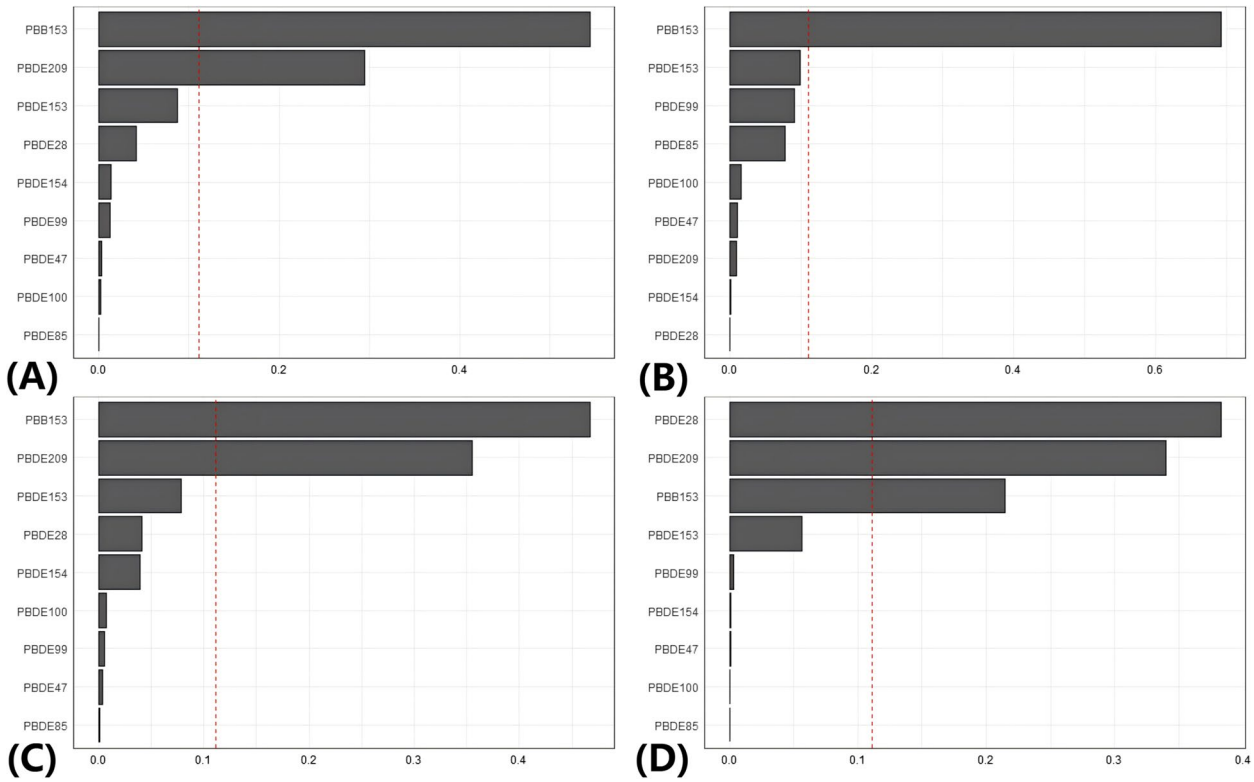

Fig. 3 Effects of individual BFRs to blood lipid levels in the general population by WQS regression. The following covariates were adjusted: gender, age, race, education level, PIR, BMI, smoking status, diabetes, and research cycle. **A** Proportion of effect of single BFR on TC; **B** Proportion of effect of single BFR on HDL-C; **C** Proportion of effect of single BFR on LDL-C; **D** Proportion of effect of single BFR on RC. QGC: quantile g-computation; WQS: weighted quantile sum

negatively correlated with TC and LDL-C [32]. Similarly, another study of 150 female participants from Shantou, China, reported that PBDE-190 levels in adipose tissue were inversely associated with TC, while total PBDEs were positively associated with TC [45]. Moreover, research has indicated that exposure to PBDE99 during the prenatal period is associated with reduced levels of TG in childhood [31]. In contrast, several studies have yielded results consistent with our findings. A study reported a positive association between PBDE99, PBDE47, and PBDE28 with TC among 388 pregnant women based on the HOME project [33, 34]. However, the current research on the relationship between BFR exposure and blood lipids remains limited, and the findings are inconclusive. The discrepancies across studies may be attributable to variations in the sources of BFRs, ethnic differences among participants, gender differences, and the control of confounding factors in the analyses. Some studies have investigated the potential causal relationship between BFR exposure and blood lipids using animal models. For example, one study reported elevated plasma TC levels in female offspring of C57BL/6N mice exposed perinatally to PBDE-71, although similar changes were not observed in male offspring [46].

One potential mechanism linking BFR exposure to altered lipid profiles is through the disruption of thyroid hormone pathways, which regulate hepatic cholesterol metabolism and lipoprotein receptor gene expression [47–49]. Additionally, a study demonstrated that PBDE-47 upregulated microRNA-34a-5p, leading to NAD + deficiency, impaired mitophagy, and induced mitochondrial dysfunction and oxidative damage in the liver [50]. BFR exposure may also induce oxidative stress and cause inflammation [51, 52]. All of these may disrupt lipid metabolism. Future studies are needed to clarify the mechanism of blood lipid changes induced by exposure to BFRs.

This study proposed a potential association between BFR exposure and elevated RC levels. Our results showed that PBB153 and three PBDEs included in the analyses were positively associated with RC, with a stronger effect than that observed for TC and LDL-C after adjusting for all covariates. A large-scale study conducted in the Danish population found that individuals with RC levels above 1 mg/dL, compared to those with levels below

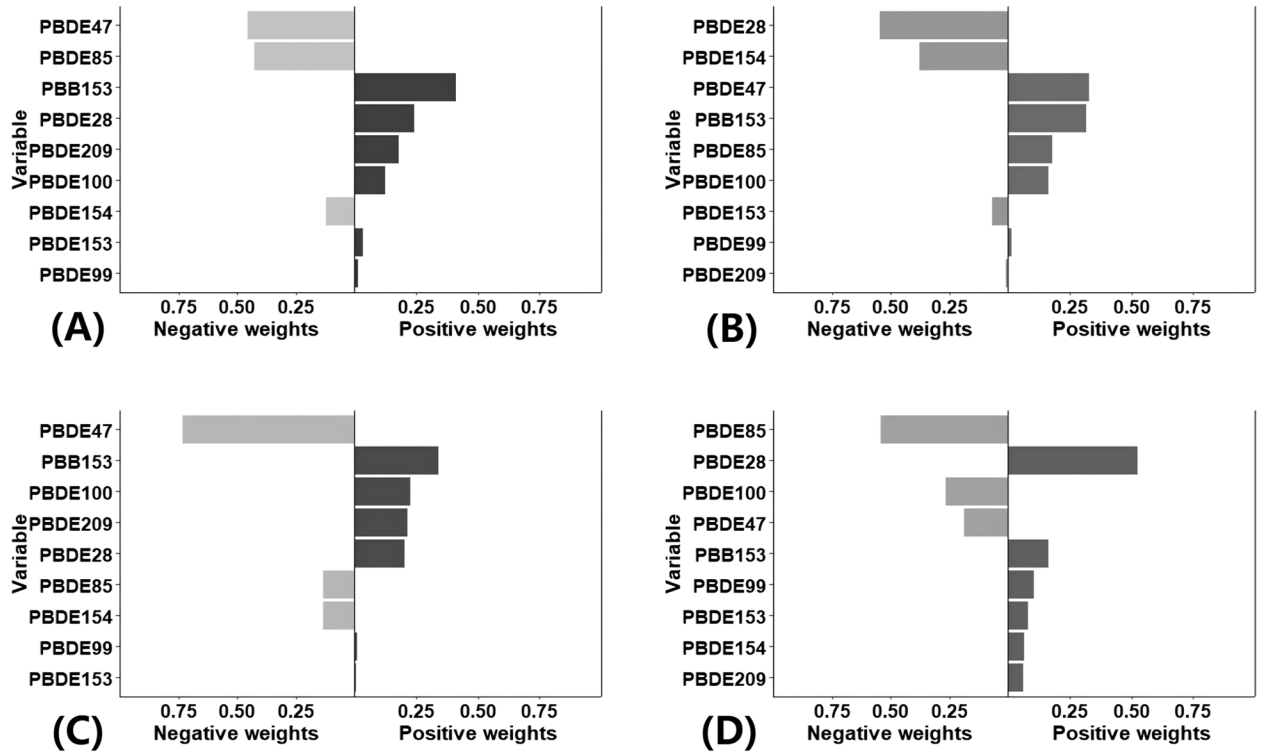

Fig. 4 Effects of individual BFRs on blood lipids in the general population by QGC analysis. The following covariates were adjusted: gender, age, race, education level, PIR, BMI, smoking status, diabetes, and research cycle. A: Effect of single BFR on TC; B: Effect of single BFR on HDL-C; C: Effect of single BFR on LDL-C; D: Effect of single BFR on RC. QGC: quantile g-computation; WQS: weighted quantile sum

0.5 mg/dL, had hazard ratios (HRs) for mortality of 2.2 (95% CI: 1.3–3.5) from cardiovascular disease and 2.1 (95% CI: 1.4–3.3) from other causes [53, 54]. Additionally, many studies have reported a potential causal association between RC and various cardiovascular diseases, including ischemic heart disease, myocardial infarction, and aortic stenosis through Mendelian randomization (MR) [55, 56]. Identifying risk factors for elevated RC is therefore of great significance, as controlling RC levels could play a crucial role in promoting human health.

The overall effect of BFR exposure on lipid profiles was assessed using two distinct analytical methods: WQS regression and QGC analysis. Both approaches showed that mixed serum BFRs were positively correlated with RC, LDL-C, and TC. The findings indicated that PBB153 was the most influential BFR contributing to the mixtures for TC and LDL-C. Additionally, PBDE28 was identified as the most influential BFR contributing to the mixtures for RC, while PBB153 exhibited a comparatively minimal contribution. Following a stratified analysis based on sex, the results demonstrated that, for males, the WQS and QGC models consistently exhibited positive associations between serum BFRs and TC and RC, while associations with HDL-C were not statistically significant. However, mixed serum BFRs were positively associated with TC, LDL-C, and HDL-C in females. The extant studies on this subject is limited, and further research is required to explore the mechanism causing this gender difference.

The WQS regression analysis demonstrated a positive correlation between mixed BFRs and HDL-C, yet this relationship did not attain statistical significance in QGC analysis. In QGC analyses, interaction and non-linear effects between exposures are captured, potentially leading to more significant impacts of certain exposures. In contrast, WQS regression combines exposures through linear weighting, which may overlook these complex interactions. Additionally, WQS assumes that all exposures affect the outcome in the same direction, potentially masking opposing effects, while QGC allows each exposure to have an independent direction [43, 44]. Moreover, the inability to account for NHANES sampling weights in WQS regression and QGC analyses could lead to differences in results compared to those from the multivariable regression model. Therefore, it is important to integrate findings from multiple models when evaluating the effect of multiple factors on health outcomes.

This study has several strengths. It was the first large-scale cross-sectional study to systematically explore the association between exposure to BFRs and TC, LDL-C, RC, and HDL-C. This study utilized data from the

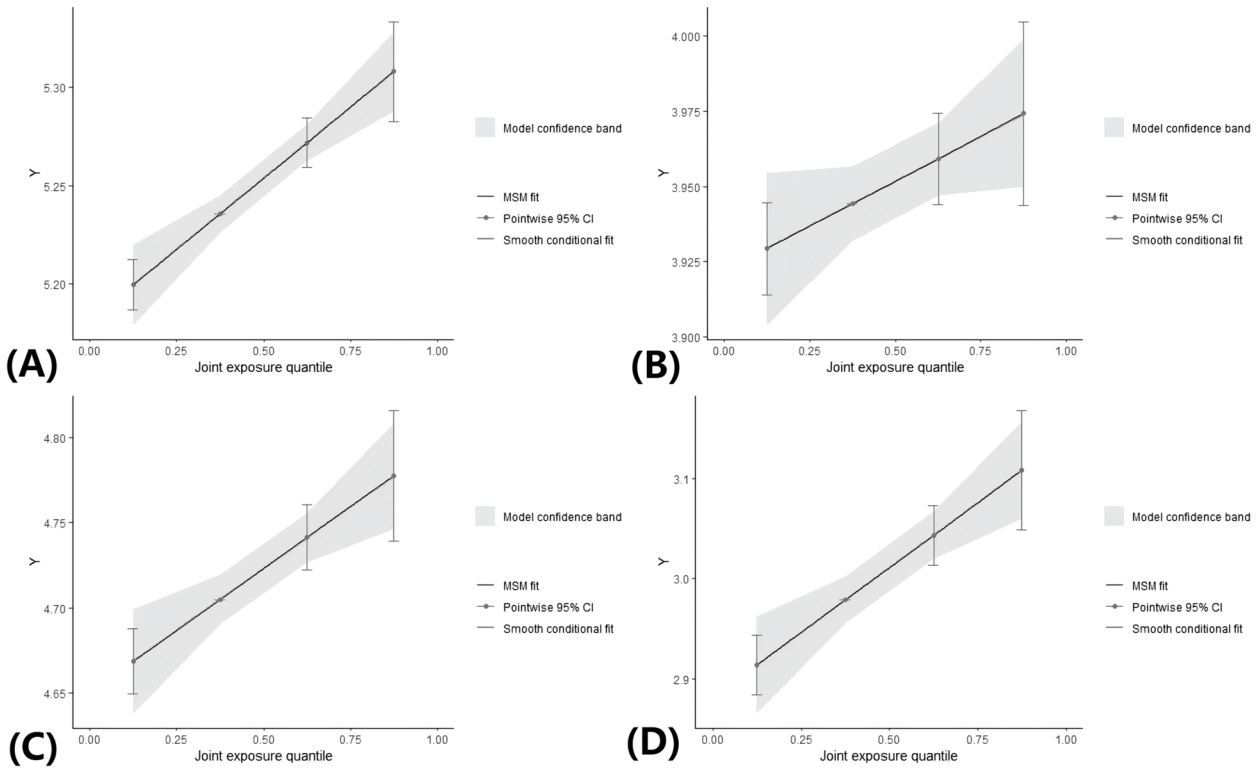

Fig. 5 Overall effect of mixed BFRs on blood lipids in the general population by QGC analyses. The following covariates were adjusted: gender, age, race, education level, PIR, BMI, smoking status, diabetes, and research cycle. A: Overall effect of BFRs on TC; B: Overall effect of BFRs on HDL-C; C: Overall effect of BFRs on LDL-C; D: Overall effect of BFRs on RC. QGC: quantile g-computation; WQS: weighted quantile sum

Table 4 Gender-stratified associations between mixed serum BFRs and blood lipids using WQS and QGC models

Model	Outcomes	Gender	β (95% CI)	*P*-value
WQS	TC	Male	0.030 (0.009, 0.051)	**0.006**
		Female	0.046 (0.027, 0.066)	**< 0.001**
	LDL-C	Male	0.026 (−0.005, 0.058)	0.101
		Female	0.033 (0.001, 0.064)	**0.041**
	RC	Male	0.056 (0.005, 0.107)	**0.032**
		Female	0.041 (−0.006, 0.088)	0.087
	HDL-C	Male	0.018 (−0.004, 0.041)	0.113
		Female	0.027 (0.006, 0.049)	**0.013**
QGC	TC	Male	0.040 (0.022, 0.057)	**< 0.001**
		Female	0.041 (0.023, 0.058)	**< 0.001**
	LDL-C	Male	0.043 (0.017, 0.069)	**0.001**
		Female	0.043 (0.017, 0.070)	**0.001**
	RC	Male	0.079 (0.036, 0.121)	**< 0.001**
		Female	0.062 (0.019, 0.105)	**0.005**
	HDL-C	Male	0.005 (−0.019, 0.029)	0.680
		Female	0.022 (0.001, 0.043)	**0.037**

The following covariates were adjusted: gender, age, race, education level, PIR, BMI, smoking status, diabetes, and research cycle. *QGC* Quantile g-computation, *WQS* Weighted quantile sum

NHANES, which is representative of the general population. Furthermore, our analyses employed novel methods, including WQS and QGC models, to investigate the mixed effects of BFRs. The primary outcomes of the stratified analyses were consistent with the overall population, thereby enhancing the robustness of the study. The findings offered compelling evidence that BFRs are detrimental to cardiovascular health.

This study also has some limitations. Based on the cross-sectional study design, our results can only demonstrate an association between exposure to BFRs and blood lipid profiles, but not a causal relationship. The study population was drawn exclusively from the United States, and therefore the results cannot be generalized to other countries. Many participants were excluded because of missing information, and participants taking statins, those with a history of cancer, and pregnant women were also excluded, which may prevent the results from adequately reflecting the characteristics of the general population. Despite adjustments made for primary confounders, the possibility of residual confounding remains unconfirmed. Lifestyle includes diet, work and other factors, a potential source of both BFR

exposure and blood lipid variation, were not included due to limitations in the data. Similarly, other co-occurring endocrine disruptors, such as heavy metals and phthalates, were not considered, potentially underestimating the synergistic or antagonistic effects of environmental pollutants. In addition, Due to the inherent limitation of the detection rate, BFRs with a detection rate below 70% were excluded from our analyses to minimize the impact of measurement error. However, for the included BFRs, some samples 897still exhibited concentrations the LOD, which were imputed as LOD/$\sqrt{2}$ according to NHANES guidelines. This imputation approach, while widely used, may introduce some degree of error and potentially bias the results. Furthermore, the analyses were limited to nine major PBDE congeners and PBB153 available in the NHANES. While these congeners account for a significant portion of human exposure, analyzing additional PBDE congeners could offer a more comprehensive understanding of their associations with blood lipids. Future studies with a broader range of BFRs and larger datasets are needed to validate our findings and further elucidate their health impacts.

Conclusion

This study demonstrates that BFR exposure is associated with increased levels of TC, LDL-C, and RC, indicating an elevated risk of dyslipidemia and cardiovascular diseases. These results highlight the potential public health implications of BFR exposure and underscore the need for further research into the underlying mechanisms and preventive strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02527-4.

Supplementary Material 1.

Authors' contributions

Y.W. and Z.H.Z. contributed to the of the work and writing of the Manuscript. N.S., X.Q., H.L.and F.W. contributed to the acquisition and analysisof data. Z.Z.Z. and J.L. contributed to Production of graphs and tables. H.X. contributed to the conception of the work and Revision of the manuscript. All authors reviewed the manuscript.

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Data availability

The data are available from NHANES (https://www.cdc.gov/nchs/nhanes/).

Declarations

Competing interests

The authors declare no competing interests.

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