BMC Public Health

RESEARCH

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Associations between exposure to brominated flame retardants and hyperlipidemia risk in U.S. Adults

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Abstract

Background Environmental exposure to toxic brominated flame retardants (BFRs) has been confirmed to have detrimental effects on human health. The impact of serum BFRs on hyperlipidemia risk has not been sufficiently examined. Our objective is to identify both the individual and combined effects of serum BFRs on hyperlipidemia and to further investigate the most influential chemicals.

Methods We included 7,009 individuals with complete details on 9 types of serum BFRs, hyperlipidemia, and other covariates from the NHANES in 2007–2016. Multivariate logistic regression was conducted to evaluate the individual impact of BFRs exposure on hyperlipidemia risk. We assessed the cumulative effect of BFRs on hyperlipidemia risk through weighted quantile sum (WQS) regression, quantile g-computation (QGC), and Bayesian kernel machine regression models.

Results PBDE 28, PBDE 47, PBDE 85, PBDE 99, PBDE 100, PBDE 154, PBDE 209, and PBB153 were found to be positively associated with hyperlipidemia risk. The results of WQS and QGC revealed consistent positive correlation. PBDE209 emerged as the most significant chemicals exerting influence. The restricted cubic splines regression further identified significant dose-response relationship.

Conclusion Exposure to individual and combined serum BFRs has been associated with an increased risk of hyperlipidemia. The causal relationship still requires confirmation through large-scale cohort studies.

Keywords Brominated flame retardants, Hyperlipidemia, Joint effect, BKMR, NHANES

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Introduction

Brominated flame retardants (BFRs), which are composed of a diverse array of organobromine compounds, have been widely employed in various applications, including electronic equipment, plastics, and textiles. Its primary function is the mitigation of product flammability [1, 2]. Nevertheless, polybrominated diphenyl ethers (PBDEs) and 2,2′,4,4′,5,5′-hexabromobiphenyl (PBB153) have been recognized as hazardous BFRs and emerged as the inaugural brominated persistent organic pollutants (POPs) [3]. Identified in various matrices and organisms, BFRs have been found to present potential exposure hazards for humans [4]. Furthermore, organisms are prone to bioaccumulate elevated concentrations of BFRs from their surroundings, subsequently leading to their transfer through food webs [5–7]. Hence, BFRs exposure among human may occur through food of animal origin consumption and dust ingestion. The accumulation of BFRs in the human body has been discovered in a range of physiological tissues and fluids, including serum, adipose tissue, and bodily fluids [8–10]. Concerns surrounding BFRs have heightened due to their enduring presence, extensive distribution, and environmental biotoxicity [11]. Previous epidemiological investigations have demonstrated that BFRs have a positive association with various adverse health conditions, including thyroid disorders, neurobehavioral disorders, reproductive health issues, immune system dysfunction, endocrine system disorders, and atherosclerosis [12–17]. Nevertheless, research concentrated on the toxic effect of BFRs on the metabolism, particularly in relation to the risk of hyperlipidemia, are still relatively limited.

Hyperlipidemia is a metabolic disorder resulting from disruptions in lipid metabolism within the human body, leading to elevated concentrations of serum lipids that exceed usual levels [18]. It exhibits a high prevalence among the population, affecting more than 53% of Americans [19]. Although the traditional risk factors for hyperlipidemia (including smoking, excessive alcohol consumption, and insufficient exercise) have been well explored [20], the effects of environmental pollutants such as BFRs co-exposure remain relatively inconclusive. Previous studies have indicated a positive correlation between elevated BFR levels and the increased likelihood of hypertriglyceridemia, obesity, and dyslipidemia [17, 21]. Additionally, multiple animal studies also indicated that exposure to environmental chemicals, such as PBDEs, can potentially dysregulate lipid metabolism [22]. For instance, both male and female rats exhibited elevated blood cholesterol levels when exposed to PBDE mixtures [17, 23]. Given the ubiquitous presence of BFRs in the environment and their effects on lipid levels, it is essential to investigate the relationship between BFRs and hyperlipidemia.

Thus, we conducted a cross-sectional study based on the National Health and Nutrition Examination Survey (NHANES) to investigate the toxic effects of exposure to both individual and multiple BFRs on the risk of hyperlipidemia. Several novel statistical models were utilized for the evaluation of BFRs co-exposure, including weighted quantile sum regression (WQS), Bayesian kernel machine regression (BKMR), and quantile-based g-computation (qgcomp). These methods have been widely used in previous studies to explore the health impacts of mixed exposures and are well-established in environmental epidemiology for their effectiveness in capturing the complex interactions among mixed exposures and health outcomes [4, 24]. Our study may provide extensive epidemiological evidence regarding the association between BFRs co-exposure and hyperlipidemia risk in the population.

Materials and methods

Study setting

NHANES was developed to assess the nutritional status and health of U.S. participants and is conducted every two years [25]. Details such as dietary, laboratory, examination, and demographic data could be accessible at https://www.cdc.gov/nchs/nhanes/. Individuals would provide written consent when they were enrolled. This research combined data from 2007–2008, 2009–2010, 2011–2012, 2013–2014, and 2015–2016 survey cycles of NHANES. Participants with missing serum BFRs level variables, lacking details correlated with hyperlipidemia, and those having insufficient details on other covariates were excluded. Collectively, 7009 respondents were enrolled in this research, which was exhibited in Fig. 1.

Outcome measures

Hyperlipidemia was determined by the adult National Cholesterol Education Program guidelines (2002). During individual interviews, respondents that met any of the following criteria was identified with hyperlipidemia, including: ① TC ≥ 200 mg/dL ② TG ≥ 150 mg/dL ③ LDL-C ≥ 130 mg/dL ④ HDL-C ≤ 40 mg/dL in males or ≤ 50 mg/dL in females. In addition, respondents could be considered have hyperlipidemia if they have taken lipid-lowering medications for treatment.

Measurements of serum BFRs

According to the details of NHANES Laboratory Procedures Manual, PBB153 and PBDEs were extracted from serum based on automated liquid-liquid extraction [4]. The analysis of serum samples for BFRs was performed using isotope dilution gas chromatography high-resolution mass spectrometry. Table S1 illustrates the detection rates and distribution of BFRs. To enhance the representativeness of the data and the reliability of our study, we

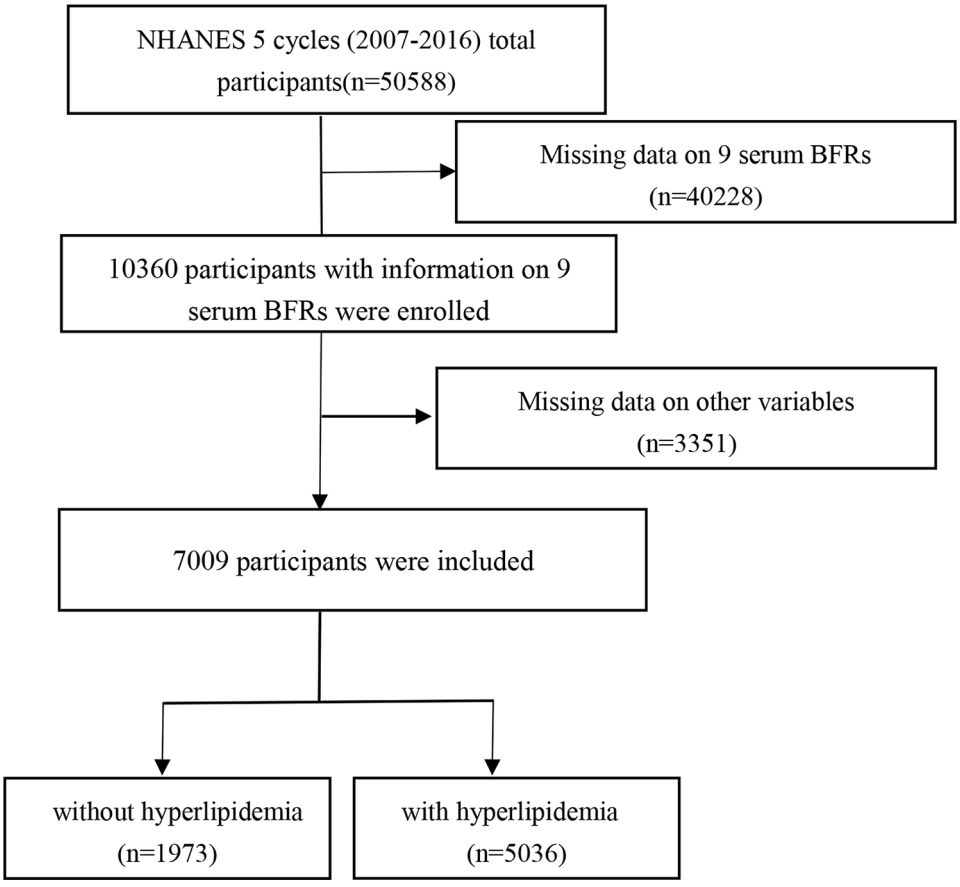

Fig. 1 Flowchart of the study population

selected PBB153 and eight PBDEs with a detection rate above 75% as key exposure variables. In this study, eight PBDEs include 2,4,4′-Tribromodiphenyl ether (PBDE28), 2,2′,4,4′-Tetrabromodiphenyl ether (PBDE47), 2,2′,3,4,4′-Tentabromodiphenyl ether (PBDE85), 2,2′,4,4′,5-Pentabromodiphenyl ether (PBDE99), 2,2′,4,4′,6-Pentabromodiphenyl ether (PBDE100), 2,2′,4,4′,5,5′-Hexabromodiphenyl ether (PBDE153), 2,2′,4,4′,5,6′-Hexabromodiphenyl ether (PBDE154), and Decabromodiphenyl ether (PBDE209). Concentrations of serum BFRs below the lower limit of detection (LLOD) were determined by dividing the LLOD value by the square root of two, following the methods provided in the NHANES dataset [4, 26, 27].

Covariates

To minimize the impact of confounders and provide a more accurate assessment of the relationship between BFRs and hyperlipidemia risk, we included demographic characteristics (gender, age, race, and marital status), socioeconomic characteristics (family poverty income ratio), and health-related factors (body mass index, alcohol use, and serum cotinine) as covariates, based on published research and clinical diagnostic knowledge [2, 4]. The categories for covariates were as follows: gender (male, female), race (mexican american, other hispanic, non-hispanic white, non-hispanic black, other race/multi-race), marital status (married, living with partner, widowed, divorced, separated, and never married), family poverty income ratio (PIR) (< 1, 1–3,≥3), body mass index (BMI) (< 18.5,18.5–25, ≥ 25), and alcohol use (yes, no). To precisely reflect smoking status and estimate the degree of environmental tobacco smoke exposure, we prefer serum cotinine levels to self-reported survey data regarding smoking [28–31]. All these variables were included to adjust for potential confounders and to examine their effects on hyperlipidemia risk.

Statistical analysis

To conduct baseline comparisons classified by hyperlipidemia condition, Chi-square tests was utilized for categorization, whereas the t-test was employed for continuous variables. The mean value and standard deviation were used for continuous variables, while categorical variables were expressed as n (%). Data of serum BFRs were ln-transformed to achieve normality and were then divided into 4 quartiles. In order to explore the potential co-exposure patterns, we constructed a Pearson correlation

analysis among nine Ln-transformed BFRs. Multivariate logistic regression was implemented to examine the association between individual BFRs and hyperlipidemia. In this analysis, concentrations of nine serum BFRs were input as either ln-transformed variables or categorical variables with four quartiles. The calculation of odds ratios and corresponding 95% confidence intervals were used to explore single serum BFRs's effect on hyperlipidemia. Model 1 was crude. The second model have modified covariates for age, gender, race, marital status, alcohol use, BMI, family PIR, and serum cotinine.

To comprehensively investigate the toxic effects of mixed serum BFRs on hyperlipidemia risk, we employed various statistical models. Firstly, the WQS model was utilized to quantify the combined effect of 9 serum BFRs on hyperlipidemia risk. WQS regression is designed for analyzing complex environmental mixtures characterized by high collinearity among their components, as it creates a composite index that captures the cumulative impact of the mixture [25, 32, 33]. To construct this index, we categorized each component into quantiles and utilized a two-step process for weight estimation. Our data was performed with 1000 bootstrap iteration, and split into validation and training sets. Specifically, 40% of the data were randomly allocated to a training set, while the remaining 60% were assigned into a validation set. The co-exposure level of serum BFRs was represented by the WQS index, which range from 0 to 1 and comprised weighted sums of 9 single BFRs [29, 34].

In addition, BKMR model was performed to determine combined impacts of serum BFRs mixture upon hyperlipidemia due to its strength in permitting possible nonlinearity and non-additive effects among 9 serum BFRs [35, 36]. In BKMR model, the relative roles played by element in mixture towards hyperlipidemia incidence was estimated using posterior inclusion probability (PIP) [33]. Then quantile-based g computation (qgcomp) model, was introduced aiming to overcome shortcomings of WQS models in determining heterogeneity of direction towards co-exposure. The qgcomp model could calculate the weights in positive and negative direction for factors of the mixtures. The restricted cubic splines (RCS) was also adopted to assess the possible non-linear relationships between serum BFRs and hyperlipidemia risk based on the R packages ("rms") [37]. Three knots were set up at the percentiles of the 5th, 50th, and 75th in RCS regression in accordance to the criterion of minimum absolute value of Akaike information [38].

R software (version 4.2.3) has been utilized for all analyses. Significance level was considered as p-value < 0.05. The analysis was conducted using the following R packages: gwqs (version 3.0.5), qgcomp (version 2.15.2), bkmr (version 0.2.2), and rcssci (version 0.3.0).

Results

Sample characteristics

In total, 7009 participants were recruited in the study, with an average age of 49.37 years (SD = 17.67). The majority had higher BMI (71.34%) and had alcohol drinking (72.08%). 5036 participants were diagnosed as having hyperlipidemia, whereas 1973 were classified as non-hyperlipidemia. Age, sex, race, marital status, BMI, and alcohol use were found to differ significantly between different status of hyperlipidemia. More details were summarized in Table 1.

Distribution and correlation of serum BFRs

The detailed distributions for concentrations towards 9 serum BFRs were exhibited in Table S1, with detection rate above 75%. And PBDE47 had the highest concentration among 9 serum BFRs, while PBDE154 had the lowest concentration.

The illustration of correlations among the 9 serum BFRs after ln transformation was displayed in Fig. 2. The serum BFRs including PBDE85 and PBDE47 (r = 0.94), PBDE99 and PBDE47 (r = 0.93), PBDE154 and PBDE99 (r = 0.92) exhibited strong correlations. PBDE 154 showed a correlation coefficient of 0.9 with PBDE 100, while PBDE 85 showed a correlation coefficient of 0.91 with PBDE 99. Strong correlations may indicate co-exposure or co-toxicity effect among BFRs. Significant correlations were all observed among 9 serum BFRs.

Associations between single BFRs and hyperlipidemia risk

The findings regarding the association of single BFRs with hyperlipidemia risk assessed by multivariate logistic regression were provided in Table 2. As continuous variables, all serum BFRs (PBDE28, PBDE47, PBDE85, PBDE99, PBDE100, PBDE153, PBDE154, PBDE209, and PBB153) with ln transformation had positive association with hyperlipidemia risk, while adjusting no covariates. In model 2, the results showed that for each unit increase in ln-transformed PBDE28, PBDE47, PBDE100, PBDE154, PBDE209, and PBB153, there shown a 21% (OR: 1.21, 95%CI: 1.09–1.33), 13% (OR: 1.13, 95%CI: 1.03–1.24), 14% (OR: 1.14, 95%CI: 1.05–1.25), 10% (OR: 1.10, 95%CI: 1.01–1.20), 37% (OR: 1.37, 95%CI: 1.22–1.54), and 12% (OR: 1.12, 95%CI: 1.04–1.20) increased risk of hyperlipidemia (all P value < 0.05). After dividing serum BFRs into 4 quartiles, PBDE28, PBDE47, PBDE99, PBDE100, PBDE154, PBDE209 and PBB153 with concentrations in highest quartiles was all linked to greater likelihood of hyperlipidemia risk (OR: 1.28,95%CI:1.08–1.52; OR: 1.24,95%CI:1.05–1.46; OR: 1.19,95%CI:1.01–1.41; OR: 1.30,95%CI:1.10–1.53; OR: 1.24,95%CI:1.05–1.47; OR: 1.46,95%CI:1.24–1.73; OR: 1.39,95%CI:1.13–1.71, respectively).

Table 1 Characteristics of participants by hyperlipidemia, NHANES 2007–2016

Characteristics	Total (*N* = 7009)	Non-hyperlipidemia (*N* = 1973)	Hyperlipidemia (*N* = 5036)	*P* value
Age, N (%)	49.37 (17.67)	41.69 (17.28)	52.38 (16.89)	< 0.001
Gender, N (%)				0.045
Female	3553 (50.69%)	962 (48.76%)	2591 (51.45%)	
Male	3456 (49.31%)	1011 (51.24%)	2445 (48.55%)	
Race, N (%)				< 0.001
Mexican American	1042 (14.87%)	257 (13.03%)	785 (15.59%)	
Non-Hispanic Black	1455 (20.76%)	500 (25.34%)	955 (18.96%)	
Non-Hispanic White	3067 (43.76%)	804 (40.75%)	2263 (44.94%)	
Other Hispanic	746 (10.64%)	176 (8.92%)	570 (11.32%)	
Other Race-Including Multi-Racial	699 (9.97%)	236 (11.96%)	463 (9.19%)	
Marital status, N (%)				< 0.001
Divorced	770 (10.99%)	178 (9.02%)	592 (11.76%)	
Living with partner	545 (7.78%)	205 (10.39%)	340 (6.75%)	
Married	3643 (51.98%)	881 (44.65%)	2762 (54.85%)	
Never married	1271 (18.13%)	555 (28.13%)	716 (14.22%)	
Separated	244 (3.48%)	72 (3.65%)	172 (3.42%)	
Widowed	536 (7.65%)	82 (4.16%)	454 (9.02%)	
Family PIR, N (%)				0.705
<1	1509 (21.53%)	431 (21.84%)	1078 (21.41%)	
1–3	2929 (41.79%)	809 (41.00%)	2120 (42.10%)	
≥ 3	2571 (36.68%)	733 (37.15%)	1838 (36.50%)	
BMI, N (%)				< 0.001
<18.5	101 (1.44%)	59 (2.99%)	42 (0.83%)	
18.5–25	1908 (27.22%)	842 (42.68%)	1066 (21.17%)	
≥ 25	5000 (71.34%)	1072 (54.33%)	3928 (78.00%)	
Alcohol use, N (%)				0.023
Yes	5052 (72.08%)	1461 (74.05%)	3591 (71.31%)	
No	1957 (27.92%)	512 (25.95%)	1445 (28.69%)	
Cotinine (Mean ± SD)	56.56 (128.42)	58.45 (128.13)	55.82 (128.53)	0.440

Notes: Abbreviations: SD: standard deviation; PIR: family poverty income ratio

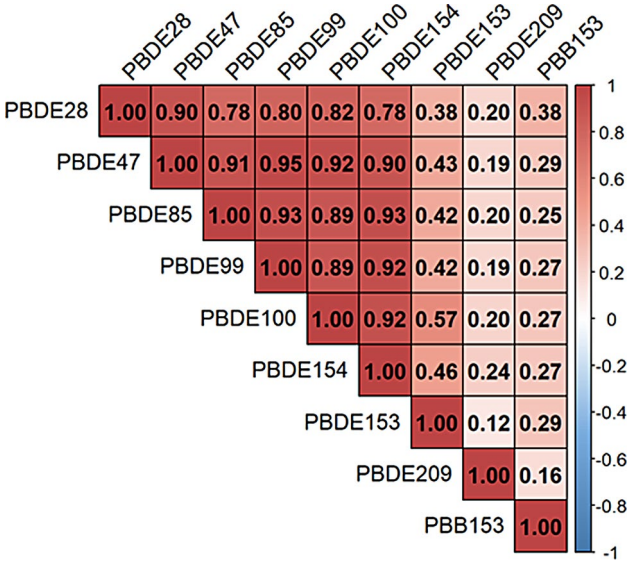

Fig. 2 Pearson's correlation matrix among Ln-transformed BFRs in the study population

Association of mixture BFRs exposure with hyperlipidemia risk in WQS regression and QGC analysis

Findings from WQS confirmed that doubling of serum BFRs may elevate the risk of hyperlipidemia (OR: 1.21, 95% CI: 1.09–1.34) while adjusted all covariates. PBDE209 made the most single contribution to hyperlipidemia risk, followed by PBB153 and PBDE100. PBDE99 had lowest weight and had relative low contribution to hyperlipidemia risk (Fig. 3). The qgcomp model analysis found that serum BFRs co-levels were also significantly correlated with higher possibility of hyperlipidemia (OR: 1.20, 95%CI: 1.1–1.32) (Figure S1).

BKMR analysis to evaluate the correlations of mixed serum BFRs and hyperlipidemia

According to the results of the combined effect of BFRs on hyperlipidemia in Fig. 4A, co-exposure to BFRs was positively associated with hyperlipidemia risk. Specifically, hyperlipidemia risk was significantly increased when BFRs mixtures were at the 25th to 35th percentiles in comparison to the 50th percentile. And we also found a positive trend when all BFRs were at above the 60th

Table 2 Associations between single BFRs and hyperlipidemia in the NHANES

Outcomes	Categorical models					Continuous models	
	Q1	Q2	Q3	Q4	*P* trend	OR (95%CI)	*P* value
PBDE28							
Model 1	1.0 (ref.)	1.42 (1.23, 1.63)	1.69 (1.47, 1.96)	2.31 (1.99, 2.69)	< 0.001	1.73 (1.58,1.89)	< 0.001
Model 2	1.0 (ref.)	1.12 (0.96, 1.30)	1.15 (0.98, 1.34)	1.28(1.08, 1.52)	0.0058	1.21 (1.09,1.33)	< 0.001
PBDE47							
Model 1	1.0 (ref.)	1.25 (1.08, 1.44)	1.33 (1.15, 1.54)	1.69 (1.46, 1.96)	< 0.001	1.34 (1.24,1.46)	< 0.001
Model 2	1.0 (ref.)	1.10 (0.94, 1.28)	1.09 (0.93, 1.28)	1.24 (1.05, 1.46)	0.0179	1.13 (1.03–1.24)	0.007
PBDE85							
Model 1	1.0 (ref.)	1.13 (0.98, 1.31)	1.32 (1.14, 1.53)	1.50 (1.29, 1.74)	< 0.001	1.23 (1.15,1.33)	< 0.001
Model 2	1.0 (ref.)	1.07 (0.92, 1.25)	1.11 (0.94, 1.30)	1.18 (1.00, 1.39)	0.0537	1.08 (0.99–1.17)	0.079
PBDE99							
Model 1	1.0 (ref.)	1.17 (1.01, 1.35)	1.26 (1.09, 1.46)	1.47 (1.27, 1.71)	< 0.001	1.22 (1.14,1.31)	< 0.001
Model 2	1.0 (ref.)	1.10 (0.94, 1.29)	1.04 (0.89, 1.22)	1.19 (1.01, 1.41)	0.0793	1.08 (1.00,1.17)	0.054
PBDE100							
Model 1	1.0 (ref.)	1.35 (1.17, 1.56)	1.33 (1.15, 1.53)	1.66 (1.43, 1.92)	< 0.001	1.30 (1.20,1.41)	< 0.001
Model 2	1.0 (ref.)	1.18 (1.00, 1.38)	1.15 (0.98, 1.35)	1.30 (1.10, 1.53)	0.0048	1.14 (1.05,1.25)	0.003
PBDE153							
Model 1	1.0 (ref.)	0.92 (0.79, 1.06)	0.99 (0.85, 1.15)	1.11 (0.96, 1.29)	0.106	1.11 (1.03,1.19)	0.009
Model 2	1.0 (ref.)	0.92 (0.79, 1.08)	1.00 (0.85, 1.18)	1.08 (0.91, 1.28)	0.2651	1.06 (0.97–1.16)	0.179
PBDE154							
Model 1	1.0 (ref.)	1.33 (1.15, 1.54)	1.25 (1.08, 1.44)	1.55 (1.33, 1.79)	< 0.001	1.25 (1.16,1.35)	< 0.001
Model 2	1.0 (ref.)	1.17 (1.00, 1.37)	1.04 (0.88, 1.22)	1.24 (1.05, 1.47)	0.0460	1.10 (1.01,1.20)	0.024
PBDE209							
Model 1	1.0 (ref.)	1.32 (1.14, 1.53)	1.30 (1.12, 1.50)	1.48 (1.28, 1.71)	< 0.001	1.39 (1.25,1.54)	< 0.001
Model 2	1.0 (ref.)	1.28 (1.10, 1.50)	1.17 (1.00, 1.38)	1.46 (1.24, 1.73)	0.0001	1.37 (1.22,1.54)	< 0.001
PBB153							
Model 1	1.0 (ref.)	2.27 (1.97, 2.62)	2.81 (2.43, 3.26)	3.03 (2.61, 3.52)	< 0.001	1.50 (1.43,1.58)	< 0.001
Model 2	1.0 (ref.)	1.38 (1.16, 1.62)	1.34 (1.10, 1.63)	1.39 (1.13, 1.71)	0.0076	1.12 (1.04,1.20)	0.002

Notes: CI, confidence interval; OR: odds ratio; Q, quartile; Continuous, Ln-transformed concentration of serum BFRs. Model 1 was a crude model without any adjustment. Model 2 was adjusted for age, gender, race, marital status, family income to poverty ratio, BMI, alcohol use and serum cotinine level

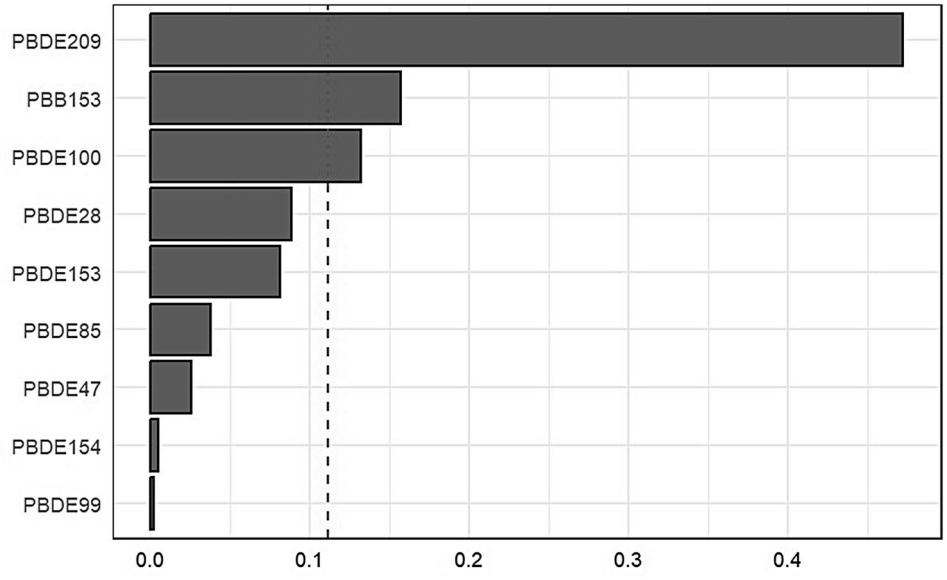

Fig. 3 Estimated weights of serum BFRs for hyperlipidemia by WQS models adjusted for age, gender, race, marital status, family income to poverty ratio, BMI, alcohol use and serum cotinine level. Notes: The red line indicates the threshold for identifying BFRs of concern, where the weight surpasses the reference value

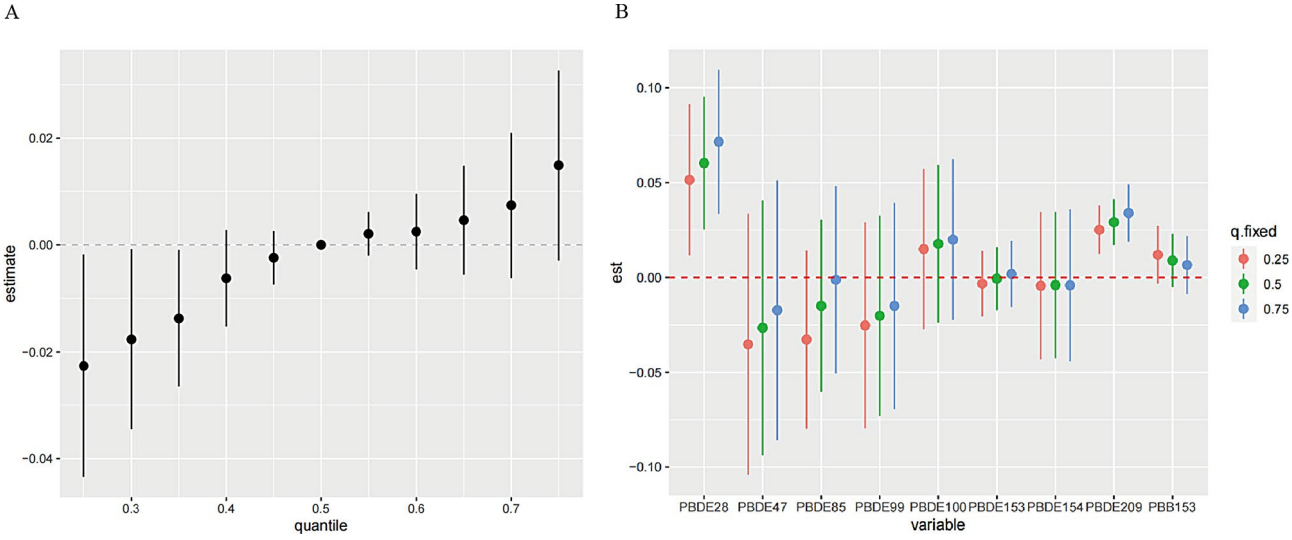

Fig. 4 Analysis of hyperlipidemia risk and BFRs exposure using the BKMR model. (**A**) Combined effects of the serum BFRs as a mixture on hyperlipidemia risk by BKMR models. (**B**) Relationship of single BFRs with hyperlipidemia risk when an individual BFRs exposure was at its 75th percentile as compared to its 25th percentile, when all other BFRs held at the 25th, 50th, or 75th percentile, respectively. Models were adjusted for age, gender, race, marital status, family income to poverty ratio, BMI, alcohol use and serum cotinine level

percentile, relative to when all BFRs were at their 50th percentile. We further compared the single exposure-response relationship to the 25th percentile while setting the remaining BFRs at the 25th, 50th, or 75th percentile. As shown in Fig. 4B, PBDE28 and PBDE209 exhibited significantly positive associations with an increased risk of hyperlipidemia when the levels of the remaining BFRs were at the 25th, 50th, and 75th percentiles. In addition, we explored the interaction relationships among 9 serum BFRs (Figure S2), and a possible interaction between PBB153 and PBDE154, as well as PBB153 and PBDE47 was identified. Table S2 presents the PIP within the BKMR model, with PBDE209 (1.00) displaying the highest PIP value, followed by PBDE28 (0.9960) and PBDE85 (0.4458).

Figure 5 displayed the findings from RCS model. A significant dose-response relationship has been observed among PBDE28, PBDE47, PBDE100, PBDE154, PBDE209, and PBB153 and the hyperlipidemia risk (P for overall < 0.05). A linear dose-response relationship for these BFRs concentrations with hyperlipidemia risk was established (P for nonlinear > 0.05).

Discussion

Our research represents a recent contribution to estimating the association between individual and mixtures of serum BFRs and hyperlipidemia risk in U.S. adults. Logistic regression models confirmed that individual BFRs, such as PBDE 28, PBDE 47, PBDE 85, PBDE 99, PBDE 100, PBDE 154, PBDE 209, and PBB 153, are positively correlated with hyperlipidemia. A positive association between the BFRs mixture and the risk of hyperlipidemia was also consistently observed across the WQS, qgcomp, and BKMR models. In WQS and BKMR model, PBDE209 emerged as the chemical exerting the greatest influence. The results of RCS regression provided additional support to these findings.

In this study, we observed significant positive associations between several BFRs, such as PBDE209 and PBDE100, and the risk of hyperlipidemia. Specifically, PBDE209 was identified as a chemical showing notable contribution to the association. This finding could be further validated in an experimental animal study, where adult male mice exposed to PBDE 209 for 60 days showed growing levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) in comparison to the control group [39]. This phenomenon may be attributed to the molecular-level effects of enduring organic exposure, which induces enlargement of fat cells and subsequently leads to an increase in adipose tissue volume. This disruption in lipid metabolism may lead to higher levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) [39]. Nevertheless, Zhang et al. evaluated the links between BFRS and lipid profiles in adipose tissues among female, revealing a negative association between PBDE 209 and triglycerides [40]. This may be attributed to the variations in BFRs exposure levels among studies or the influence of demographic characteristics, lifestyle factors, or other potential confounders. In addition, evidence indicated that PBDE100 may impact hyperlipidemia through influencing blood glucose levels [41]. And hyperlipidemia was the usual complication linked to inadequate glycemic control in diabetes. Insulin

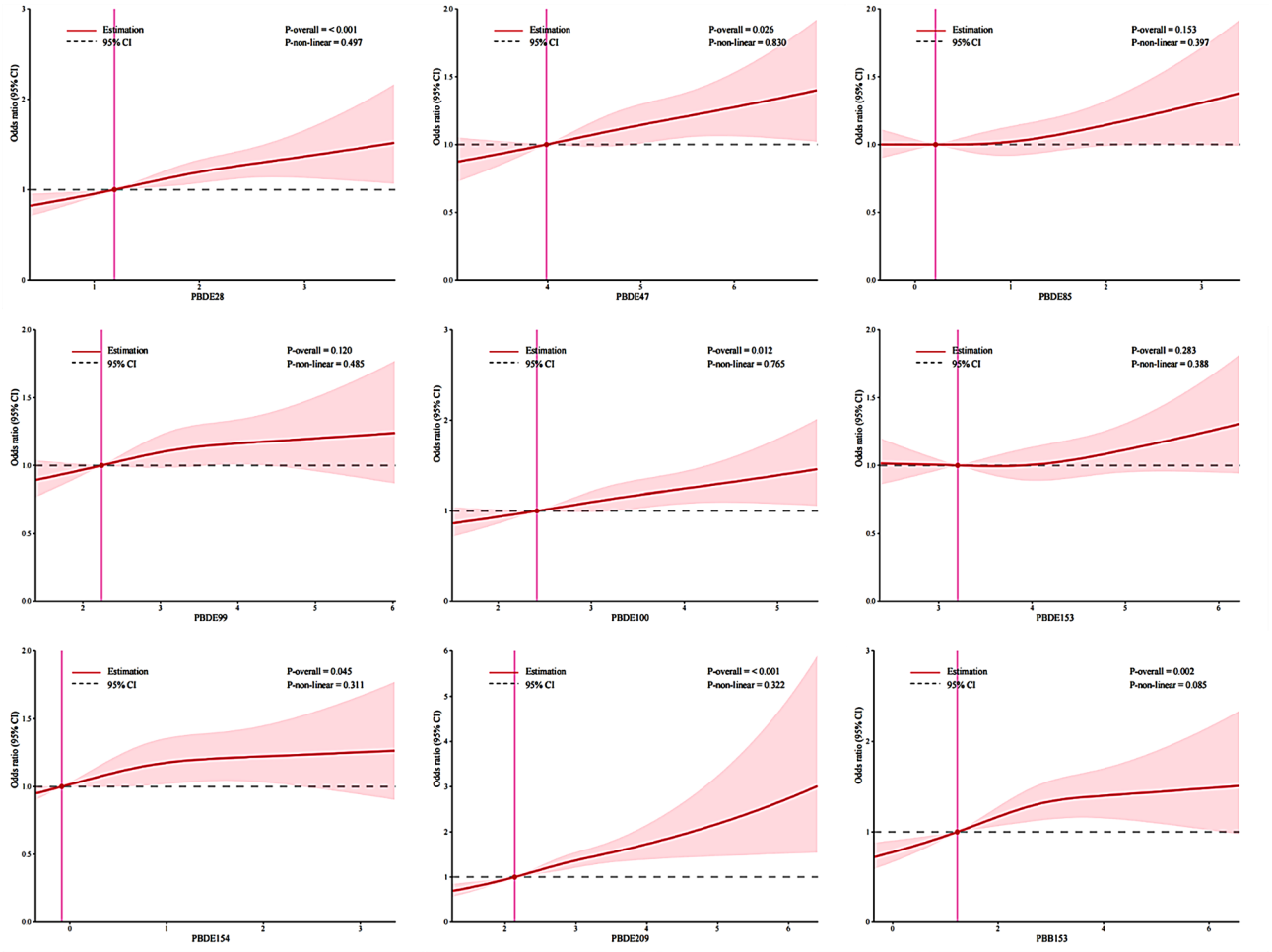

Fig. 5 Dose-response relationship between serum BFRs (ln-transformed) and hyperlipidemia risk. The model was adjusted for covariates including age, gender, race, marital status, family income to poverty ratio, BMI, alcohol use and serum cotinine level

deficiency or resistance can result in reduced lipoprotein lipase activity in diabetic patients, subsequently causing dyslipidemia [42].

Furthermore, the findings demonstrated that PBB153 were positively link to hyperlipidemia risk. The dose of PBB mixture exposure may link to decreased levels in serum triglyceride and cholesterol, thereby influencing blood lipid levels [43]. PBB153 may contribute to hyperglycemia and dyslipidemia, increasing the risk of hyperlipidemia events. Moreover, exposure to PBB153 was a risk factor for subsequent disorders, such as abdominal obesity, and metabolic syndrome, further increasing the risk of hyperlipidemia [44, 45].

The positive correlations were also observed between PBDE 28, PBDE 47, PBDE 99, and PBDE154 and hyperlipidemia risk. As renowned endocrine disruptors, enduring presence of PBDEs in adipose tissue had the potential to interfere with the regular functions of lipid metabolism, thereby posing a health risk to humans [46, 47]. Evidence suggests that elevated serum levels of PBDEs accumulate in adipose tissue and may appear to interfere with related hormone, potentially increasing the risk of hyperlipidemia [48]. Elevated concentrations of PBDEs in blood serum can have a lasting impact on the balance of lipids in the blood and liver. This could temporarily influence lipid metabolism by reversibly inducing liver nuclear receptors. Consequently, this process may result in dyslipidemia [40, 49]. In summary, the predictable negative effects of PBDEs on lipid levels demonstrated a universal toxicological response. The accumulation of PBDEs in human tissue may be a risk factor for hyperlipidemia, disrupting the original balance and even cause serious consequences [50]. Therefore, it is crucial to concentrate on the exposure burden of BFRs and further investigate the underlying mechanisms between BFRs and hyperlipidemia risk.

The results obtained from BKMR, WQS, and the QGC model consistently indicated an upward trend between mixed BFRs and hyperlipidemia risk. Moreover, PBDE209 was found to be the most significant chemical exerting influence. Previous studies also identified the same conclusion that exposure to BFRs mixture was

positively associated with low HDL and hypertriglyceridemia risk in adults [2]. Additionally, the RCS analysis also revealed the positive linear relationship between serum PBDE28, PBDE47, PBDE100, PBDE154, PBDE209, and PBB153 and hyperlipidemia risk. However, further investigation was required to examine the toxic impact of serum BFRs and to elucidate the biological processes.

This study has several strengths. Firstly, we investigated the relationships between serum BFRs and the risk of hyperlipidemia using various methods among a relatively large population. Secondly, the study meticulously examined the individual and co-exposure impact of serum BFRs exposure on hyperlipidemia risk, thereby addressing gaps in prior research. Despite above strengths, several limitations also should be acknowledged. First, we exclusively investigated the association between concentrations of 9 BFRs in serum and hyperlipidemia risk, and further analysis should be conducted to assess the impact of other serum BFRs. Moreover, the findings of these analyses may be susceptible to bias due to residual and unmeasured confounders. For example, since BFRs are strongly lipophilic compounds, poor dietary habits such as increased fat intake may lead to hyperlipidemia and higher exposure to PBDEs, as well as resulting in higher BFRs concentrations in serum. These confounding factors may affect the association between them. In addition, the potential confounding effects of other environmental chemicals on lipids, particularly Per- and Polyfluoroalkyl Substances (PFAS), could theoretically interact with BFRs. We did not examine the impact of co-exposure to PFAS and other emerging contaminants on hyperlipidemia. Future research should further consider the effects of mixed exposures to BFRs, PFAS, and other chemicals to understand their combined effects on lipid levels. Finally, the study design employed in this research was a cross-sectional study, which may limit its ability to infer causal relationships. Given the listed limitations, it is essential to conduct further large-scale prospective investigations to support these findings.

Conclusion

In summary, we identified a positive association between individual and mixed serum BFRs and an elevated risk of hyperlipidemia, with PBDE 209 emerging as the primary driver due to its higher weights and posterior inclusion probabilities. Our findings linking PBDE209 to hyperlipidemia are corroborated by experimental animal studies, confirming the concordance between human and animal data. These findings emphasized the significance of incorporating serum BFRs mixtures in epidemiological studies for evaluating the association between BFRs exposure and hyperlipidemia risk. These findings would contribute to heightening public awareness of preventing BFRs exposures. Prospective research having repeatable metrics are required to validate underlying mechanism of serum BFRs's toxic effect on hyperlipidemia risk.

Abbreviations

NHANES	National Health and Nutrition Examination Survey
BFRs	Brominated flame retardants
PBDEs	Polybrominated diphenyl ethers
WQS	Weighted quantile sum
QGC	Quantile-based g computation
BKMR	Bayesian kernel machine regression
RCS	Restricted cubic splines
BMI	Body mass index
PIR	Income-poverty ratio
LOD	Limits of detection

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22010-0 .

Supplementary Material 1

Acknowledgements

We thank NHANES for its data support.

Author contributions

Conceptualization: J.L, and N. W; Data curation: J. L, Z.L, L. W and L. W; Investigation: X. L and Y. C; Methodology: J. L and N. W; Resources: L. L and Y. H; Software: J. L, N. W, X. Y, Y. L and Y. Z; Supervision: H. Z and Y. F; Validation: L. L and Y. H; Visualization: X. L and Y. C; Writing–original draft: J. L, Z. L, L. W and L. W; Writing–review & editing: L. L and Y. H.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No.72274047).

Data availability

The data that support the findings of this study are openly available in NHANES at https://wwwn.cdc.gov/Nchs/Nhanes/. The data used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 8 June 2024 / Accepted: 19 February 2025
Published online: 12 March 2025

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