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Article

Association between polychlorinated biphenyls and periodontitis: Results from the NHANES 1999–2002

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Abstract: Background: Periodontitis is prevalent among large population, which may induce in bone destruction, attachment loss and finally tooth loss. Polychlorinated biphenyl (PCB) is one of the persistent organic pollutants (POPs), which are endocrine disruptors may destroy the integrity of tissue through possible mechanisms. Recent research has suggested that PCBs can accumulate in adipose tissue and increase the risk of periodontal disease by disturbing the immune system. This cross-sectional study investigated the relationship between PCBs and periodontitis in the general population. **Methods:** In general, cross-sectional associations of PCBs with the prevalence of periodontal disease were investigated in 263 patients in the National Health and Nutrition Examination Survey 1999–2002. Multivariate and stratified analysis was used to measure the association between PCBs and periodontitis. **Results:** From 1999 to 2002, the total number of patients in the National Health and Nutrition Examination Survey (NHANES) database was 21,004, and 3082 patients were finally enrolled after removing the patients who had not been tested for PCBs. Fully adjusted multivariable logistic regressions was performed on PCB lipid adjustments, and the results suggested a positive correlation between PCB180 and periodontitis. Subgroup analysis showed a negative correlation between PCB180 lipid adjustment and periodontitis in patients aged < 20 years (*P* for interaction = 0.002). **Conclusion:** PCB180 is positively correlated with periodontitis of the age over than 20s. However, further studies need to be investigated that whether PCBs affected biomechanical pathways to destroy tissue integrity. This study provides new insights for the prevention of periodontitis from the perspective of environmental exposure.

Keywords: polychlorinated biphenyls; persistent organic pollutant; periodontitis; PCB180; tissue integrity; biomechanical pathways

1. Introduction

Oral bacterial infection and inflammation can cause a common oral disease, which is called periodontitis. Plaque biofilm is constructed by bacteria deposited on tooth surfaces [1], resulting in bone destruction, attachment loss and eventually tooth loss. Studies have revealed that local oral inflammation and systemic inflammation such as type 2 diabetes mellitus together caused to periodontitis [2]. Also, a recent study investigated that periodontitis is with the prevalence of 45%–50% and is one of the sixth most prevalent diseases in humans [3,4]. In the United States (U.S.), approximately 8.9% of adults have severe periodontitis [5].

Persistent organic pollutants (POPs) are lipophilic stable chemicals that bio-accumulate in adipose tissue of living organism [6]. With the development of equipment and cooling systems, polychlorinated biphenyls (PCBs) were widely used

in a range of industrial applications from 1930 to 1979 in U.S. Considering about health effects and environmental persistence, the U.S. stopped producing PCBs in 1977. PCBs penetrate the food chain from external sources and accumulate in animals' fatty tissues. PCBs are found in fatty foods like fish because of their high lipid solubility. Fish is the primary source of exposure for the general population. Also, PCBs can be absorbed from mother's milk or inhaled through contaminated air [7]. Furthermore, human beings are most exposed to conglomerations of these congeners rather than individual types. Several investigations have pointed that background exposure to PCBs is associated with hypertension, diabetes and periodontitis [8–11].

Several studies investigated PCB180. PCB180 alter leptin signaling and lipid metabolism in 3T3-L1 adipocytes, reducing pSTAT3/STAT3 ratio, leading to the increase in lipid content. Also, PCB180 may increase the transcription of inflammatory cytokines, such as IL-6 and TNF-α [12]. PCB180 exposure decreases the amount of NMDA receptors in cerebellum, which mainly contribute to the impairment of the ability to learn the Y maze task [13]. Also, low-dose exposure to POPs including PCB180 may increase the diabetogenic effect than a simple obesogenic effect [14]. However, there are few investigations described the correlation between PCBs and periodontitis.

Therefore, the current study aims to investigate the association of PCBs with periodontitis, and to assess detailed relationship by using publicly available database.

2. Materials and methods

2.1. Study design and data sources

Our research study was based on U.S population—the National Health and Nutrition Examination Survey (NHANES). This study was using the complex multi-stage probability designs. The persons included in this research are in 15 counties across the country. The data in this study came from two continuous NHANES cycles from 1999 to 2002.

2.2. Study sample

We set the following criteria for this study: participants with both complete periodontal examination data and complete PCB lipid adjustments data are included. We excluded those with incomplete periodontal examination and PCB lipid adjustments data. The final intersection of periodontal examination data and PCB data were taken, and 3082 participants were included in the analysis. **Figure 1** presented the flow-chart of this study. The data collection protocol was approved by the Ethics Review Board of the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention, and all participants signed an informed consent form (NCHS protocol number: NHANES 1999–2002, protocol #2005–06). The study was conducted in accordance with the Declaration of Helsinki, since we used de-identified NHANES data, the institutional review board of stomatological hospital and dental school of Tongji University waived the requirement for ethics approval.

2.3. Periodontal classification

Periodontal pocket depth (PD) and attachment loss (AL) at six sites (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual [or palatal], mid-lingual [or palatal] and disto-lingual [or palatal]) for every tooth are included in the periodontal examination [15]. We divided the study participants into two categories [16] according to the CDC-AAP criteria for the diagnosis of periodontitis [17]: Those with periodontitis (two sites with AL ≥ 3 mm and two sites with PD ≥ 4 mm [not on the same tooth] or one site with PPD ≥ 5 mm and those without periodontitis (without any of the above-mentioned features of periodontitis).

2.4. Measurement of PCB lipid adjustments

The Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention receives serum specimens for analysis and stores them under suitable frozen (−20 °C) conditions.

High-resolution gas chromatography/isotope-dilution high-resolution mass spectrometry (HRGS/ID-HRMS) is used to assess PCB lipid adjustment in serum. The analytes of interest are separated using either a C18 solid-phase extraction (SPE) or liquid-liquid extraction process, followed by a multi-column automated cleanup and enrichment procedure. Serum samples are spiked with 13C12-labeled internal standards. Using a Hewlett-Packard 6890 gas chromatograph, the analytes are chromatographed on a DB-5 ms capillary column (30m × 0.25 mm × 0.25 μm film thickness). A Micromass AutoSpec ULTIMA or Finnigan MAT95 mass spectrometer operating in the EI mode are used to quantify specific analytes by ID-HRMS using selected ion monitoring (SIM) at 10,000 resolving power. Every analyte's concentration is determined using a unique standard linear calibration.

2.5. Covariates

The continuous variable used was age, expressed in years. Male and female were the designations for sex. Mexican Americans, non-Hispanic whites, non-Hispanic blacks, other Hispanics, and Other Races—including Multi-Racial, are all classified using the computed variable of race in the NHANES. Less than 9th grade, 9–11th grade, high school, some college, and college graduate are the categories for educational achievement. There were four categories for marital status: never married, divorced in the past, married currently, and others (widowed, living with a partner, separated). The annual income of the household was used as a continuous variable. had you ever been informed you had diabetes or high blood pressure by a doctor? It was either yes or no if you had ever had five or more drinks a day and smoked at least 100 cigarettes in your lifetime. The heights and weights of all individuals were converted into metric measurements to the nearest inch and pound, and then BMI was calculated using a computer. Following WHO standards, the participants were included in one of three categories: underweight to normal weight (≤ 24.9 kg/m^2), overweight (> 25, < 30 kg/m^2), or obese (≥ 30 kg/m^2).

2.6. Statistical analysis

All of the analyses were carried out using the statistical software programs R (2The R Foundation) and Free Statistics software version 1.9.2. Mean ± standard deviation, and frequencies (percentages) were used to describe data and weighted by WTSPO4YR. The t-test was used to analyze the normal distribution and the Kruskal-Wallis test to analyze the skewed distribution in continuous variables. Multivariate logistic regression was used to investigate the relationship between PCB and periodontitis. In multivariate logistic regression, PCB was analyzed as a continuous and categorical variable, with model 1 adjusting for Age + Gender + Race + Education + Marriage + Income， model 2 adjusting for variables from model 1 as well as Smoking + drinking，and model 2 adjusting for variables from model 1 as well as Diabetes + high blood pressure. In addition, we used a constrained cubic spline to flexibly model the association of PCBs with periodontitis. Interaction among subgroups was inspected by the likelihood ratio test. *P*-values < 0.05 (two-sided) were considered statistically significant.

3. Results

3.1. Baseline characteristics of study participants

From the study period (1999–2002), a total number of 21,004 people from U.S. were included in this study. **Figure 1** shows the number of eligible participants and participants analyzed in this study. Participants with a lack of clear documentation of PCB measurements were excluded. Therefore, 3082 participants were finally included. PCB52, 66, 74, 99, 101, 105, 118, 128, 138, 146, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183187 were included in this study. The average age was 43.391 ± 18.441 years, of which the average age of periodontitis was 54.008 ± 13.352. The incidence of periodontitis in this study was 0.09%, of which 57.68% were males and 42.32% were females. There were statistically significant differences in age, education level, marital status, annual household income, smoking, and alcohol consumption between periodontitis group and non-periodontitis group (**Table 1**).

Table 1. Characteristics of study subjects in NHANES, 1999–2002.

Variables	Level	Overall	Non-periodontitis	Periodontitis	*p*
n		167028794.4	151976608.8	15052185.63	
Gender	Male	48.17%	47.23%	57.68%	0.0151
	Female	51.83%	52.77%	42.32%	
Age		43.391 ± 18.441	42.339 ± 18.391	54.008 ± 15.352	< 0.0001
Race	Mexican American	7.46%	7.47%	7.36%	0.3736
	Other Hispanic	6.67%	6.46%	8.85%	
	Non-Hispanic white	69.82%	69.86%	69.39%	
	Non-Hispanic black	10.14%	10.05%	11.12%	
	Other races	5.90%	6.16%	3.27%	

Table 1. (*Continued*).

Variables	Level	Overall	Non-periodontitis	Periodontitis	*p*
Education level	Less than 9th grade	6.44%	5.63%	14.65%	< 0.0001
	9–11th grade	15.02%	14.44%	20.82%	
	High school grad	23.45%	23.65%	21.38%	
	Some college degree	29.67%	30.21%	24.19%	
	College graduate	25.43%	26.07%	18.96%	
Marital status	Married	54.26%	53.79%	59.04%	< 0.0001
	Widowed	6.25%	5.80%	10.81%	
	Divorced	6.82%	6.25%	12.55%	
	Separated	2.49%	2.43%	3.18%	
	Never married	25.32%	26.93%	9.11%	
	Living with partner	4.86%	4.82%	5.31%	
Annual household income		7.423 ± 3.037	7.488 ± 3.054	6.768 ± 2.781	0.0023
Diabetes	Yes	5.56%	5.32%	8.03%	0.0817
	No	93.67%	93.99%	90.45%	
	Borderline	0.76%	0.69%	1.52%	
High blood pressure	Yes	24.03%	23.51%	29.32%	0.0847
	No	75.97%	76.49%	70.68%	
Drinks	Yes	14.63%	13.55%	25.52%	0.0001
	No	85.37%	86.45%	74.48%	
Smoke	Yes	49.36%	47.89%	64.13%	0.0001
	No	50.64%	52.11%	35.87%	
BMI.comp (mean (SD))		27.225 ± 5.886	27.209 ± 5.899	27.381 ± 5.758	0.7214
PCB052		6.168 ± 3.644	6.208 ± 3.709	5.772 ± 2.877	0.1009
PCB066		4.918 ± 2.423	4.933 ± 2.444	4.769 ± 2.196	0.3397
PCB074		10.953 ± 11.135	10.644 ± 10.966	14.068 ± 12.317	0.0002
PCB099		8.371 ± 8.720	8.175 ± 8.648	10.350 ± 9.208	0.0013
PCB101		6.106 ± 3.961	6.141 ± 4.042	5.748 ± 3.006	0.1169
PCB105		4.604 ± 3.746	4.572 ± 3.372	4.919 ± 6.399	0.4005
PCB118		13.641 ± 18.533	13.294 ± 17.844	17.141 ± 24.189	0.0234
PCB128		3.749 ± 1.238	3.765 ± 1.250	3.587 ± 1.103	0.0389
PCB138		30.841 ± 31.663	29.718 ± 30.730	42.184 ± 38.134	< 0.0001
PCB146		6.142 ± 5.441	5.982 ± 5.243	7.766 ± 6.948	0.0001
PCB153		44.461 ± 42.935	42.778 ± 41.814	61.454 ± 49.944	< 0.0001
PCB156		7.273 ± 5.967	7.055 ± 5.677	9.465 ± 8.041	0.0001
PCB157		3.854 ± 1.262	3.849 ± 1.235	3.908 ± 1.508	0.6066
PCB167		3.959 ± 1.503	3.955 ± 1.474	4.001 ± 1.774	0.7162
PCB170		13.327 ± 12.223	12.725 ± 11.435	19.403 ± 17.270	< 0.0001
PCB172		4.097 ± 1.853	4.065 ± 1.726	4.419 ± 2.819	0.0412
PCB177		4.142 ± 1.971	4.122 ± 1.946	4.340 ± 2.203	0.1412
PCB178		4.214 ± 2.057	4.177 ± 1.968	4.583 ± 2.777	0.031
PCB180		31.813 ± 32.951	30.139 ± 31.199	48.715 ± 43.748	< 0.0001
PCB183		4.658 ± 2.899	4.611 ± 2.857	5.123 ± 3.265	0.0204
PCB187		9.988 ± 11.142	9.569 ± 10.798	14.219 ± 13.471	< 0.0001

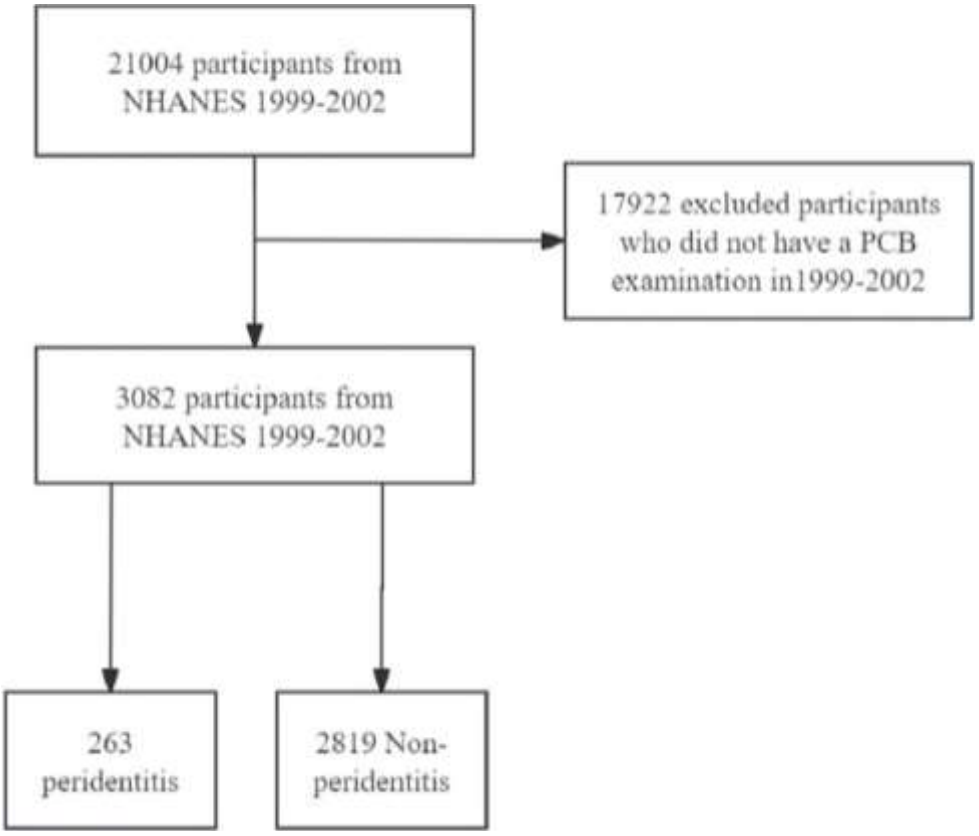

Figure 1. Sample selection flowchart from NHANES 1999–2002.

Note: A total of 21,004 subjects who underwent both periodontitis and PCBs testing and were excluded from the NA were eliminated from the trial, allowing 263 with periodontitis and 2819 with non-periodontitis to enter the study.

3.2. Association of PCBs and its congeners with periodontitis using multivariate and stratified analysis

Table 2 shows the association between PCBs and periodontitis by using a multiple logistic regression model. When PCB is used as a continuous variable, there is a correlation between PCB and periodontitis, with a 1% increase in the probability of periodontitis for every 1 unit of PCB. In addition, PCBs were grouped into quartiles, and the highest quartile and lowest quartile increased the risk of periodontitis approximately nine-fold in the unadjusted model (OR, 9.65; 95% CI, 2.74–12.97), *p* for trend < 0.0001. Similar results were obtained in the adjusted model-1, with p for trend = 0.014 (OR, 3.04, 95% CI, 1.15−8.03); model-2, with *p* for trend = 0.021 (OR, 2.69, 95% CI, 1.04−7.00) and for all covariate-adjusted models, with *p* for trend = 0.041, including age, sex, ethnicity, education, marital marriage, annual household income, smoking, alcohol consumption, BMI, diabetes, and hypertension (OR, 2.64, 95% CI, 0.80−8.74). The results showed PCB180 were not considered to be affected after adding potential confounders.

Table 2. Multivariate and stratified analysis of association between PCB and periodontitis.

PCB (g/L)	Crude		Model-1		Model-2		Model-3	
	***β* (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**
PCB052	0.96 (0.89, 1.03)	0.223	0.97 (0.90, 1.05)	0.431	0.98 (0.90, 1.06)	0.556	0.98 (0.89, 1.07)	0.54
Subgroups								
Q1	1 (Reference)							
Q2	0.85 (0.58, 1.25)	0.409	0.96 (0.60, 1.52)	0.841	0.96 (0.58, 1.59)	0.873	0.95 (0.51, 1.75)	0.0821
Q3	0.93 (0.58, 1.50)	0.758	0.99 (0.56, 1.74)	0.966	1.02 (0.56, 1.84)	0.948	1.00 (0.51, 1.98)	0.991
Q4	0.68 (0.40, 1.15)	0.145	0.78 (0.42, 1.47)	0.408	0.81 (0.43, 1.54)	0.480	0.80 (0.37, 1.73)	0.472
P for Trend		0.243		0.504		0.591		0.564
PCB066	0.96 (0.88, 1.06)	0.437	0.96 (0.89, 1.03)	0.216	0.96 (0.90, 1.03)	0.263	0.96 (0.89, 1.04)	0.298
Subgroups								
Q1	1 (Reference)							
Q2	0.96 (0.62, 1.47)	0.838	0.99 (0.61, 1.61)	0.981	0.97 (0.59, 1.63)	0.91	0.96 (0.52, 1.77)	0.858
Q3	0.90 (0.60, 1.36)	0.598	1.01 (0.62, 1.64)	0.964	1.02 (0.62, 1.69)	0.932	1.01 (0.54, 1.88)	0.971
Q4	0.58 (0.36, 0.93)	0.024	0.63 (0.38, 1.04)	0.067	0.66 (0.40, 1.10)	0.095	0.65 (0.35, 1.22)	0.129
P for Trend		0.037		0.134		0.189		
PCB074	1.02 (1.01, 1.03)	< 0.001	1.0 (0.99, 1.01)	0.577	1.0 (0.99, 1.01)	0.844	1.0 (0.99, 1.01)	0.892
Subgroups								
Q1	1 (Reference)							
Q2	0.95 (0.53, 1.70)	0.856	1.03 (0.52, 2.03)	0.925	1.02 (0.50, 2.10)	0.946	1.00 (0.42, 2.37)	1
Q3	0.88 (0.56, 1.36)	0.541	0.62 (0.35, 1.08)	0.083	0.60 (0.34, 1.07)	0.078	0.61 (0.31, 1.21)	0.115
Q4	2.06 (1.31, 3.25)	0.003	1.00 (0.52, 1.91)	0.99	1.00 (0.50, 2.00)	0.999	1.04 (0.45, 2.42)	0.898
P for Trend		0.003		0.646		0.674		0.797
PCB099	1.02 (1.01, 1.03)	< 0.001	1.0 (0.98, 1.01)	0.863	1.0 (0.99, 1.01)	0.992	1.0 (0.989, 1.02)	0.918

Table 2. (*Continued*).

PCB (g/L)	Crude		Model-1		Model-2		Model-3	
	***β* (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**
Subgroups								
Q1	1 (Reference)							
Q2	0.93 (0.51, 1.71)	0.816	0.99 (0.51, 1.93)	0.966	0.96 (0.48, 1.92)	0.902	0.96 (0.42, 2.19)	0.908
Q3	1.08 (0.65, 1.79)	0.772	0.91 (0.51, 1.65)	0.744	0.90 (0.49, 1.67)	0.712	0.90 (0.43, 1.90)	0.715
Q4	1.77 (1.07, 2.93)	0.029	0.93 (0.53, 1.62)	0.783	0.92 (0.51, 1.67)	0.758	0.93 (0.45, 1.91)	0.79
P for Trend		0.015		0.74		0.727		0.755
PCB101	0.97 (0.91, 1.03)	0.276	0.98 (0.93, 1.04)	0.551	0.98 (0.93, 1.04)	0.544	0.98 (0.92, 1.05)	0.517
Subgroups	1 (Reference)							
Q1								
Q2	0.69 (0.52, 0.92)	0.013	0.80 (0.58, 1.11)	0.154	0.80 (0.57, 1.44)	0.187	0.79 (0.52, 1.20)	0.196
Q3	0.95 (0.59, 1.53)	0.827	1.05 (0.61, 1.82)	0.831	1.04 (0.59, 1.84)	0.872	1.04 (0.54, 2.00)	0.878
Q4	0.67 (0.42, 1.07)	0.091	0.89 (0.52, 1.50)	0.621	0.88(0.51, 1.50)	0.59	0.85 (0.45, 1.61)	0.521
P for Trend		0.4		0.988		0.941		0.868
PCB105	1.02 (0.99, 1.04)	0.166	0.99 (0.93, 1.05)	0.632	0.99 (0.94, 1.05)	0.733	0.99 (0.93, 1.06)	0.805
Subgroups	1 (Reference)							
Q1								
Q2	0.63 (0.44, 0.92)	0.018	0.67 (0.45, 1.01)	0.056	0.68 (0.44, 1.06)	0.08	0.68 (0.40, 1.15)	0.111
Q3	0.66 (0.45, 0.97)	0.035	0.70 (0.44, 1.12)	0.12	0.70 (0.43, 1.14)	0.129	0.69 (0.39, 1.23)	0.148
Q4	0.75 (0.49, 1.15)	0.184	0.56 (0.35, 0.89)	0.019	0.59 (0.37, 0.95)	0.034	0.61 (0.35, 1.06)	0.068
P for Trend		0.2		0.027		0.045		0.066
PCB118	1.01 (1.00, 1.01)	0.001	1.0 (0.99, 1.00)	0.315	1.0 (0.99, 1.01)	0.467	1.0 (0.99, 1.01)	0.599

Table 2. (*Continued*).

PCB (g/L)	Crude		Model-1		Model-2		Model-3	
	***β* (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**
Subgroups	1 (Reference)							
Q1								
Q2	0.98 (0.60, 1.60)	0.929	0.98 (0.57, 1.69)	0.946	0.97 (0.55, 1.71)	0.901	0.96 (0.48, 1.92)	0.89
Q3	1.04 (0.64, 1.69)	0.869	0.69 (0.38, 1.24)	0.19	0.70 (0.39, 1.28)	0.211	0.71 (0.34, 1.47)	0.261
Q4	1.97 (1.19, 3.27)	0.011	0.84 (0.46, 1.55)	0.538	0.89 (0.48, 1.68)	0.689	0.94 (0.44, 2.04)	0.84
P for Trend		0.018		0.409		0.541		0.672
PCB128	0.86 (0.73, 1.02)	0.09	0.95 (0.80, 1.12)	0.489	0.95 (0.80, 1.13)	0.555	0.95 (0.78, 1.15)	0.505
Subgroups	1 (Reference)							
Q1								
Q2	0.77 (0.51, 1.18)	0.227	0.84 (0.51, 1.38)	0.442	0.83 (0.50, 1.38)	0.427	0.82 (0.44, 1.53)	0.435
Q3	0.68 (0.43, 1.09)	0.104	0.84 (0.50, 1.42)	0.482	0.86 (0.50, 1.48)	0.542	0.84 (0.44, 1.61)	0.507
Q4	0.69 (0.44, 1.07)	0.096	0.93 (0.55, 1.59)	0.777	0.94 (0.53, 1.65)	0.798	0.91 (0.47, 1.76)	0.705
P for Trend		0.089		0.706		0.754		0.664
PCB138	1.01 (1.01, 1.01)	< 0.001	1.0 (1.00, 1.01)	0.308	1.0 (1.00, 1.01)	0.322	1.0 (1.00, 1.01)	0.304
Subgroups	1 (Reference)							
Q1								
Q2	0.82 (0.40, 1.65)	0.558	0.73 (0.33, 1.61)	0.399	0.72 (0.32, 1.62)	0.375	0.71 (0.27, 1.89)	0.385
Q3	1.87 (1.17, 2.99)	0.011	1.23 (0.68, 2.20)	0.457	1.16 (0.64, 2.09)	0.585	1.16 (0.59 0, 2.30)	0.578
Q4	2.64 (1.64, 4.25)	< 0.001	1.17 (0.65, 2.11)	0.57	1.12 (0.61, 2.08)	0.673	1.14 (0.55, 2.34)	0.646
P for Trend		< 0.001		0.243		0.316		0.289
PCB146	1.04 (1.02, 1.06)	< 0.001	1.01 (0.99, 1.03)	0.552	1.01 (0.98, 1.03)	0.587	1.01 (0.98, 1.03)	0.539

Table 2. (*Continued*).

PCB (g/L)	Crude		Model-1		Model-2		Model-3	
	***β* (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**
Subgroups	1 (Reference)							
Q1								
Q2	0.94 (0.99, 1.03)		0.99 (0.47, 2.11)	0.983	0.99 (0.45, 2.16)	0.977	0.98 (0.38, 2.52)	0.95
Q3	1.55 (0.79, 3.05)	0.198	1.32 (0.63, 2.76)	0.418	1.29 (0.59, 2.82)	0.469	1.27 (0.50, 3.28)	0.515
Q4	2.23 (1.39, 3.59)	0.002	1.17 (0.69, 2.00)	0.516	1.17 (0.67, 2.06)	0.531	1.20 (0.62, 2.32)	0.488
P for Trend		< 0.001		0.383		0.408		0.371
PCB153	1.01 (1.00, 1.01)	< 0.001	1.0 (1.00, 1.00)	0.197	1.0 (1.00, 1.00)	0.246	1.0 (1.00, 1.00)	0.251
Subgroups	1 (Reference)							
Q1								
Q2	1.39 (0.70, 2.74)	0.334	1.33 (0.64, 2.78)	0.409	1.28 (0.61, 2.70)	0.465	1.26 (0.51, 3.09)	0.518
Q3	2.76 (1.60, 4.76)	< 0.001	1.73 (0.70, 2.74)	0.119	1.62 (0.76, 3.43)	0.177	1.62 (0.67, 3.94)	0.205
Q4	4.13 (2.31, 7.37)	< 0.001	1.86 (0.89, 3.89)	0.089	1.76 (0.81, 3.83)	0.134	1.76 (0.68, 4.57)	0.176
P for Trend		< 0.001		0.073		0.117		0.133
PCB156	1.05 (1.03, 1.07)	< 0.001	1.01 (0.99, 1.04)	0.299	1.01 (0.98, 1.04)	0.348	1.01 (0.98, 1.04)	0.371
Subgroups	1 (Reference)							
Q1								
Q2	1.15 (0.56, 1.04)	0.688	1.16 (0.56, 1.04)	0.682	1.14 (0.52, 2.50)	0.71	1.11 (0.44, 2.84)	0.767
Q3	2.22 (1.19, 4.15)	0.014	1.68 (0.89, 3.17)	0.1	1.66 (0.83, 3.33)	0.132	1.63 (0.71, 3.75)	0.179
Q4	3.12 (1.89, 5.18)	< 0.001	1.52 (0.88, 2.65)	0.12	1.46 (0.82, 2.60)	0.1168	1.46 (0.74, 2.87)	0.195
P for Trend		< 0.001		0.079		0.111		0.117
PCB157	1.04 (0.89, 1.20)	0.625	1.03 (0.90, 1.18)	0.64	1.03 (0.90, 1.18)	0.616	1.03 (0.89 1.19)	0.652

Table 2. (*Continued*).

PCB (g/L)	Crude		Model-1		Model-2		Model-3	
	***β* (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**
Subgroups	1 (Reference)							
Q1								
Q2	0.74 (0.47, 1.17)	0.185	0.78 (0.46, 1.31)	0.307	0.76 (0.44, 1.32)	0.287	0.74 (0.39, 1.47)	0.31
Q3	0.70 (0.45, 1.09)	0.111	0.83 (0.50, 1.37)	0.422	0.84 (0.49, 1.43)	0.468	0.83 (0.44, 1.56)	0.451
Q4	0.94 (0.61, 1.51)	0.865	1.07 (0.64, 1.81)	0.771	1.07 (0.64, 1.80)	0.769	1.05 (0.56, 1.96)	0.84
P for Trend		0.623		0.913		0.882		0.948
PCB167	1.02 (0.93, 1.12)	0.681	0.97 (0.89, 1.06)	0.474	0.98 (0.90, 1.07)	0.599	0.98 (0.89, 1.08)	0.622
Subgroups	1 (Reference)							
Q1								
Q2	0.83 (0.55, 1.25)	0.355	0.90 (0.57, 1.43)	0.635	0.90 (0.55, 1.45)	0.613	0.89 (0.50, 1.60)	0.617
Q3	0.60 (0.39, 0.92)	0.02	0.68 (0.42, 1.09)	0.096	0.69 (0.41, 1.15)	0.133	0.68 (0.37, 1.25)	0.154
Q4	0.89 (0.56, 1.42)	0.626	0.86 (0.49, 1.50)	0.551	0.88 (0.50, 1.55)	0.616	0.87 (0.44, 1.71)	0.596
P for Trend		0.279		0.307		0.371		0.535
PCB170	1.03 (1.02, 1.04)	< 0.001	1.01 (1.00, 102)	0.033	1.01 (1.00, 1.02)	0.054	1.00 (1.00, 1.02)	0.071
Subgroups								
Q1								
Q2	2.03 (0.93, 4.47)	0.075	1.84 (0.77, 4.36)	0.148	1.76 (0.74, 4.17)	0.17	1.75(0.62, 4.95)	0.207
Q3	3.27 (1.59, 6.73)	0.002	1.90 (0.78, 4.61)	0.137	1.78 (0.72, 4.43)	0.181	1.78 (0.59, 5.40)	0.22
Q4	5.07 (2.47, 10.42)	< 0.001	1.97 (0.76, 5.13)	0.145	1.76 (0.68, 4.53)	0.206	1.74 (0.54, 5.59)	0.258
P for Trend		< 0.001		0.22		0.325		0.355
PCB172	1.08 (1.02, 1.15)	0..015	1.03 (0.97, 1.09)	0.343	1.02 (0.97, 1.08)	0.408	1.02 (0.96, 1.09)	0.393

Table 2. (*Continued*).

PCB (g/L)	Crude		Model-1		Model-2		Model-3	
	***β* (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**
Subgroups								
Q1								
Q2	0.86 (0.58, 1.29)	0.461	0.97 (0.60, 1.56)	0.888	0.96 (0.58, 1.58)	0.84	0.95 (0.52, 1.73)	0.814
Q3	0.70 (0.42, 1.16)	0.157	0.79 (0.44, 1.42)	0.393	0.78 (0.42, 1.43)	0.37	0.76 (0.37, 1.54)	0.337
Q4	1.01 (0.63, 1.60)	0.981	0.90 (0.52, 1.55)	0.685	0.91 (0.52, 1.57)	0.695	0.89 (0.46, 1.73)	0.659
P for Trend		071		0.511		0.513		0.465
PCB177	1.05 (0.98, 1.11)	0.145	0.99 (0.93, 1.05)	0.681	0.99 (0.93, 1.06)	0.76	0.99 (0.93, 1.07)	0.857
Subgroups								
Q1								
Q2	0.62 (0.42, 0.92)	0..021	0.64 (0.41, 1.00)	0.05	0.65 (0.41, 1.03)	0.061	0.64 (0.37, 1.12)	0.09
Q3	0.74 (0.44, 1.24)	0.247	0.79 (0.44, 1.42)	0.393	0.78 (0.42, 1.43)	0.369	0.78 (0.38, 1.59)	0.385
Q4	0.99 (0.64, 1.56)	0.98	0.83 (0.51, 1.37)	0.433	0.85 (0.51, 1.43)	0.494	0.86 (0.47, 1.57)	0.521
P for Trend		0..986		0.553		0.593		0.612
PCB178	1.07 (1.01, 1.14)	0.025	1.01 (0.95, 1.08)	0.737	1.01 (0.95, 1.07)	0.75	1.01 (0.94, 1.09)	0.697
Subgroups								
Q1								
Q2	0.68 (0.46, 1.00)	0.05	0.70 (0.44, 1.11)	0.014	0.70 (0.43, 1.15)	0.138	0.69 (0.38, 1.25)	0.155
Q3	0.63 (0.40, 1.02)	0.057	0.66 (0.37, 1.15)	0.124	0.64 (0.36, 1.16)	0.121	0.62 (0.32, 1.22)	0.122
Q4	1.06 (0.68, 1.65)	0.798	0.78 (0.48, 1.21)	0.294	0.79 (0.48, 1. 29)	0.301	0.77 (0.43, 1.339)	0.287

Table 2. (*Continued*).

PCB (g/L)	Crude		Model-1		Model-2		Model-3	
	***β* (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**
P for Trend		0.943		0.245		0.237		0.203
PCB180								
Subgroups	1.01 (1.01, 1.11)	< 0.001	1.0 (1.00, 1.01)	0.06	1.0 (1.00, 1.01)	0.064	1.0 (1.00, 1.01)	0.078
Q1								
Q2	1.26 (0.45, 3.57)	0.646	1.32 (0.43, 4.05)	0.589	1.28 (0.40, 4.08)	0.634	1.26 (0.31, 5.14)	0.67
Q3	3.99 (1.78, 8.94)	0.002	2.74 (1.03, 7.31)	0.044	2.53 (0.94, 6.85)	0.063	2.51 (0.75, 8.39)	0.101
Q4	9.65 (2.74, 12.97)	< 0.001	3.04 (1.15, 8.03)	0.028	2.69 (1.04, 7.00)	0.044	2.64 (0.80, 8.74)	0.087
P for Trend		< 0.001		0.014		0.021		0.041
PCB183	1.05 (1.01, 1.08)	0.012	0.99 (0.95, 1.03)	0.558	0.99 (0.95, 1.03)	0.599	0.99 (0.95, 1.04)	0.69
Subgroups								
Q1								
Q2	0.54 (0.32, 0.89)	0.017	0.56 (0.32, 0.98)	0.043	0.57 (0.32, 1.00)	0.05	0.56 (0.29, 1.09)	0.074
Q3	0.87 (0.59, 1.27)	0.448	0.89 (0.55, 1.44)	0.59	0.88 (0.52, 1.48)	0.588	0.86 (0.46, 1.61)	0.536
Q4	1.16 (0.79, 1.69)	0.444	0.74 (0.49, 1.12)	0.141	0.76 (0.50, 1.16)	0.17	0.73 (0.45, 1.26)	0.195
P for trend		0.23		0.303		0.349		0.336
PCB187	1.02 (1.01, 1.03)	< 0.001	1.0 (1.00, 1.01)	0.27	1.0 (1.00, 1.01)	0.314	1.01 (1.00, 1.02)	0.256

Table 2. (*Continued*).

PCB (g/L)	Crude		Model-1		Model-2		Model-3	
	***β* (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**	***P* value**
Subgroups								
Q1								
Q2	1.26 (0.60, 2.65)	0.535	1.32 (0.58, 2.98)	0.647	1.26 (0.55, 2.88)	0.543	1.25 (0.47, 3.36)	0.56
Q3	1.94 (1.04, 3.63)	0.038	1.22 (0.56, 2.67)	0.578	1.18 (0.51, 2.72)	0.662	1.20 (0.45, 3.20)	0.639
Q4	3.64 (2.04,6.49)	< 0.001	1.53 (0.69, 3.38)	0.261	1.39 (0.64, 3.03)	0.361	1.41 (0.56, 3.55)	0.361
P for Trend		< 0.001		0.314		0.42		0.399

Note:
The cutoff value for the subgroup was to divide the PCB into the 4th percentile;
Multiple linear regression;
Model-1 was adjusted for Sex, Age, BMI, Education, Race, Marital Status, Annual Household Income;
Model-2 was adjusted for Model1 +cigarettes and Drink; Model-3 was adjusted for Model2 + Hypertension + Diabetes.

3.3. Inflection point analysis and subgroup analysis of PCB and periodontitis

The relationship between all PCB subtypes and periodontitis was linear (Appendix **Figure A1**; **Figure 2**; P for non-linearity ≥ 0.05). The results of Spearman correlations showed positive correlations between each two PCBs. PCB170 and PCB180 had the strongest correlation (r = 0.97), followed by the correlation of PCB138 and PCB153 (r = 0.96) and the correlation of PCB146 and PCB153 (r = 0.93) (Appendix **Figure A2**). In the subgroup analysis, we could see a negative correlation between changes in PCB180 and the prevalence of periodontitis in those aged < 20 years old (OR, 0.51, 95% CI, 0.37−0.68; P < 0.001). Also, with the age increasing, PCB180 showed a positive correlation with the prevalence of periodontitis in those aged from 20–39 years old (OR, 1.02, 95% CI,1.00−1.04; *P = 0.05*) and aged from 40–59 years old (OR, 1.01, 95% CI,1.00−1.01; P = 0.01), with P for interaction = 0.002 (**Figure 3**).

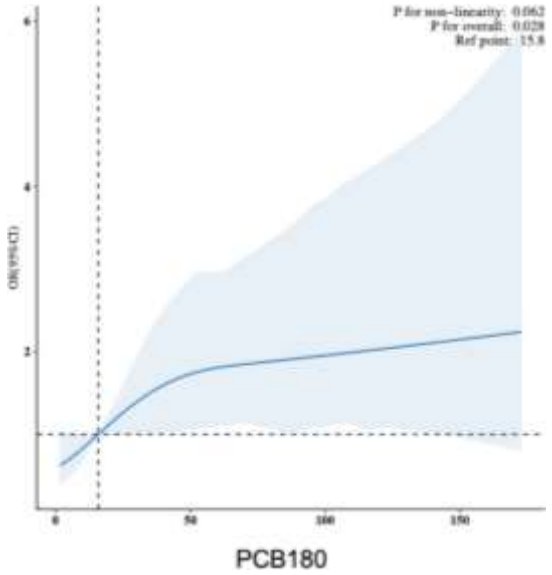

Figure 2. Association of PCB180 with periodontitis among participants in NHANES 1999–2002.

Note: Odds ratios (ORs) were adjusted for sex, age, BMI, education, race, marital status, annual household income, cigarettes, drink, hypertension and diabetes. The solid line represents ORs, and the shaded areas represent 95% confidence intervals. NHANES: National Health and Nutrition Examination Survey; OR: odds ratio.

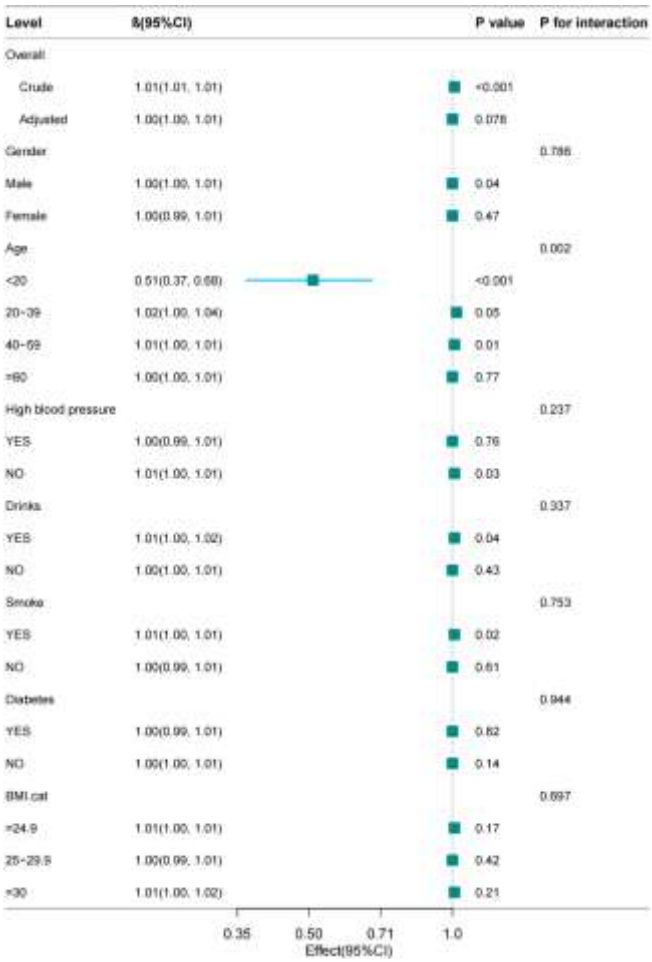

Figure 3. Forest plot investigates the association between PCB180 and periodontitis after adjusting for all covariates.

4. Discussion

To the best of our knowledge, this study is the first to provide a novel idea of the association of PCB180 with periodontitis risk. This cross-sectional study used a nationally representative sample of American people. We investigated the association between periodontitis and PCB052, PCB066, PCB074, PCB099, PCB101, PCB105, PCB118, PCB128, PCB138, PCB146, PCB153, PCB156, PCB157, PCB167, PCB170, PCB172, PCB177, PCB178, PCB180, PCB183 and PCB187. Subgroup analysis suggested an interaction between age groups. There was a significant negative correlation between PCB and periodontitis in patients younger than 20 years of age. We also observed a potential linear relationship between periodontitis and PCB180.

The NHANES database detected PCBs by using mixed sample testing since 2004 while this method may cause a great deviation in the statistical results, so we chose single sample test data from 1999 to 2002 to ensure the accuracy of the analysis results. Some studies show that the pathogenesis of aggressive periodontitis is much more complicated than periodontitis, in which the patient is mostly under 30 years old. Also, the latest version of the periodontitis classification has deleted aggressive periodontitis and the new classification of periodontitis mainly investigates the periodontal condition of the population over than 30 years old may to eliminate the impact of aggressive periodontitis [18]. However, the purpose of our study is to explore the relationship between PCBs and periodontitis, hence, we included people of all ages in our study.

Our data reveled that periodontitis may be affected by age, education level, marriage, income, drinks and smoke, and periodontitis and non-periodontitis can be found different in gender. We also found there is difference in PCB74, 99, 118, 128, 138, 146, 153, 156, 170, 172, 178, 180, 183, 187 between non-periodontitis group and periodontitis group ($P < 0.05$). The proportion of people in periodontitis group was higher than non-periodontitis group except PCB128. The data showed that all PCBs have linear relationship with periodontitis. However, only PCB180 was significantly associated with periodontitis in the multivariate and stratified analysis after we adjusted the model.

Recent studies have revealed the complex pathogenesis of periodontal disease rather than virulent microorganisms [19]. The susceptibility of an individual to periodontitis depends on identified and unidentified characteristics of the host, including the nonspecific and specific immune system [20]. The patients who exhibit periodontal inflammation or destruction that shows disproportionate to the degree of local irritants were suspected have immunodeficiency. Also, the patients who have innate impaired immune responses at a higher risk for periodontal disease [21].

Several reports have showed that exposure to POPs may be harmful to the health of general population [22,23]. Brominated flame retardants (BFRs) are widely used to mitigate the flammability of various materials. A recent study revealed that a significant association between specific serum BFRs (PBDE-47, PBDE-99, and PBDE-154) and periodontitis and its severity. Another study also investigated that several BFRs, including PBDE-28, PBDE-47, PBDE-85, PBDE-99, PBDE-100, PBDE-154, PBDE-183, and PBB-153, were found to be positively associated with periodontitis [24,25]. Regarding potential mechanisms, PCBs may affect the immune

system. A study for the first time evaluated the immunotoxic effect of PCB29-pQ, an active quinone-type PCB metabolite. After PCB29-pQ exposure, the morphology and structure of the mouse spleen and lungs were changed, and partial types of lymphocyte subsets in the spleen were significantly reduced. The activation of caspase-3, the significant up-regulation of Bax and the decrease of Bcl-2 indicated occurrence of apoptosis. Also, PCB29-pQ caused the imbalance of Th1/Th2 cytokines and promoted the Th1-type immune response. PCB29-pQ induced spleen immune dysfunction targeting the apoptosis pathway and Th1/Th2 cytokines imbalance in mice [26–30]. Experimental and epidemiologic evidence have demonstrated that POPs markedly affect the function of cellular, subcellular, or molecular components of the immune system [31,32]. Reduction of immune activity may evolve into an immune deficit and increased susceptibility to neoplasm and diseases. Enhancing the normal immune response may evolve into autoimmunity and allergy. A previous study reported the positive associations between serum concentrations of POPs, such as PCBs, and rheumatoid arthritis [33]. The current study also shows that exposure to PCB180 may increase the susceptibility of periodontitis.

Our data also showed the positive association only between PCB180 and population over than 20-years-old with periodontitis. The immune system declines about 2%–3% a year from our 20 s and the human immune system dramatically changes begins with the sixth decade of life, which undergoes a state of immune-senescence continuously [34,35]. This phenomenon may be due to the gradual decline of the immune system after the age of 20, which is unable to fight the effects of PCBs. Previous study has reported the potential link between exposure to PCBs and auditory impairment [36]. A study also described PCBs mediated the pathology in multiple organs, such as liver, gut, vascular tissues, brain as well as immune system [30]. PCBs also can activate the aryl hydrocarbon receptor, which is an important pleiotropic signal transducer and a cytosolic evolutionary conserve ligand-activated transcription factor and related to breast cancer and ocular disease [37,38]. Since there are few studies demonstrated the detection concentration of PCB, more studies are needed in the future to investigate the concise detection concentration of PCBs, which are beneficial for detailed research. Also, the mechanism that how PCB180 affect periodontitis need to be investigated by basic experiments in the near future.

This study has some limitations. First, there are some limitations to this study, the cross-sectional study design in this paper limits our determination of a causal relationship between PCB exposure and periodontitis. We are unable to conclude whether PCB exposure caused periodontitis, or if there is a reverse causal relationship. In order to more accurately assess the potential causal relationship between them, we take a cautious approach in interpreting the results of the current study, and for further studies we consider adopting a longitudinal study design, which will help to reveal the temporal association between exposure and outcomes. Second, Since the NHANES database only reports the concentration of PCB metabolites, we are unable to accurately identify specific patterns of exposure to PCBs by individuals, including exposure through different routes such as food, air, or water. This lack of information limits our understanding of the relationship between PCB exposure and health outcomes and may affect our ability to propose targeted interventions. In order to gain a more complete understanding of the health effects of PCB exposure, we will further

collect and analyze more detailed information on PCB exposure pathways in the future. Third, although we controlled for some known confounders, this study may not adequately account for all potential confounders, such as an individual's eating habits, geographic location of residence, and other environmental contaminants to which they may be exposed. Finally, in view of the complexity of the NHANES survey design, this study used PCB as a continuous variable and 4quantile method for sensitivity analysis, subgroup analysis, and restriction cubic spline plot for detailed statistical analysis to further ensure the robustness of the relationship between PCB and periodontitis.

5. Conclusions

Taken together, our cross-sectional study indicates a positive association between PCB180 and the population with periodontitis of the age over than 20 s. Effective preventions are needed to stop the accumulation and spread of PCBs to ensure the human health and environment safety.

Author contributions: Conceptualization, TC; methodology, TC; investigation, YL and TC; data curation, YL and TC; writing—original draft preparation, YL; writing—review and editing, YL and TC. All authors have read and agreed to the published version of the manuscript.

Ethical approval: Not applicable.

Conflict of interest: The authors declare no conflict of interest.

Abbreviations

PCB	Polychlorinated biphenyl
POP	Persistent organic pollutants
HRGS/ID-HRMS	High-resolution gas chromatography/isotope-dilution high-resolution mass spectrometry
SPE	Solid-phase extraction
SIM	Selected ion monitoring

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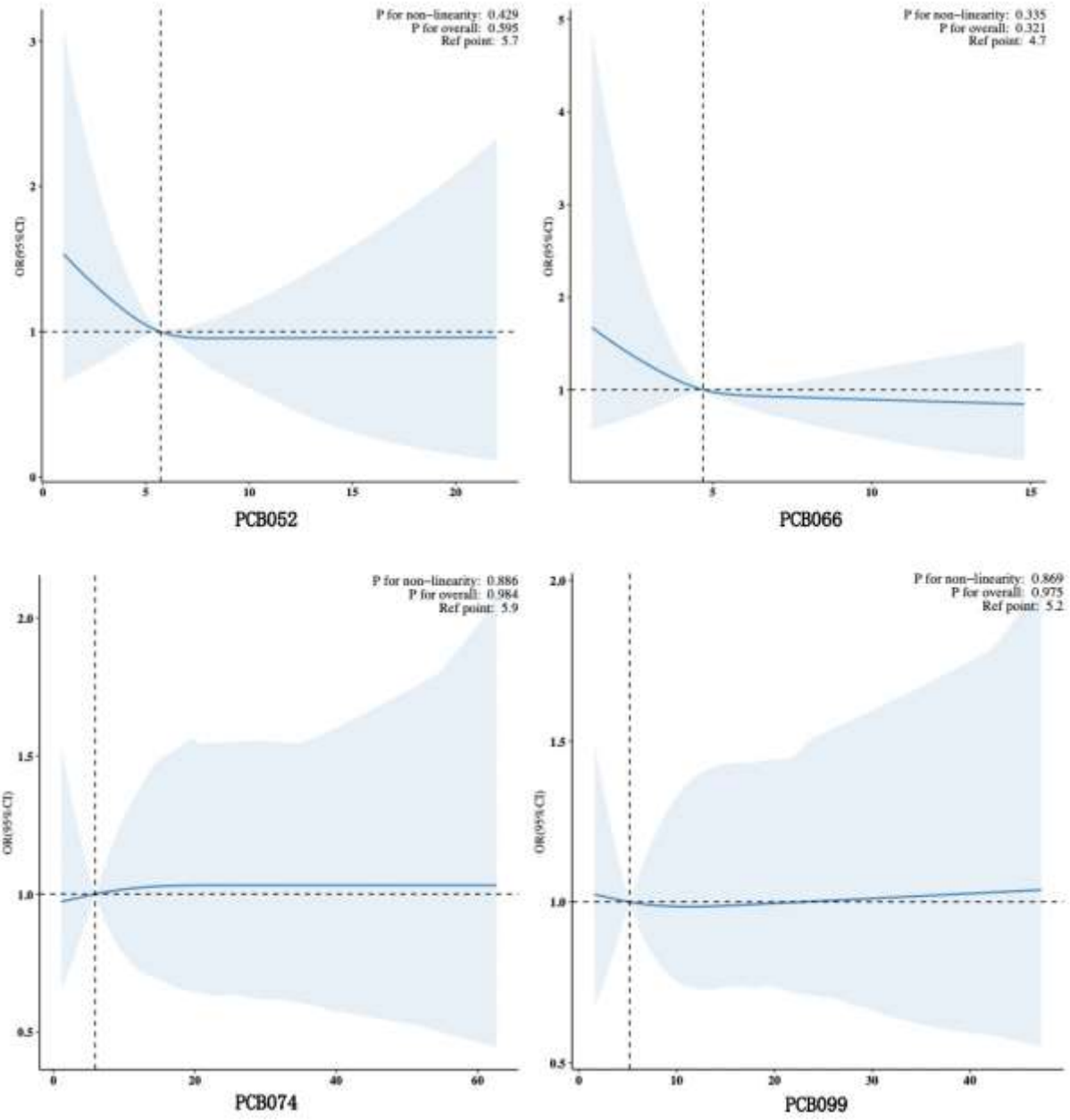
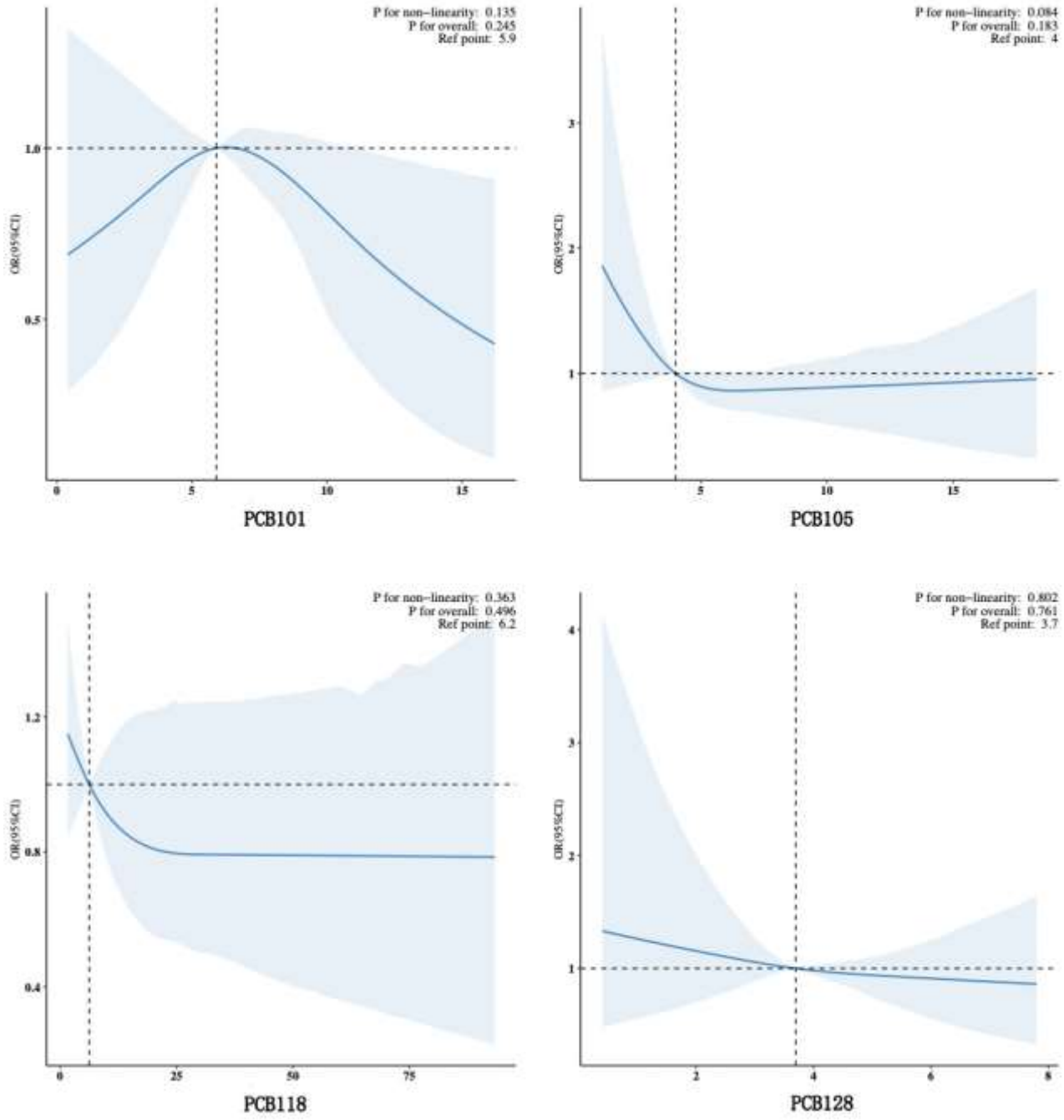
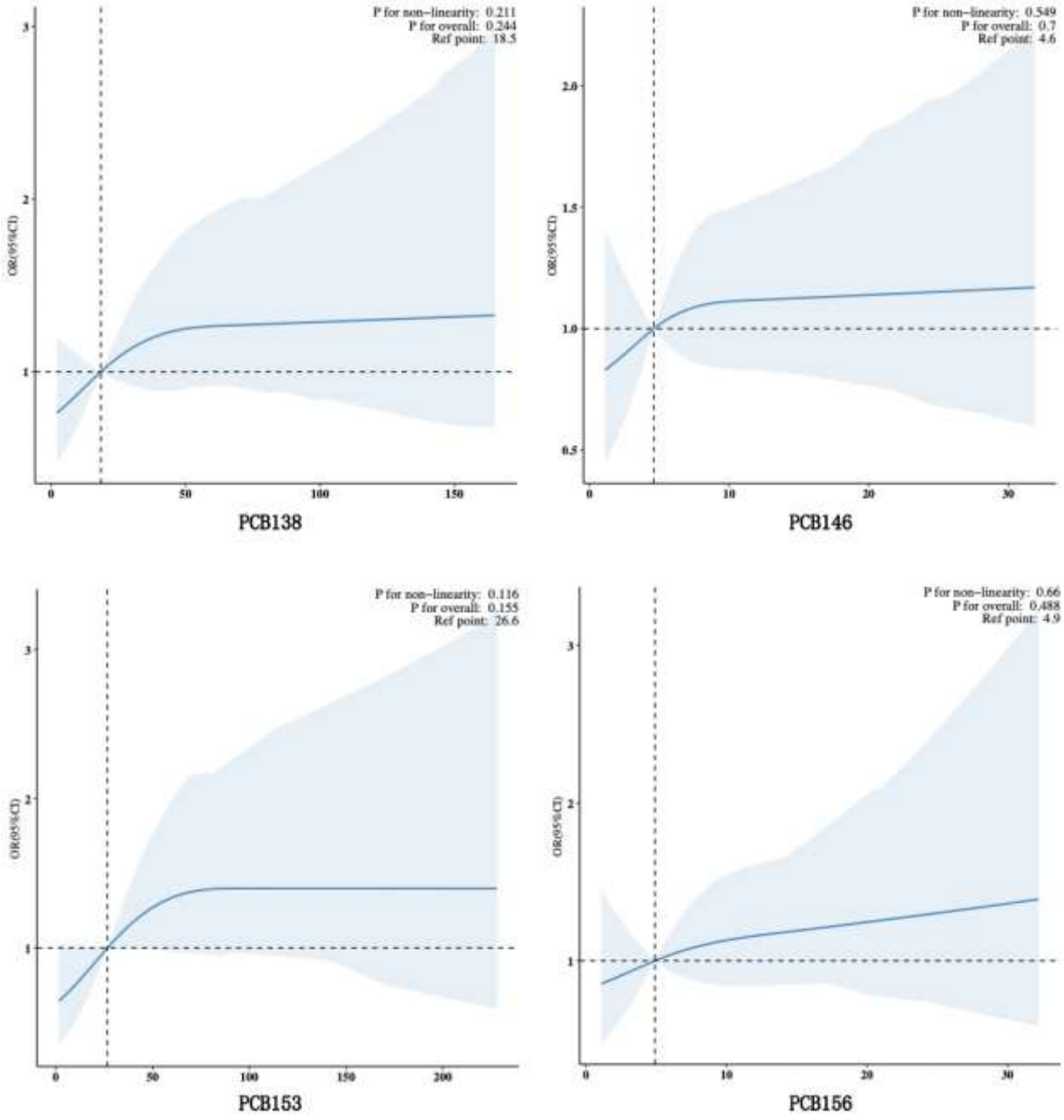
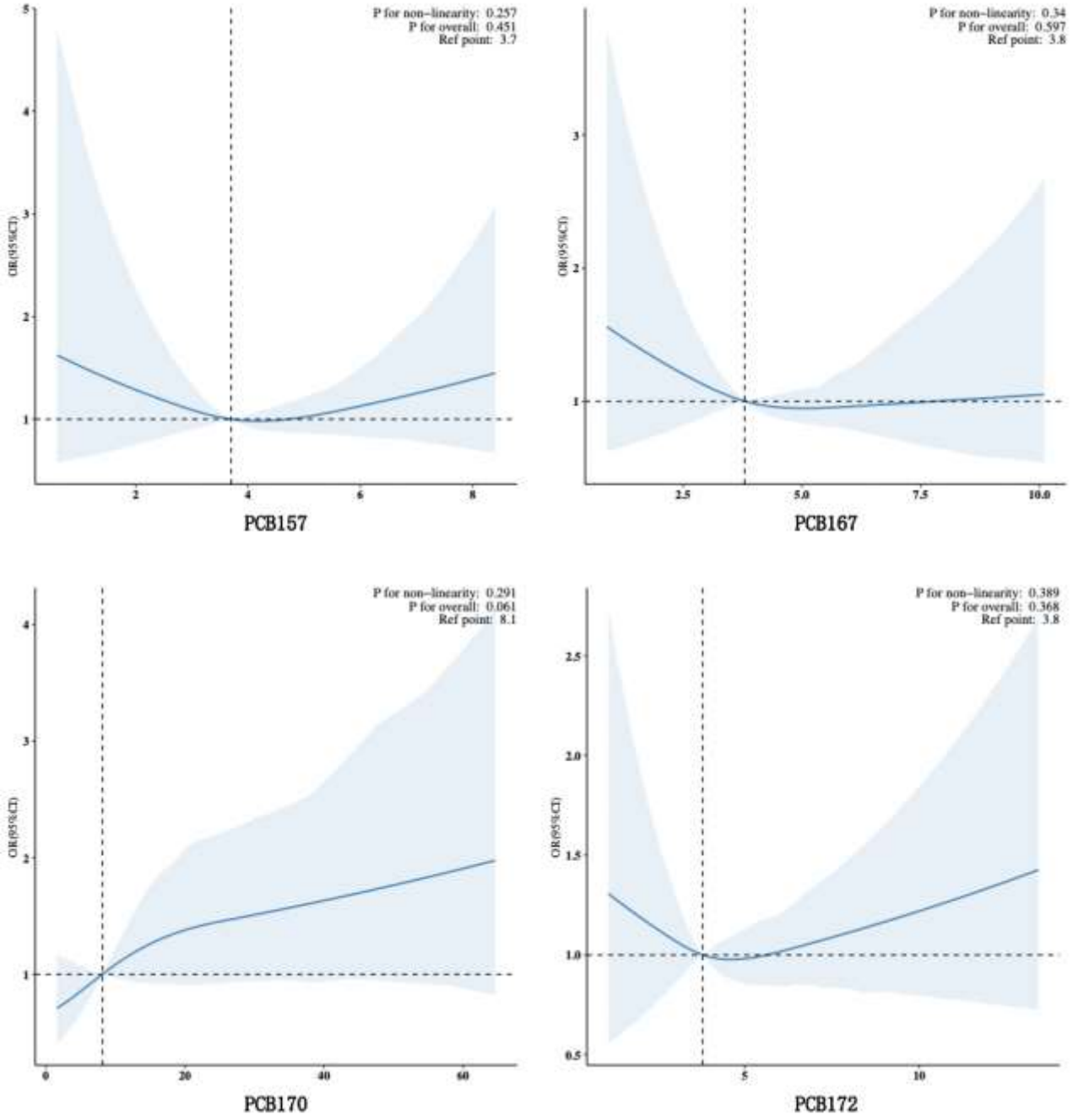
Appendix

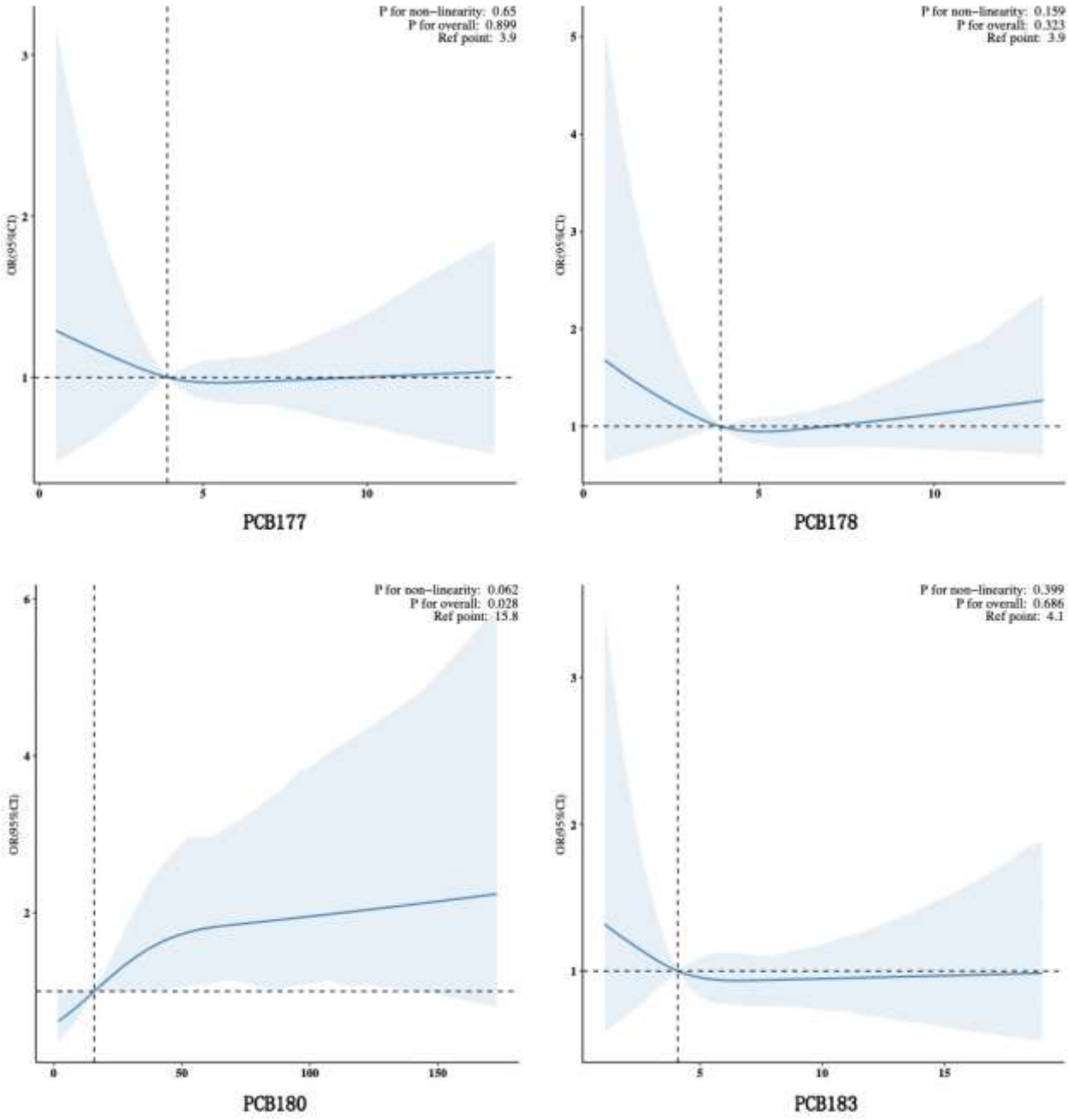
Association of polychlorinated biphenyls with periodontitis among participants in NHANES 1999–2002 and spearman correlation matrix of 21 polychlorinated biphenyls in NHANES from 1999–2002.




P for non−linearity: 0.135
P for overall: 0.245
Ref point: 5.9
OR(95%CI)
PCB101
P for non−linearity: 0.084
P for overall: 0.183
Ref point: 4
OR(95%CI)
PCB105
P for non−linearity: 0.363
P for overall: 0.496
Ref point: 6.2
OR(95%CI)
PCB118
P for non−linearity: 0.802
P for overall: 0.761
Ref point: 3.7
OR(95%CI)
PCB128


P for non−linearity: 0.211
P for overall: 0.244
Ref point: 18.5
OR(95%CI)
PCB138
P for non−linearity: 0.549
P for overall: 0.7
Ref point: 4.6
OR(95%CI)
PCB146
P for non−linearity: 0.116
P for overall: 0.155
Ref point: 26.6
OR(95%CI)
PCB153
P for non−linearity: 0.66
P for overall: 0.488
Ref point: 4.9
OR(95%CI)
PCB156


P for non-linearity: 0.257
P for overall: 0.451
Ref point: 3.7
OR(95%CI)
PCB157
P for non-linearity: 0.34
P for overall: 0.597
Ref point: 3.8
OR(95%CI)
PCB167
P for non-linearity: 0.291
P for overall: 0.061
Ref point: 8.1
OR(95%CI)
PCB170
P for non-linearity: 0.389
P for overall: 0.368
Ref point: 3.8
OR(95%CI)
PCB172


P for non−linearity: 0.65
P for overall: 0.899
Ref point: 3.9
OR(95%CI)
PCB177
P for non−linearity: 0.159
P for overall: 0.323
Ref point: 3.9
OR(95%CI)
PCB178
P for non−linearity: 0.062
P for overall: 0.028
Ref point: 15.8
OR(95%CI)
PCB180
P for non−linearity: 0.399
P for overall: 0.686
Ref point: 4.1
OR(95%CI)
PCB183

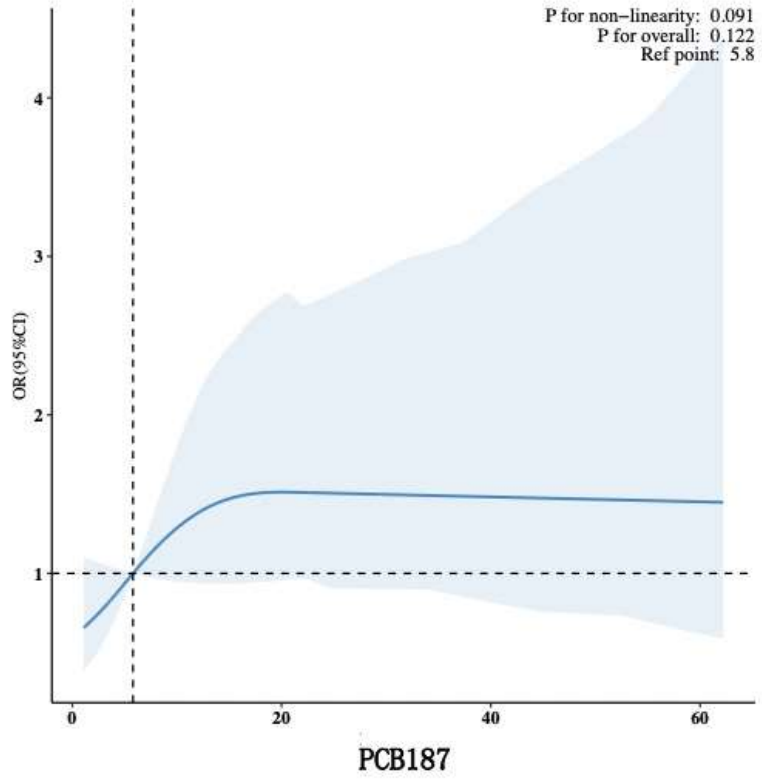


Figure A1. Odds ratios (ORs) were adjusted for sex, age, BMI, education, race, marital status, annual household income, cigarettes, drink, hypertension and diabetes.

Note: The solid line represents ORs, and the shaded areas represent 95% confidence intervals. NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

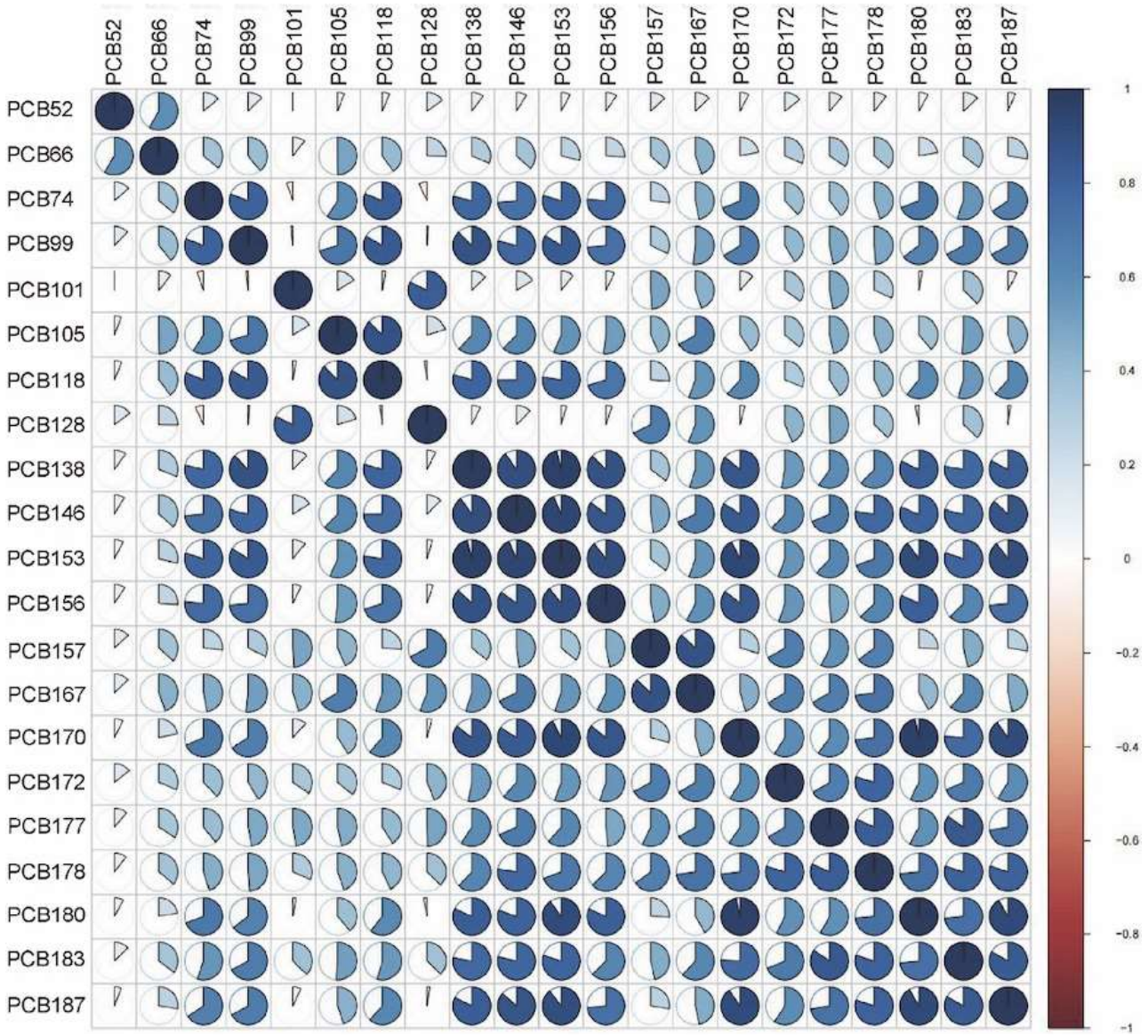


Figure A2. Spearman's correlation. Spearman correlation matrix of 21 polychlorinated biphenyls in NHANES from 1999–2002.

Note: PCB: polychlorinated biphenyls.