The bisphenol F and bisphenol S and cardiovascular disease: results from NHANES 2013–2016

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Abstract

Background: Bisphenol F (BPF) and bisphenol S (BPS) have replaced bisphenol A (BPA) in the manufacturing of products containing polycarbonates and epoxy resins; however, the effects of these substitutes on the risk of cardiovascular disease (CVD), including congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke, have not been assessed.

Objective: To examine the association of urinary BPS and BPF with CVD risk in a U.S. representative U.S. population.

Methods: Cross-sectional data from 1267 participants aged 20–80 years from the 2013–2016 National Health and Nutrition Examination Survey (NHANES) were analyzed. Survey-weighted multiple logistic regression was used to assess the association between BPA, BPF, BPS and CVD. The Bayesian kernel machine regression (BKMR) model was applied to assess the mixture effect.

Results: A total of 138 patients with CVD were identified. After adjusting for potential confounding factors, the T3 tertile concentration of BPS increased the risk of total CVD (OR: 1.99, 95% CI 1.16–3.40). When stratified by age, we found that BPS increased the risk of CVD in the 50–80 age group (OR: 1.40, 95% CI 1.05–1.87). BPS was positively associated with the risk of coronary heart disease, and the T3 tertile concentration of BPS increased the coronary heart disease risk by 2.22 times (95% CI 1.04–4.74). No significant association was observed between BPF and CVD. Although the BKMR model did not identify the mixed exposure effect of BPS, the risk of CVD increased with increasing compound concentration.

Conclusion: Our results suggest that BPS may increase the risk of total CVD and coronary heart disease in the US population, and prospective studies are needed to confirm the results.

Keywords: Bisphenol S, Bisphenol F, CVD, Coronary heart disease

Introduction

Bisphenol is a chemical epoxy resin compound containing two hydroxyl phenyl groups [27, 45]. Bisphenol, as an endocrine disruptor, has adverse effects at very low doses [45]. Bisphenol A (BPA) has long been used in plastics [5, 8]. Higher concentrations of BPA have been associated with CVD [4], obesity [41], diabetes [44], and hypertension [6], and brain [39], reproductive system damage [33]. However, due to these adverse effects, some countries...
have started to ban or restrict the use of BPA in consumer products.

Bisphenol S (BPS) and bisphenol F (BPF) are two substitutes for BPA [37]. BPF and BPS can be found in food packaging items, beverage containers, paper products [27], personal care products (e.g., body wash, hair care products, makeup, lotions, toothpaste) [24], food (e.g., dairy products, meat and meat products, vegetables, canned foods, cereals) [23], and baby bottles [42]. Recently, health concerns have been raised about these substitutes as well. Higher concentrations of BPS and BPF were associated with depressive symptoms [12], asthma, and hay fever [27]. Due to endocrine-disrupting effects similar to BPA [10, 20, 37], we hypothesized that exposure to BPS or BPF is associated with an increased risk of CVD in humans [10].

Cardiovascular disease (CVD) is recognized as the leading cause of death, with an estimated annual mortality of 17.9 million worldwide and more than 800,000 deaths occurring in the USA (AHA report 2020) [47]. Approximately 80% of CVD deaths are attributable to heart attacks and strokes, and one-third occur in people ≤70 years [47]. Atherosclerosis is the most common form of vascular disease and constitutes the major cause of death, causing 17.5 million CVD deaths annually (31% of the global mortality) [43]. Although traditional risk factors for CVD, such as family history, diabetes, hypertension, dyslipidemia, and obesity, have been identified, nearly 20% of CVD patients do not have any of these risk factors [19, 51, 52]. Environmental factors, including nonylphenol (NP), bisphenol A (BPA), polychlorinated biphenyl (PCB), organo-chlorine pesticide (OCP), and phthalate (PAE) [10], exert additional synergistic or additive effects on these traditional risk factors, further increasing the risk of CVD [2, 17, 50].

Using the National Health and Nutrition Examination Survey (NHANES), we performed a cross-sectional analysis using a representative U.S. adult population to examine the association between BPS and BPF exposure and CVD, including congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke.

Materials and methods

Study population

Our study is based on data from the National Health and Nutrition Examination Survey (NHANES) 2013–2016. Detailed descriptions of the NHANES study design and methods are available elsewhere (National Center for Health Statistics, NCHS). “The NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States” (https://www.cdc.gov/nchs/nhanes/about_nhanes.htm). The survey is unique in its combination of interviews, physical examinations, and laboratory tests designed with multilevel probability sampling. All participants provided informed consent when they were recruited to participate in the study [4]. The National Center for Health Statistics Research Ethics Review Board approved the implementation of the protocol for the NHANES [4]. From 2013 to 2016, a total of 1,267 NHANES participants with available bisphenol and CVD data were included in the final analysis. The whole data integration process is shown in the figure below (Fig. 1).

CVD

CVD was determined by a combination of a self-reported physician diagnosis and the completion of a standardized medical condition questionnaire. The participants were asked five separate questions: "Has a physician or other health care professional ever told you that you have had congestive heart failure/ coronary heart disease/ angina pectoris/ heart attack/ stroke?" If the participant answered "yes" to any of the five separate questions above, the participant was determined to be a patient with CVD (https://wwwn.cdc.gov/Nchs/Nhanes/2015-2016/MCQ_I.htm). We excluded all participants who said they did not know and those who refused to answer.

Bisphenol exposure

As part of the NHANES ongoing biological surveillance program, in one third of NHANES participants, BPS and BPF were measured using online solid-phase extraction high-performance liquid chromatography with atmospheric pressure chemical ionization–mass spectrometry (https://wwwn.cdc.gov/nchs/data/nhanes/2015-2016/manuals/2016_MEC_Laboratory_Procedures_Manual.pdf). The lower limits of detection of BPS, BPF and BPA were 0.1, 0.2 and 0.2 ng/mL, respectively. The NHANES quality assurance and quality control (QA/QC) protocols meet the 1988 Clinical Laboratory Improvement Act mandates.

Covariates

From demographics and questionnaire data, we selected the following as potential confounding variables in our analysis: age, sex, race/ethnicity, education level, the family poverty-income ratio (PIR), smoking status, alcohol drinking status, physical activity, blood pressure, and diabetes. Data on energy intake were acquired from the dietary intake data collected in two 24 dietary recall interviews. Based on the body measurement examination data and questionnaire data, we obtained body mass index (BMI, kg/m²) and blood pressure data. Based on
measurements in the laboratory data, we obtained urine creatinine data, and low-density lipoprotein (LDL) data. The PIR, as a proxy for socioeconomic status, was estimated using guidelines and adjustment for family size, year and state [27]. Urinary creatinine is used to describe the degree of urine dilution [27]. Urine creatinine analysis was performed on a Roche Mod P using an enzymatic (creatinate) method [14].

Statistical analysis
The survey procedure using the NHANES database was adapted to the complex survey design and included appropriate sample weights for this random subsample to obtain accurate estimates representing the civilian population of the United States (https://www.cdc.gov/nchs/data/nhanes/nhanes_13_14/NHANES_Overview_Brochure.pdf). Categorical variables are presented as frequency and percentage, while continuous variables are presented as the mean and standard deviation (SD). Categorical variables and continuous variables were compared using the $\chi^2$ test and the $t$ test, respectively. The association between bisphenols and the risk of CVD was analysed by survey-weighted multiple logistic regression analysis, and three separate models were constructed for each bisphenol that was available in the NHANES database. The adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for CVD by the tertiles of each bisphenol were calculated. Subgroup analyses were performed to investigate the association between the bisphenols and CVD subtypes (congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke). All variables were checked for normality of distribution, and log transformations were applied on the independent variable. The levels of BPS, BPF and BPA were divided into tertiles (T1, T2, and T3) and we described them in the statistics. The restricted cubic spline (RCS) model was used to further investigate the nonlinear relationship between the bisphenols and the risk of CVD. The BKMR model estimates the multivariable exposure–response function in a flexible way that allows for nonlinearity, while adjusting for covariates including potential confounding factors, and then simultaneously conducting variable selection on the groups of correlated exposures as well as on the individual exposures within each group to address the multicollinearity.
problem [3]. We stratified and interacted the associations of age, gender, smoking status, alcohol drinking status, blood pressure, BMI, PIR and physical activity for their association with the risk of CVD. We further used the BKMR model to explore the relationships between a mixture of BPS, BPF, and BPA exposures and the risk of CVD. We used STATA to perform a stratified analysis and interaction on the data. All data analyses were performed in STATA (version 16.0 SP) and R (version 4.0.5) software.

Results

Cohort characteristics
A total of 1267 participants were finally included in our study, of whom 138 (10.90%) had CVD. The CVD subtypes was 2.76%, 4.19%, 2.05%, 4.66%, and 3.79% for congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke, respectively. The average ages of the non-CVD and CVD patients were 47.78 ± 16.98 and 65.83 ± 11.17 years, respectively. In the overall study population, there were more non-Hispanic whites (47.10%) and non-Hispanic blacks (26.09%) among CVD group than the health group. There were significant differences in age, physical activity, smoking status, cancer, diabetes, and blood pressure (all \( P < 0.05 \)) between the non-CVD and CVD patients (Table 1).

Association between bisphenols exposure and the risk of total CVD

The T3 tertile of BPS increased the risk of total CVD by 1.99 times (95% CI 1.04–4.74) after adjusting for all the covariates, with a \( P \) for trend was of 0.011. An association between BPF, BPA and the risk of total CVD (Table 2) was not identified. When stratified by age, we found that the T3 tertile of BPS increased the risk of CVD by 1.40 times (95% CI 1.05–1.87), with a \( P \) for trend of 0.021 in the 50–80 age group, and we did not find this association in the 20–49 age group (Fig. 2).

We further performed the analysis stratified, we found that BPS increased the risk of CVD in the 50–80 year subgroup of age, overweight/obesity subgroup of BMI, PIR<2.5 subgroup of PIR, never/moderate subgroup of physical activity, and former/active smoker subgroup of smoking status (Fig. 2). We found no association between the interaction and the risk of CVD (Fig. 2). The RCS model showed that there was a linear relationship between BPS and the risk of CVD (\( P \) for nonlinear association = 0.078) in all participants (Additional file 1: Fig. S1A). The RCS model showed that there was a linear relationship between BPF and the risk of CVD (\( P \) for nonlinear association = 0.0878) in all participants (Additional file 1: Fig. S1B).

The mixed-effects between bisphenols and the risk of CVD using the BKMR model

The BKMR model did not identify a mixture exposure effect of BPS, BPF and BPA (Fig. 3).

The associations between bisphenols and subgroup CVD risk

We found that BPS was positively associated with the risk of coronary heart disease, and the T3 tertile of BPS increased the risk of coronary heart disease by 2.22 times (95% CI 1.04–4.74) after adjusting for all the covariates, with a \( P \) for trend of 0.036 (Table 3). We did not observe an association between the bisphenols and coronary heart disease, angina pectoris, heart attack or stroke.

Discussion

In this study, we identified a significant association between urinary BPS and an increased risk of total CVD, especially in people aged 50–80 years. Furthermore, urinary BPS was significantly associated with an increased risk of coronary heart disease.

Although BPA, BPS, and BPF share similar chemical properties, BPS and BPF are not safe alternatives for BPA [8]. One study tested the effects of BPS, BPF and BPA on testosterone secretion, and showed that BPS inhibited testosterone even more than BPA did [8]. Compared with BPA and BPF, BPS exposure significantly affected liver lipid and glucose metabolism [28]. It has been reported that exposure to high levels of BPS and BPF is significantly associated with obesity [25] and abnormal thyroid signalling pathways [21, 51, 52]. However, no study has reported the association between BPS and BPF and CVD in humans. In this study, we demonstrated differences in the relationship between BPS exposure and total CVD and CVD subtypes. Due to the limited use of BPA, BPS is increasingly being used as an alternative to BPA in industrial production [22]. The mechanism of action of BPS in the body is similar to that of BPA and BPF, and they have similar chemical structures [1, 34, 36]. In contrast, BPS has a similar or an even greater destructive biological effect than BPA [46]. Mice that were prenatally exposed to BPS to were significantly more susceptible to spontaneous epithelial lesions and inflammation, with an incidence greater than that observed in vehicle and BPA-exposed animals [46]. It has been proposed that humans are becoming widely exposed to BPS, and dietary intake, inhalation, and skin contact are believed to be the main sources of human exposure to BPS [38].
Previous studies have reported that urinary BPA is positively associated with an increased prevalence of total CVD in the U.S. population [4, 13]. Another study has shown a positive association between BPA

| Variables                                  | Health (%) | CVD (%)     | P        |
|--------------------------------------------|------------|-------------|----------|
| Overall                                    | 1129 (89.10) | 138 (10.90) | <0.001***|
| Age                                        | 47.78 ± 16.98 | 65.83 ± 11.17 |          |
| Gender                                     | 0.422      |             |          |
| Male                                       | 540 (47.83) | 71 (51.45)  |          |
| Female                                     | 589 (52.17) | 67 (48.55)  |          |
| Race/ethnicity                             | 0.094      |             |          |
| Mexican American                          | 160 (14.17) | 12 (8.70)   |          |
| Other Hispanic                            | 134 (11.87) | 12 (8.70)   |          |
| Non-Hispanic White                        | 448 (39.68) | 65 (47.10)  |          |
| Non-Hispanic Black                        | 241 (21.35) | 36 (26.08)  |          |
| Other Race-Including Multi-Racial         | 146 (12.93) | 13 (9.42)   |          |
| BMI (kg/m²)                                | 0.021      |             |          |
| Underweight/Normal weight                 | 335 (29.67) | 28 (20.29)  |          |
| Overweight/Obesity                        | 794 (70.33) | 110 (79.71) |          |
| Education levels                          | 0.073      |             |          |
| Less than 9th grade                       | 75 (6.64)  | 12 (8.70)   |          |
| 9–11th grade                              | 154 (13.64) | 22 (15.94)  |          |
| High school graduate                      | 237 (20.99) | 38 (27.54)  |          |
| Some college or AA degree                 | 361 (31.98) | 43 (31.16)  |          |
| College graduate or above                 | 302 (26.75) | 23 (16.66)  |          |
| Family PIR                                |            |             | 0.290    |
| PIR < 2.5                                 | 609 (53.94) | 81 (58.70)  |          |
| 2.5 ≤ PIR < 6                            | 520 (46.06) | 57 (41.30)  |          |
| Physical activity                         | 0.001**    |             |          |
| Never/Moderate                            | 698 (61.82) | 106 (76.81) |          |
| Vigorous                                  | 431 (38.18) | 32 (23.19)  |          |
| Alcohol drinking status                   | 0.136      |             |          |
| No                                        | 309 (27.37) | 46 (33.33)  |          |
| Yes                                       | 820 (72.63) | 92 (66.67)  |          |
| Smoking status                            | <0.001***  |             |          |
| Never                                     | 662 (58.64) | 52 (37.68)  |          |
| Former/Active                             | 467 (41.36) | 86 (62.32)  |          |
| Diabetes                                  | <0.001***  |             |          |
| Normal                                    | 998 (88.40) | 87 (63.04)  |          |
| Diabetes                                  | 131 (11.60) | 51 (36.96)  |          |
| Blood pressure                            | <0.001***  |             |          |
| Normal                                    | 749 (66.34) | 40 (28.99)  |          |
| Hypertension                              | 380 (33.66) | 98 (71.01)  |          |
| Creatinine (μmol/L)                       | 11,593.55 ± 6857.02 | 10,130.77 ± 5873.86 | 0.037*  |
| Energy (kcal)                              | 2132.02 ± 1031.85 | 1856.28 ± 923.27 | <0.001*** |
| LDL-C (mmol/L)                             | 2.93 ± 0.90  | 2.52 ± 0.89  | <0.001*** |
| BPS (ng/mL)                                | 1.49 ± 0.82  | 2.28 ± 0.97  | 0.479    |
| BPF (ng/mL)                                | 1.69 ± 0.12  | 1.44 ± 0.69  | 0.073    |
| BPA (ng/mL)                                | 2.24 ± 0.50  | 1.91 ± 0.38  | 0.266    |

M ± SD, Frequency (percentage). BMI body mass index, CVD cardiovascular disease, PIR poverty-income ratio; * p < 0.05; ** p < 0.01; *** p < 0.001. The bold values indicate statistically significant differences.
and CVD [26]. However, in our study, BPA was not associated with the risk of CVD. Most likely due to the stricter regulation of BPA, industries have increased the use of replacement substances [15], leading to lower BPA exposure. However, for BPS and BPF, the association with CVD risk has rarely been reported.

A very important finding in this study was that BPS exposure was associated with an increase in total CVD and coronary heart disease risk. Several animal experiments have reported the effects of BPS. BPS can decrease left ventricular contractility and rapidly depresses heart function by increasing phospholamban phosphorylation of serine 16 and decreasing threonine 17 phosphorylation in mice [9]. A study of pregnant mice showed that exposure to BPS reduced the recovery of adult male progeny from myocardial infarction [16]. BPS also increased the plasma lipid profiles of atherogenic proteins, but decreased serum hematological variables and high-density lipoprotein in male rats [32]. BPS induced cardiac oedema and arrhythmia in zebrafish embryos [29, 30]. Low doses of BPS have been shown to cause cardiac arrhythmias in female rats [11]. BPS increased the pulse rate of the dorsal vessels in Lumbriculus variegatus [48]. These animal studies have shown that BPS is harmful to cardiovascular health.

When stratified by age, we found that exposure to BPS increased the risk of total CVD in participants between 50 and 80 years of age. BPS exposure increased the risk of total CVD in the older age group, possibly due to longer exposure and higher exposure levels than the younger age group.

Based on the data of the population included in our study, the average exposure concentration of BPS in the 20–49 age group was 1.26 ng/ml (95% CI 0.61, 4.97, \(P = 0.286\)), while the average exposure concentration of BPS in the 50–80 age group was 1.90 ng/ml (95% CI 1.05, 1.87, \(P = 0.021\)). It was clear that the older age group had higher exposure levels than the younger age group.

| Variables | Model 1 | | Model 2 | | Model 3 |
|-----------|---------|---|---------|---|---------|
|           | OR (95% CI) | \(P\) | OR (95% CI) | \(P\) | OR (95% CI) | \(P\) |
| Bisphenol S |         |     |         |     |         |     |
| T1        | 1.00    | 1.00 | 1.00    | 1.00 | 1.00    | 1.00 |
| T2        | 0.89 (0.40, 1.99) | 0.767 | 0.97 (0.42, 2.24) | 0.941 | 0.98 (0.44, 2.20) | 0.956 |
| T3        | 1.37 (0.80, 2.35) | 0.240 | 1.96 (1.12, 3.40) | 0.019* | 1.99 (1.16, 3.40) | 0.014** |
| P for trend | 0.236 |     |         |     |         |     |
| Bisphenol F |         |     |         |     |         |     |
| T1        | 1.00    | 1.00 | 1.00    | 1.00 | 1.00    | 1.00 |
| T2        | 1.57 (0.88, 2.78) | 0.120 | 1.72 (0.93, 3.20) | 0.083 | 1.69 (0.88, 3.27) | 0.111 |
| T3        | 1.54 (0.82, 2.89) | 0.174 | 1.72 (0.82, 3.61) | 0.142 | 2.02 (0.86, 4.72) | 0.101 |
| P for trend | 0.197 |   | 0.173 |     |         |     |
| Bisphenol A |         |     |         |     |         |     |
| T1        | 1.00    | 1.00 | 1.00    | 1.00 | 1.00    | 1.00 |
| T2        | 0.51 (0.27, 0.96) | 0.039 | 0.63 (0.30, 1.32) | 0.095 | 0.66 (0.33, 1.30) | 0.218 |
| T3        | 0.69 (0.40, 1.20) | 0.180 | 0.63 (0.27, 1.46) | 0.272 | 0.65 (0.29, 1.45) | 0.283 |
| P for trend | 0.185 |   | 0.264 |     |         |     |

Model 1: unadjusted model
Model 2: adjusted for urine creatinine, sex, age, race, education level, PIR, physical activity, alcohol drinking status, smoking status, BMI, blood pressure, and diabetes
Model 3: adjusted for urine creatinine, sex, age, race, education level, PIR, physical activity, alcohol drinking status, smoking status, BMI, blood pressure, diabetes, LDL-C, and energy intake; * \(p < 0.05\); ** \(p < 0.01\); *** \(p < 0.001\). The bold values indicate statistically significant differences.
**Fig. 2** Forest Plot of the Primary Outcome According to Subgroups. The \( P \) value is the trend of stratified analysis. \( P \)-i. is the \( p \) value the interaction between BPS and the subgroup. Adjusted for sex, age, race, education level, PIR, physical activity, alcohol drinking status, smoking status, BMI, blood pressure, diabetes, LDL-C level, energy intake, and urine creatinine concentration.

**Fig. 3** BKMR model was used to assess the mixture effects between bisphenols and the risk of CVD. A Combined effects of the bisphenols mixture on CVD risk estimated by the BKMR model, adjusting for sex, age, race, education level, PIR, physical activity, alcohol drinking status, smoking status, BMI, blood pressure, diabetes, LDL-C, energy, and urine creatinine. B Univariate exposure–response functions and 95% confidence interval for each bisphenol with the other two bisphenols fixed at the median.
body’s immune response [34, 36]. These factors may account for the increased risk of CVD in the 50–80 age group. Further studies have shown that exposure to BPS in zebrafish can alter the immune function of offspring, increase lysozyme activity, change oxidative stress and inflammatory cytokines, and lead to decreased immune defended in zebrafish [35]. The study found that immune system pathways were also affected by exposure to BPS in zebrafish embryos [7].

Our study has the following advantages. First, the toxicity of bisphenols has long been reported, but the possible health-damaging effects of low-concentration BPS and BPF in the human body have not been reported. For the first time, we found through large sample populational data that BPS may be related to CVD and may be positively related to CHD. There are some limitations to our study. We used data from a cross-sectional study to preclude the inference of the cause–effect relationship. The data we used to define CVD were self-reported by participants, and the accuracy of the data may be biased. In addition, one limitation in our study was that there was only on bisphenol measurement due to the short biological half-life.

**Conclusion**

We found that BPS level are significantly associated with the risks of total CVD and coronary heart disease in the U.S population from a cross-sectional study, and the prospective studies are needed to explore on the mechanisms of BPS and BPF on CVD.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s12302-021-00586-9.

**Additional file 1: Fig S1.** The restricted cubic spline model was used to analyze the relationship between Bisphenols and the risk of CVD. A BPS; B BPF; C BPA. The analysis adjusted for gender, age, race, education level, PIR, physical activity, alcohol drinking status, smoking status, BMI, blood pressure, cancer, diabetes, LDL-C level, energy intake, and urine creatinine concentration; * p< 0.05; ** p< 0.01; *** p< 0.001. The bold values indicate statistically significant differences.

**Table 3** Associations of Bisphenols with CVD subgroup risk

| variables | Congestive heart failure (n = 35) | Coronary heart disease (n = 53) | Angina pectoris (n = 26) | Heart attack (n = 59) | Stroke (n = 48) |
|-----------|-------------------------------|---------------------------------|-------------------------|---------------------|---------------|
| Bisphenol S |                               |                                 |                          |                     |               |
| T1        | Reference                      | Reference                       | Reference               | Reference           | Reference     |
| T2        | 1.05 (0.32, 3.51)              | 1.09 (0.39, 3.05)               | 2.89 (0.86, 9.68)       | 0.54 (0.23, 1.30)   | 0.85 (0.22, 3.27) |
| T3        | 0.87 (0.28, 2.69)              | 2.22 (1.04, 4.74)               | 3.15 (0.81, 12.19)      | 0.98 (0.47, 2.02)   | 2.64 (0.82, 8.52) |
| P for trend | 0.794                        | 0.036*                         | 0.089                   | 0.936               | 0.109         |
| Bisphenol F |                               |                                 |                          |                     |               |
| T1        | Reference                      | Reference                       | Reference               | Reference           | Reference     |
| T2        | 1.34 (0.46, 3.87)              | 2.55 (0.93, 6.99)               | 1.70 (0.58, 5.02)       | 3.07 (1.21, 7.78)   | 1.48 (0.42, 5.19) |
| T3        | 1.08 (0.33, 3.59)              | 2.24 (0.58, 8.65)               | 3.98 (0.93, 17.12)      | 2.72 (0.72, 10.30)  | 0.96 (0.25, 3.73) |
| P for trend | 0.904                        | 0.295                          | 0.073                   | 0.164               | 0.924         |
| Bisphenol A |                               |                                 |                          |                     |               |
| T1        | Reference                      | Reference                       | Reference               | Reference           | Reference     |
| T2        | 0.67 (0.23, 1.93)              | 0.84 (0.31, 2.34)               | 1.21 (0.35, 4.16)       | 0.39 (0.12, 1.28)   | 0.91 (0.36, 2.30) |
| T3        | 0.58 (0.18, 1.89)              | 0.73 (0.17, 3.12)               | 0.84 (0.15, 4.67)       | 1.52 (0.46, 4.98)   | 0.57 (0.22, 1.46) |
| P for trend | 0.356                        | 0.655                          | 0.873                   | 0.593               | 0.275         |

Adjusted for sex, age, race, education level, PIR, physical activity, alcohol drinking status, smoking status, BMI, blood pressure, cancer, diabetes, LDL-C level, energy intake, and urine creatinine concentration; * p< 0.05; ** p< 0.01; *** p< 0.001. The bold values indicate statistically significant differences.
Declarations

Ethics approval and consent to participate
The NHANES agreement has been reviewed and approved by the NCHS Research Ethics Committee. All participants provided written informed consent before participating.

Consent for publication
All participants provided written informed consent prior to participation.

Competing interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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