The Bisphenol F and Bisphenol S and Cardiovascular disease: results from NHANES 2013-2016

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Research

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Abstract

Background

Bisphenol F (BPF) and bisphenol S (BPS) are replacing 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) have not been assessed.

Objective

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

Method

A cross-sectional data with 1,266 participants aged 20 to 80 years from the 2013–2016 National Health and Nutrition Examination Survey (NHANES) was analyzed. The logistic regression was used to assess the association between BPF, BPS and CVD. The Bayesian kernel machine regression (BKMR) model was applied to assess the mixed effect.

Results

A total of 138 patients with CVD were identified. After adjusting for potential confounding factors, T3 concentration of BPS increased the risk of total CVD (OR: 1.98, 95%CI: 1.20–3.28). When stratified by age, we found that BPS increased the risk of CVD in the 50–80 age groups (OR:1.40, 95%CI: 1.05–1.87). BPS was positively associated with the risk of stroke and T3 of BPS increased the stroke risk by 3.46 times (95%CI: 1.09–10.95). No significant association was observed between BPF and CVD. Although BKMR model did not identify the mixed exposure effect of BPS, the risk of CVD increased, with the increase of compound concentration.

Conclusion

Our results suggest that BPS may increase the risk of total CVD and stroke in the U.S population, and prospective studies are needed to confirm the results.

Introduction

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)(Virani et al. 2021). Approximately 80% of CVD deaths are contributable to heart attacks and strokes, and one-third occurring in people < 70 years old(Virani et al. 2021). 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 global mortality)(Stefanadis et al. 2017). 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(Zhang, Huang, et al. 2018; Khot et al. 2003). Environmental factors, including nonylphenol (NP), bisphenol A (BPA), polychlorinated biphenyl (PCB), organo-chlorine pesticide (OCP), and phthalate (PAE) (Fu et al. 2020), exert additional synergistic or additive effects on these traditional risk factors, then further raise the risk of CVD(Bhatnagar 2017; Xu et al. 2020; Kaufman et al. 2016).

Bisphenol is a kind of chemical epoxy resin compound containing two hydroxyl phenyl groups(Mendy et al. 2020; Thoene et al. 2018). Bisphenol, as an endocrine disruptor, has adverse effects at very low doses(Thoene et al. 2018). Bisphenol A (BPA) has long been used in plastics(Eladak et al. 2015; Casey and Neidell 2013). The higher concentrations of BPA were associated with CVD(Cai et al. 2020), obesity(Shankar, Teppala, and Sabanayagam 2012), diabetes(Stojanoska et al. 2017), and hypertension(Commodore-Mensah et al. 2018), brain(Santoro et al. 2019), and reproductive system damage(Pivonello et al. 2020). However, due to these adverse effects, some countries starting to ban or restrict the use of BPA in consumer products.

Bisphenol S (BPS) and bisphenol F (BPF) are two substitutes for BPA(Rochester and Bolden 2015). BPF and BPS can be found in food packaging items, beverage containers, paper products(Mendy et al. 2020), personal care products (e.g., body wash, hair care products, makeup, lotions, toothpaste)(Liao and Kannan 2014), food (e.g., dairy products, meat and meat products, vegetables, canned foods, cereals)(Liao and Kannan 2013), and baby bottles(Simoneau et al. 2011). Recently, health concerns have been raised about these substitutes as well. The higher concentrations of BPS and BPF were associated with depressive symptoms(Hao et al. 2021), asthma, and hay fever(Mendy et al. 2020). Due to the endocrine-disrupting effects like BPA(Fu et al. 2020; Rochester and Bolden 2015; Kuruto-Niwa et al. 2005), we hypothesized that exposure to BPS or BPF is associated with an increased risk of CVD in humans(Fu et al. 2020).

Taking the advantage of 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 a multi-level probability sampling. All participants provided informed consent when they were recruited to participate in the study(Cai et al. 2020). The National Center for Health Statistics Research Ethics Review Board has approved the implementation of the protocol for NHANES(Cai et al. 2020). From 2013 to 2016, a total of 1,266 NHANES participants with available bisphenols data 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 self-reported physician diagnosis and completion of a standardized medical condition questionnaire. 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. We excluded all participants who said they didn't know and those who refused to answer.

Bisphenol exposure

As part of NHANES ongoing biological surveillance program, in a 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 and BPF were 0.1ng/mL and 0.2ng/mL, respectively. The NHANES quality assurance and quality control (QA/QC) protocols meet the 1988 clinical laboratory improvement act mandates(https://wwwn.cdc.gov/nchs/data/nhanes/2015-2016/manuals/2016_MEC_Laboratory_Procedures_Manual.pdf).

Covariates

From demographics and questionnaire data, we selected the following as potential confounding variables in our analysis: age, gender, race/ethnicity, education levels, family poverty-income ratio poverty income ratio (PIR), smoking, alcohol drinking status, physical activity, blood pressure, diabetes, cancer. Data on energy intake was acquired from dietary intake data in two 24 dietary recall interviews. Based on the body measures examination data, we got body mass index (BMI, kg/m²) and partial blood pressure data. Based on measurements in laboratory data, we obtained urine creatinine data, total cholesterol data, serum cotinine data, high-density lipoprotein (HDL) data, low-density lipoprotein (LDL) data. PIR, as a proxy for socioeconomic status, was estimated using guidelines and adjustment for family size, year and state(Mendy et al. 2020). Urinary creatinine is used to describe the degree of urine dilution(Mendy et al. 2020).The urine creatinine analysis was performed on the Roche Mod P using an enzymatic (creatinase) method(Jain 2017).

Statistical analysis

The survey procedure of 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). Sampling weights were used to account for the complex NHANES survey design, according to recommendations from the NCHS and the CDC. Categorical variables are presented in form of frequency and percentage, while continuous variables are presented in the form of the mean and standard deviation (SD). Categorical variables and continuous variables were compared using the χ^2 test and the t-test, respectively. The association between bisphenols and the risk of CVD was analyzed by survey-weighted multiple logistic regression analysis, and three separate models were constructed for each bisphenol available in the NHANES database. The adjusted

odds ratios (ORs) and 95% confidence intervals (95%CI) for CVD by the tertiles of each bisphenol were calculated. Subgroup analyses were performed to investigate the association between 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 appropriate transformations were applied when it is necessary. BPS and BPF levels were divided into tertiles (T1, T2, and T3). RCS was used to further investigate the non-linear relationship between bisphenols and the risk of CVD. The BKMR estimates the multivariable exposure-response function in a flexible way that allows for nonlinear, 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 (Bobb et al. 2018). We further used BKMR to explore the relationships between a mixture of BPS, BPF, and BPA and the risk of CVD. All data analyses were performed in STATA (version 16.0 SP) and R (version 4.0.5) software.

Results

Cohort characteristics

A total of 1,266 participants were finally included in our study, of them, 138 (10.90%) had CVD. The prevalence of 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. The average age of the non-CVD and CVD patients was 47.78 ± 16.98 and 65.83 ± 11.17 years old, respectively. Non-Hispanic whites (47.10%) and non-Hispanic blacks (26.09%) participants had a higher prevalence in the overall study population. There were significant differences in age, physical activity, smoking status, cancer, diabetes, blood pressure (All $P < 0.05$) between the non-CVD and CVD patients (Table 1).

Table 1
Participant characteristics (N = 1266) in NHANES 2013–2016.

Variables	Health(%)	CVD (%)	<i>P</i>
Overall	1128(89.10)	138(10.90)	
Age	47.78 ± 16.98	65.83 ± 11.17	< 0.001***
Gender			0.427
Male	540(47.87)	71(51.45)	
Female	588(52.13)	67(48.55)	
Race/ethnicity			0.096
Mexican American	160(14.18)	12(8.70)	
Other Hispanic	133(11.79)	12(8.70)	
Non-Hispanic White	448(39.72)	65(47.10)	
Non-Hispanic Black	241(21.37)	36(26.09)	
Other Race-Including Multi-Racial	146(12.94)	13(9.42)	
BMI (kg/m²)			0.147
Underweight	18(1.60)	2(1.45)	
Normal weight	316(28.01)	26(18.84)	
Overweight	351(31.12)	48(34.78)	
Obesity	443(39.27)	62(44.93)	
Education levels			0.071
Less than 9th grade	75(6.65)	12(8.70)	
9-11th grade	154(13.65)	22(15.94)	
High school graduate	236(20.92)	38(27.54)	
Some college or AA degree	361(32.00)	43(31.16)	
College graduate or above	302(26.77)	23(16.67)	
Family PIR			0.325
PIR < 1	246(21.81)	28(20.29)	
1 ≤ PIR < 2.5	362(32.09)	53(38.41)	
2.5 ≤ PIR < 6	520(46.10)	57(41.30)	
Physical activity			0.002**
Note: M ± SD, Frequency(percentage). BMI, body mass index. CVD, cardiovascular disease. PIR, poverty-income ratio.			

Variables	Health(%)	CVD (%)	<i>P</i>
Never	323(28.63)	51(36.96)	
Moderate	374(33.16)	55(39.86)	
Vigorous	431(38.21)	32(23.19)	
Alcohol drinking status			0.136
No	308(27.30)	46(33.33)	
Yes	820(72.70)	92(66.67)	
Smoking status			< 0.001***
Never	661(58.60)	52(37.68)	
Former	239(21.19)	58(42.03)	
Active	228(20.21)	28(20.29)	
Cancer			< 0.001***
No	1037(91.93)	107(77.54)	
Yes	91(8.07)	31(22.46)	
Diabetes			< 0.001***
Normal	998(88.48)	87(63.04)	
Diabetes	130(11.52)	51(36.96)	
Blood pressure			< 0.001***
Normal	748(66.31)	40(28.99)	
Hypertension	380(33.69)	98(70.01)	
Cotinine (ng/mL)	57.49 ± 49	62.27 ± 124.54	0.790
Creatinine (μmol/L)	11599.05 ± 6857.57	10130.77 ± 5873.86	0.019
Energy (kcal)	2132.44 ± 1032.21	1856.28 ± 923.27	< 0.001***
Total cholesterol (mmol/L)	4.90 ± 1.01	4.52 ± 1.04	< 0.001***
HDL-C (mmol/L)	1.41 ± 0.42	1.39 ± 0.42	0.275
LDL-C (mmol/L)	2.93 ± 0.90	2.52 ± 0.89	< 0.001***
BPS (ng/mL)	1.49 ± 5.83	2.28 ± 8.79	0.479
BPF (ng/mL)	1.69 ± 7.13	1.44 ± 3.69	0.073
BPA (ng/mL)	2.24 ± 5.50	1.91 ± 2.38	0.266
Note: M ± SD, Frequency(percentage). BMI, body mass index. CVD, cardiovascular disease. PIR, poverty-income ratio.			

Association between bisphenols exposure and the risk of total CVD

T3 of BPS increased the risk of total CVD by 1.98 times (95%CI:1.20–3.28) compared to the T1 after adjusting covariates, with a *P* for trend was 0.010. The association between BPF and the risk of total CVD (Table 2) wasn't identified.

When stratified by age, we found that T3 of BPS increased the risk of CVD by 1.40 times (95%CI:1.05–1.87), with a *P* for trend was 0.021 in the 50–80 age groups, and we did not find this association in the 20–49 age groups (Fig. 3).

We further performed the analysis stratified by sex, we did not find any association between bisphenols and the risk of CVD in males and females (eAppendix.). RCS showed that there was a linear relationship between BPS and the risk of CVD (*P* for nonlinear association = 0.9268) in all participants (eFig.2A). RCS showed that there was a linear relationship between BPF and the risk of CVD (*P* for nonlinear association = 0.0878) in all participants (eFig.2B).

Table 2
The associations of Bisphenols with total CVD risk in U.S. adults 2013–2016.

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	1.07(0.61,1.88)	0.811	1.22(0.68,2.17)	0.496	1.31(0.70,2.47)	0.389
T3	1.44(0.84,2.49)	0.178	1.91(1.05,3.48)	0.035*	1.98(1.20,3.28)	0.009**
P for trend		0.189		0.038*		0.010*
Bisphenol F						
T1	1.00	1.00	1.00	1.00	1.00	1.00
T2	0.56(0.28,1.12)	0.097	0.62(0.32,1.22)	0.163	0.64(0.33,1.25)	0.185
T3	1.53(0.82,2.88)	0.903	1.08(0.57,2.03)	0.805	1.21(0.57,2.55)	0.612
P for trend		0.963		0.789		0.620
Bisphenol A						
T1	1.00	1.00	1.00	1.00	1.00	1.00
T2	0.51(0.27,0.97)	0.042	0.59(0.31,1.10)	0.095	0.57(0.30,1.09)	0.088
T3	0.71(0.40,1.26)	0.236	0.74(0.39,1.43)	0.358	0.66(0.28,1.55)	0.324
P for trend		0.238		0.331		0.292
Model 1: unadjusted model;						
Model 2: adjusted for gender, age, race, education level, PIR, serum cotinine, physical activity, alcohol drinking status, smoking status, BMI, blood pressure, cancer, diabetes;						
Model 3: adjusted for gender, age, race, education level, PIR, serum cotinine, physical activity, alcohol drinking status, smoking status, BMI, blood pressure, cancer, diabetes, total cholesterol, HDL-C, LDL-C, energy, urine creatinine.						

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

The BKMR model did not identify the mixed exposure effect of BPS, BPF and BPA.

The associations between Bisphenols and Subgroup CVD risk

We found that BPS was positively associated with the risk of stroke, and T3 of BPS increased the risk of stroke by 3.46 times (95%CI:1.09–10.95) after adjusting for all the covariates, with the *P* for trend was 0.032 (Table 3). We did not observe the association between bisphenols with congestive heart failure, coronary heart disease, angina pectoris, and heart attack.

Table 3
The associations of Bisphenols with CVD subgroup risk.

variables	Congestive heart failure	Coronary heart disease	Angina pectoris	Heart attack	Stroke
Bisphenol S					
T1	Reference	Reference	Reference	Reference	Reference
T2	1.04(0.29,3.75)	0.65(0.26,1.59)	0.91(0.26,3.18)	0.53(0.20,1.46)	3.86(1.35,11.02)
T3	0.87(0.29,2.60)	1.58(0.79,3.17)	1.83(0.51,6.57)	1.03(0.44,2.42)	3.46(1.09,10.95)
P for trend	0.806	0.207	0.377	0.981	0.032*
Bisphenol F					
T1	Reference	Reference	Reference	Reference	Reference
T2	0.81(0.21,3.06)	1.15(0.36,3.68)	1.48(0.37,5.85)	1.29(0.53,3.14)	0.39(0.17,0.88)
T3	1.01(0.29,3.49)	1.25(0.33,4.67)	2.71(0.64,11.36)	1.51(0.46,4.91)	0.66(0.21,2.12)
P for trend	1.000	0.737	0.168	0.482	0.433
Bisphenol A					
T1	Reference	Reference	Reference	Reference	Reference
T2	0.65(0.28,1.53)	0.60(0.20,1.83)	1.19(0.40,3.53)	0.42(0.13,1.30)	0.93(0.34,2.55)
T3	0.56(0.19,1.63)	0.60(0.11,3.26)	0.73(0.10,5.29)	1.77(0.47,6.65)	0.66(0.21,2.11)
P for trend	0.278	0.526	0.783	0.475	0.510
Adjusted for gender, age, race, education level, PIR, serum cotinine, physical activity, alcohol drinking status, smoking status, BMI, blood pressure, cancer, diabetes, total cholesterol, HDL-C, LDL-C, energy, urine creatinine.					

Discussion

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

Although BPA, BPS, and BPF share similar chemical properties, BPS and BPF are not safe alternatives to BPA(Eladak et al. 2015). It has been reported that exposure to high levels of BPS and BPF was significantly associated with obesity(Liu et al. 2019) and abnormal thyroid signaling pathways(Zhang, Ren, et al. 2018). However, there was no study to report the association between BPS and BPF and CVD in human. In this study, we demonstrated differences in the relationship between BPS exposure and the total CVD and its CVD subtypes. Due to the limited use of BPA, BPS is increasingly being used as an alternative to BPA in industrial production(Li et al. 2020). The mechanism of action of BPS is similar to that of BPA and BPF in the body. In contrast, BPS has a similar or even greater biological destructive effect than BPA(Tucker et al. 2018). Prenatal exposure to BPS in mice to was significantly more susceptible to spontaneous epithelial lesions and

inflammation, with an incidence greater than observed in vehicle and BPA-exposed animals(Tucker et al. 2018). 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(Russo, Barbato, and Grumetto 2017).

Previous studies have reported that urinary BPA is positively associated with an increased prevalence of total CVD in the U.S. population(Cai et al. 2020; Hu et al. 2019). Another study has shown a positively association between BPA and CVD(Melzer et al. 2010). However, in our study, BPA was not associated with the risk of CVD. Probably due to the stricter regulation of BPA, industry has increased the use of replacement substances(Karrer et al. 2018), leading to lower of BPA exposure.

For BPS and BPF, the association with CVD risk was rarely reported. In this study, we found that BPS increased the risk of CVD, while BPF was not associated with the risk of CVD. In animal studies, exposure to high doses of BPS and BPF has been significantly correlated with abnormal thyroid function(Lee et al. 2019) and obesity(Zhang et al. 2019). In a population study, the higher concentrations of BPS and BPF have been shown to be associated with depressive symptoms(Hao et al. 2021), asthma and hay fever(Mendy et al. 2020).

A very important finding in this study was that BPS exposure was associated an increase of total CVD and stroke risk. Several experiments have reported the effects of BPS. An experiment in mice showed that BPS can decrease left ventricular contractility, increasing phospholamban phosphorylation at serine 16 and decrease threonine 17 phosphorylation, and demonstrates a rapid of BPS to depress heart function(Ferguson, Lorenzen-Schmidt, and Pyle 2019). A study of pregnant mice showed that exposure to BPS reduced recovery from myocardial infarction of adult male progeny(Kasneci et al. 2017). BPS increased the plasma lipid profile of atherogenic proteins, but decrease serum hematological variables and high-density lipoprotein in male rats(Pal et al. 2017). BPS also induced cardiac edema and arrhythmia in zebrafish embryo(Moreman et al. 2017; Mu et al. 2018). However, no correlation between BPS and CVD has been reported in the population.

When stratified by age, we found that exposure to BPS increased the risk of total CVD 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, while the average exposure concentration of BPS in the 50–80 age group was 1.90 ng/ml. It was clear that the older age group had higher exposure levels than the younger age group. BPS dissipated quickly in an oxic soil, with a half-life of 2.8 days(Cao et al. 2020). A study of pharmacokinetics of BPS in humans after single oral administration, seven healthy young adults received BPS 8.75µg/kg orally, and total BPS was observed in serum within 1h after administration and excreted in urine with terminal half-life of 7h(Oh et al. 2018). In another study, six human volunteers administered 0.1mg/kg BPS, C_{max} was reached at 0.7h and 1.1h for BPS and its glucuronide, respectively, with plasma elimination half-lives of 7.9h and 9.3h, respectively(Khmiri et al. 2020; Waidyanatha et al. 2020). It may be that the slower metabolic rate of the elderly leads to a higher concentration accumulation of BPS in the 50–80 age group, thus increasing the risk of CVD in the 50–80 age group. Low doses of BPS have been shown to affect cardiac arrhythmias in female rats(Gao et al. 2015). BPS increased the pulse rate of the dorsal vessels in *Lumbriculus variegatus*(Vought and Wang 2018). Studies have also shown that long-term exposure to BPS can disrupt the body's immune response(Qiu et al. 2018). 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 defense in zebrafish(Qiu et al. 2019). The study found that immune system pathways were also affected by exposure to BPS in zebrafish embryos(Dong et al. 2018).

There are some limitations to our study. First, we used data from a cross-sectional- study precludes 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. Thirdly, the data came from the NHANES, and it can't represent the whole situation in the world, and it need to be verified in other population.

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Supplement

eAppendix. The associations of Bisphenols with cardiovascular disease (CVD) risk stratified by sex.				
variables	Male		Female	
	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>
Bisphenol S				
T1	1.00	1.00	1.00	1.00
T2	1.56(0.49,4.99)	0.437	1.05(0.48,2.28)	0.908
T3	2.78(0.84,9.21)	0.092	1.24(0.45,3.39)	0.670
P for trend		0.093		0.664
Bisphenol F				
T1	1.00	1.00	1.00	1.00
T2	0.36(0.10,1.23)	0.101	0.86(0.47,1.56)	0.605
T3	0.59(1.17,2.00)	0.381	2.38(0.89,6.36)	0.081
P for trend		0.410		0.081
Bisphenol A				
T1	1.00	1.00	1.00	1.00
T2	0.62(0.24,1.58)	0.301	0.57(0.21,1.53)	0.254
T3	0.45(0.12,1.70)	0.226	0.97(0.40,2.39)	0.950
P for trend		0.219		0.866
Adjusted for gender, age, race, education level, PIR, serum cotinine, physical activity, alcohol drinking status, smoking status, BMI, blood pressure, cancer, diabetes, total cholesterol, HDL-C, LDL-C, energy, urine creatinine.				

Figures

Figure 1

Eligible participants and those included in the analyses of the associations between bisphenols and risk of CVD in adults.

Figure 2

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, serum cotinine, physical activity, alcohol drinking status, smoking status, BMI, blood pressure, cancer, diabetes, total cholesterol, HDL-C, LDL-C, energy, urine creatinine.

Figure 3

Forest Plot of 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 subgroup. Adjusted for gender, age, race, education level, PIR, serum cotinine, physical activity, alcohol drinking status, smoking status, BMI, blood pressure, cancer, diabetes, total cholesterol, HDL-C, LDL-C, energy, urine creatinine. We found that BPS increased the risk of CVD in the 50-80 age group of age, overweight/obesity of BMI, PIR<2.5 of PIR, never/moderate of physical activity, former/active of smoking status.

Figure 4

The BKMR model was used to assess the mixed effects between Bisphenols and the risk of CVD. A. Combined effects of the Bisphenols mixture on CVD risk estimated by BKMR model, adjusting for gender, age, race, education level, PIR, serum cotinine, physical activity, alcohol drinking status, smoking status, BMI, blood pressure, cancer, diabetes, total cholesterol, HDL-C, LDL-C, energy, urine creatinine. B. Univariate exposure-response functions and 95% confidence interval for each Bisphenol with the other two Bisphenol fixed at the median.