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RELATIONSHIP BETWEEN THE ENVIRONMENTAL ENDOCRINE DISRUPTOR BISPHENOL A AND DYSLIPIDEMIA: A FIVE-YEAR PROSPECTIVE STUDY

Ruolin Li MD[1], Shumin Yang MD PhD[2], Rufei Gao PhD[23], Yin Deng MD [4], Jiahuan Liu MD[4], Chao Yuan MD[4], Qingmei Yao MD[4], Xinke Lv MD[4], Kanran Wang MD, PhD[2], Xiaoqi Ye MD[2], Bin Peng PhD[5], Jinbo Hu MD, PhD[2], Aijun Chen MD, PhD[1]

From: [1] Department of Dermatology，The First Affiliated Hospital of Chongqing Medical University, Chongqing, China. [2] Department of Endocrinology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China. [3] School of Public Health and Management, Chongqing Medical University, Chongqing, China. [4] The First Affiliated Hospital of Chongqing Medical University, Chongqing, China. [5] School of Public Health and Management, Chongqing Medical University, Chongqing, China.

Running title: BPA and dyslipidemia

Corresponding author: Jinbo Hu, MD, PhD and Aijun Chen, MD, PhD

The First Affiliated Hospital of Chongqing Medical University,

No.1 Youyi Street, Yuzhong District, Chongqing, China, 400016.

Email: hujinbo_568@163.com; 1360999716@qq.com

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Abstract

Objective: To investigate whether serum Bisphenol A (BPA) concentration is related to the occurrence of dyslipidemia.

Methods: A total of 574 adults were enrolled at baseline and followed up for 5 years. Concentrations of serum BPA, triglycerides (TGs), low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c) were measured. Dyslipidemia was defined as the existence of one or more following conditions: high-LDL-cholesterolemia (LDL-c≥140 mg/dL), hypertriglyceridemia (TGs≥150 mg/dL), or low-HDL-cholesterolemia (HDL-c<40 mg/dL). Participants were stratified into tertiles according to low, median and high baseline serum BPA levels. Multivariable linear and logistic regression models were used. Data from baseline and follow-up were used for cross-sectional and longitudinal analyses, respectively.

Results: In the cross-sectional analysis, compared to subjects in low BPA tertile, these in high BPA tertile showed a higher level of LDL-c (108.1±24.4 vs. 119.5±26.9 mg/dL, $P<0.05$) and a lower level of HDL-c (46.2±11.7 vs. 39.5±7.5 mg/dL, $P<0.05$). In multivariable linear regression models, Z-transformed BPA was positively associated with LDL-c (β=0.13, $P=0.002$) and negatively associated with HDL-c (β=-0.28, $P<0.001$). After cross-sectionally adjusting for confounders, subjects in higher BPA exposure was associated with a higher prevalence of low-HDL-cholesterolemia. Longitudinally, in subjects without low-HDL-cholesterolemia at baseline, each standard deviation (per-SD) increment in baseline BPA was associated with a higher incidence of low-HDL-cholesterolemia after confounders adjustment [OR (95% CI) 2.76 (95% CI 1.21, 6.29)] .

Conclusion: Cross-sectionally, higher BPA exposure is associated with a higher prevalence of low-HDL-cholesterolemia. Longitudinally, baseline BPA is an independent predictor of the 5-year incidence of low-HDL-cholesterolemia.

Keywords: bisphenol A, dyslipidemia, risk factor, prospective, low-HDL-cholesterolemia

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Abbreviations:

EDCs = endocrine-disrupting compounds, **BPA** = Bisphenol A, **SBP** = systolic blood pressure, **DBP** = diastolic blood pressure, **BMI=** body mass index, **WC=** waist circumference, **TC** = total cholesterol, **TGs** = triglycerides, **HDL-c** = high density lipoprotein cholesterol, **L-HDL-c** = low-HDL-cholesterolemia, **LDL-c** = low density lipoprotein cholesterol, **H-LDL-c** = high-LDL-cholesterolemia, **FPG** = fasting plasma glucose, **2hPG** = postprandial 2h plasma glucose, **Cr** = creatinine; **T2DM** = type 2 diabetes mellitus; **Family History of HT** = family history of hypertension, **Z-BPA** = Z-transformed BPA, **Per-SD** = 1-standard deviation, **SD** = standard deviation, **OR** = odds ratio, **CI** = confidence interval, **EIMDS** = environment, inflammation and metabolic diseases study, **JAS** = Japan Atherosclerosis Society, **NHANES** = National Health and Nutrition Examination Survey, **PPARαγ=** peroxisome proliferator-activated receptors, ARs= androgen receptors, **ERRγ=** non-classical estrogen receptors, **TRαβ** = thyroid hormone receptors, **PXRs=** progesterone X receptors, **LCAT=** Lecithin cholesterol acyl transferase, **CVD=** cardiovascular disease.

1. Introduction

Dyslipidemia, such as high low-density lipoprotein (LDL) cholesterolemia and low high-density lipoprotein (HDL) cholesterolemia, is an important cause of atherosclerotic cardiovascular disease. It was estimated that 53% of American adults have lipid abnormalities, 27% have high-LDL-cholesterolemia and 23% have low-HDL-cholesterolemia (1). In recent years, the overall prevalence of dyslipidemia among Chinese adults has significantly increased to 34% (2). Dyslipidemia has become an important chronic disease affecting human health.

The etiology of dyslipidemia depends upon genetics and the environment. Genetics alone may not fully explain the increased incidence of dyslipidemia, and modifiable environmental risk factors need to be identified. A large number of studies have shown that endocrine-

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disrupting compounds (EDCs) in the environment are associated with a range of diseases, including obesity, diabetes and vitamin D deficiency (3-5). Characterized by estrogen interference, bisphenol A (BPA) is a bisphenol compound that is an EDC. Since the 1960s, BPA has been widely used in the manufacturing of containers for storing food and beverages such as water bottles. Under high temperatures and acidic conditions, BPA can easily degrade and enter the body with food or drink and is eventually excreted through the kidneys. Previous studies have shown that BPA is associated with metabolic diseases, including obesity, hypertension, cardiovascular disease, and chronic kidney disease (6-9).

In recent years, the relationship between BPA and dyslipidemia has been widely explored, while the results from these studies seemed to be controversial. In a cross-sectional study of 1016 people aged older than 70, researchers found that LDL-c increased in the higher BPA exposure group (10). Conversely, a study showed that compared to subjects with higher BPA exposure, concentrations of triglycerides (TGs) and total cholesterol (TC) were even higher in subjects with lower BPA exposure (11). Furthermore, another study recruiting 248 mother-newborn pairs showed that BPA exposure was not associated with blood lipid levels in children, either during pregnancy or adolescence (12). An animal study showed that rats fed higher BPA concentrations showed only an increase in TGs, and the degree of increase was not dose-dependent with BPA levels (13).

Given the inconsistency of the relationship between BPA and lipid abnormalities, large sample and prospective cohort studies are needed. In this study, both cross-sectional and prospective follow-up at five years analyses were performed, which aimed to further investigate the association between BPA exposure and blood lipid levels.

2. Materials and methods

2.1. Study design

This study is a part of the environment, inflammation and metabolic diseases study (EIMDS). The EIMDS aimed to explore the environmental and inflammatory risk factors for metabolic diseases such as diabetes, hypertension and chronic kidney disease. In the current

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study, the effect of BPA on the risk of dyslipidemia was evaluated. At baseline, a total of 3510 participants living in Chongqing, China, responded to a study questionnaire and formed the EIMDS cohort. Baseline and followed-up data were used for cross-sectional and prospective analyses, respectively. This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

2.2. Study population

In the current study, the inclusion criteria were as follows: participants who signed informed consent and volunteered to participate in annual follow-ups and participants who were willing to provide fasting blood samples. The exclusion criteria were: age<20 years or>80 years, severe cardiovascular disease, severe liver impairment, malignant tumor, and acute infection (white blood cell count $\geq 10 \times 10^9$/l or hs-crp≥10 mg/l). One of every six consecutive participants was randomly selected for serum BPA measurement. After excluding 11 participants without blood lipid index data, a total of 574 subjects were included in the study.

2.3. Characteristics of participants and sample collection

At baseline, general information such as age, sex, height, weight, and body mass index (BMI) were recorded. Information on previous history, chronic illness, family history and lifestyle factors including smoking and exercise frequency were collected as well. Exercise frequency was defined as follows: physical activity level 1 was almost no exercise, level 2 was 2–3 times per week, level 3 was 3–5 times per week, level 4 was more than 5 times per week. Smoking was defined as current smoker. After 8-12 hours of fasting at night, venous blood samples were collected the next day for biochemical index assessment. Blood samples were immediately sent to the First Affiliated Hospital of Chongqing Medical University and stored at -80°C. These samples were used for the measurement of biochemical parameters, including serum BPA concentration, blood lipids, and blood glucose. At year 5, only profiles of blood lipids were collected.

2.4. Laboratory measurements

At baseline, serum BPA concentration was measured with a commercially available ELISA kit (BL Co., Ltd., Gunma, Japan). Plasma glucose levels were measured using a biochemical

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analyzer (Hitachi 7080, Tokyo, Japan) through the glucose-6-phosphate dehydrogenase method. TC, TGs, LDL-c, and HDL-c were measured by enzymatic determination on an automatic biochemical analyzer (Hitachi 7080, Tokyo, Japan) at baseline and year 5. Reagents were purchased from Leadman Biochemistry Co. Ltd. (Beijing, China). All the experimental processes were carried out in accordance with the manufacturer's instructions (15, 16).

2.5. Diagnosis of dyslipidemia at baseline and year 5

Diagnosis of dyslipidemia was established based on the concentrations of TGs, LDL-c, and HDL-c at baseline and year 5. Referring to the diagnostic criteria for dyslipidemia released by the Japan Atherosclerosis Society (JAS) in 2007, high-LDL-cholesterolemia was diagnosed in subjects whose circulating LDL-c concentration was ≥140mg/dL, hypertriglyceridemia was diagnosed in subjects whose circulating TGs concentration was ≥150 mg/dL, and low-HDL-cholesterolemia was diagnosed in subjects whose circulating HDL-c was <40 mg/dL. Subjects were diagnosed with dyslipidemia if any of the following lipid abnormalities were present: (1) TGs ≥150 mg/dL, (2) LDL-c ≥140 mg/dL, or (3) HDL-c<40 mg/dL (14).

2.6. Statistical analysis

Measurement data are described as the mean ± standard deviation (SD). According to the baseline serum BPA concentration, subjects were divided into low, median and high tertiles. If the data were normally distributed, one-way ANOVA was used to determine differences among the three tertiles and Bonferroni was used for multiple comparisons. The Kruskal-Wallis test was used for non-normally distributed variables. Classification variables are reported as frequency and proportion, and Pearson Chi-Square was used to analyze the data. We conducted correlation analyses using TGs, LDL-c and HDL-c as dependent variables and Z-transformed BPA (1-unit increase in Z-BPA indicates per-SD increment in BPA) as the independent variable. A Multiple linear regression model was established to further explore the independent relationship between Z-BPA and blood lipid profiles.

For cross-sectional and prospective analyses of the relationship between BPA exposure and dyslipidemia (including the three components), multivariable logistic regression was performed. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated based on Z-

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transformed BPA (per-SD change in BPA). A multivariable-based model was built to adjust for the confounding factors. Two criteria were used for multivariable covariate selection: (1) covariates in the model with a *P*-value<0.1, shown in Table 1 (SBP, FPG, T2DM, hypertension, family history of hypertension) and (2) if any covariate was previously shown to be a factor that affected blood lipids or BPA, it was also considered even if its *P*-value was >0.1, shown in Table 1 (age, sex, creatinine, physical activity, smoking) (17-19). The enter method was used in the logistic modeling procedure. SPSS 19.0 software (LEAD Technologies, SPSS Inc., Chicago, USA) was used for analysis, with two-tailed *P*-value <0.05 indicating statistical significance.

3. Results

Baseline serum BPA was split into tertiles according to concentration (0.17±0.07, 0.61±0.30, 3.67±1.59 ng/ml, *P*<0.001), and subjects were divided into low, median and high tertiles accordingly. The baseline characteristics of the participants are shown in Table 1. There were no significant differences in age, sex, waist circumference, BMI, family history of hypertension, frequency of exercise or smoking among the three tertiles (*P*>0.05). Compared to the low BPA tertile, SBP and DBP were significantly higher (*P*<0.05), and the 2-h postprandial blood glucose concentration was significantly lower (*P*<0.05) in the high tertile. As the serum BPA levels increased, subjects exhibited higher levels of serum LDL-c (108.1±24.4 vs. 118.2±27.4 vs. 119.5±26.9 mg/dL, *P*<0.001) and a lower level of serum HDL-c (46.2±11.7 vs. 43.8±9.9 vs. 39.5±7.5 mg/dL, *P*<0.001). No significant difference in TGs concentration (*P*=0.918) was found among the three groups. Compared to the low BPA tertile, the prevalence of dyslipidemia was significantly higher in the median and high tertiles [88 (46.1%) vs. 126 (66.0%) vs. 153 (80.0%), *P*<0.001].

Based on the analyses, figure 1 summarizes the relationship between serum BPA concentration and various blood lipid profiles. At baseline, Z-BPA was positively associated with serum LDL-c levels (*P*=0.002) and negatively associated with HDL-c concentrations (*P*<0.001), with Spearman's correlation coefficients of 0.13 and -0.26, respectively. No

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correlation between BPA levels and TGs was found. After adjusting for potential confounders, including age, sex, BMI, hypertension, diabetes and smoking, the multiple linear regression showed that Z-BPA was still negatively correlated with HDL-c and positively correlated with LDL-c (P<0.05) (Table 2).

Table 3 summarizes the associations between Z-BPA and dyslipidemia (including three components: high-LDL-cholesterolemia, low-HDL-cholesterolemia and hypertriglyceridemia) based on both the cross-sectional and prospective analyses. Confounding factors such as age, sex, BMI, FPG, SBP, serum creatinine, smoking, family history of hypertension, and the frequency of exercise were adjusted. In the cross-sectional analysis, the per-SD increment in BPA exposure was associated with low-HDL-cholesterolemia [OR (95% CI) 1.80 (1.48, 2.18)] and dyslipidemia [1.77(1.41, 2.22)].

A total of 316 subjects without low-HDL-cholesterolemia at baseline were followed for 5 years. During the follow-up, there were 6 participants lost, and 310 completed the follow-up examination. In the prospective analyses, the per-SD increment in BPA was associated with a 1.98-fold higher risk of low-HDL-cholesterolemia based on the crude model [OR (95% CI) 1.98 (1.18, 3.32)], and the OR (95% CI) was 2.76 (1.21, 6.29) in the adjusted model. In prospective analyses, serum BPA levels were not significantly associated with either high-LDL-cholesterolemia or hypertriglyceridemia.

4. Discussion

Our study found that at baseline, an increase in BPA exposure was negatively associated with circulating levels of HDL-c and positively associated with LDL-c concentration. More importantly, the prospective cohort analysis showed that each SD increase in baseline serum BPA concentration was associated with a 2.8-fold higher risk of 5-year incidence of low-HDL-cholesterolemia. These relationships still existed after adjusting for a variety of confounding factors. Our cross-sectional results are similar to those of previous cross-sectional reports, and the prospective data uncovered the relationship between BPA exposure and low-HDL-cholesterolemia incidence, which may be of significance to reveal a new risk factor for

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dyslipidemia.

In recent years, the relationship between BPA and blood lipids has been widely discussed. Our findings were consistent with previous findings. In the elderly population, the urinary concentration of BPA was linearly associated with increasing LDL-c levels, but no association between BPA and TGs was found (10). Based on the data of the US National Health and Nutrition Examination Survey (NHANES) 2003–2008, Teppala et al. found a correlation between elevated BPA exposure and lipid profiles, including increased TGs and decreased HDL levels (20). However, other studies showed inconsistent results. By analyzing the BPA concentration and metabolic parameters of 76 Italian men, BPA was found to be positively associated with TG levels (r=0.275, P=0.016) (21). In a cross-sectional study that included 296 Korean reproductive-aged women, researchers found that neither TGs nor HDL-c were significantly different between BPA quartiles (22). A study from Mexico reported that neither intrauterine BPA exposure levels nor the urinary BPA concentration during puberty were associated with blood lipid levels in adolescents (12). Nonetheless, these studies were all cross-sectional with relatively limited sample sizes, and they did not evaluate whether BPA was an independent risk factor for the incidence of dyslipidemia.

In our study, we not only explored the association between BPA exposure and HDL-c, TG and LDL-c levels, but also further investigated the relationship between serum BPA and dyslipidemia. In the cross-sectional analyses, BPA was negatively correlated with HDL-c and positively correlated with LDL-c after adjusting for potential confounders, including age, sex, BMI, hypertension, diabetes and smoking. Compared to LDL-c, serum BPA concentration was more closely correlated to HDL-c (r=0.13 *vs.* r=-0.26). Further multivariable logistic regression analysis found that the odds ratio of low-HDL-cholesterolemia increased significantly in subjects with higher BPA levels, while no relationship between BPA and high-LDL-cholesterolemia was observed. In the prospective part, subjects without low-HDL-cholesterolemia at baseline were followed up for 5 years. In the prospective analyses, after adjusting for confounding factors, each SD increase in baseline BPA was associated with a 2.8-fold higher risk of 5-year incidence of low-HDL-cholesterolemia. These data suggest that BPA

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is a predictor of low-HDL-cholesterolemia.

At present, the mechanism by which BPA causes low-HDL-cholesterolemia is unclear. In addition to estrogen receptors (ERαβ), the key receptors that BPA binds to include peroxisome proliferator-activated receptors (PPARαγ), androgen receptors (ARs), nonclassical estrogen receptors (ERRγ), thyroid hormone receptors (TRαβ), and progesterone X receptors (PXRs) (23). The activation of PPARα is involved in the metabolism of a variety of lipids, including TGs, LDL-c and HDL-c. By binding PPARα, BPA may lead to lipid metabolism disorders and affecting serum lipid concentrations (24). Lecithin cholesterol acyl transferase (LCAT) is an important enzyme in HDL-c synthesis, that can be affected by oxidative stress (25). The reduced activity of LCAT may lead to disorders of HDL metabolism (26).

The main strengths of our study included prospective design and relatively large sample size. We first demonstrated the effect of BPA on blood lipid changes during a five-year follow-up. There are also some limitations in our research. First, we did not measure urinary BPA concentrations, and some of the confounding factors that affect BPA exposure (such as the use of plastic products) were not completely excluded. Second, the study was conducted in one center, and all subjects were Chinese Asians. There was a selection bias because features of blood lipid levels may not be the same in different races. Third, no longitudinal measurements of BPA were conducted, and the exposure of BPA could not be dynamically detected. However, longitudinal measurements of BPA are difficult, and many epidemiological studies used a single baseline BPA exposure for future prediction (27-29). Baseline serum BPA concentration is considered an alternative estimate of the overall BPA exposure level (28,29). Fourth, there is a confirmed association between dyslipidemia and cardiovascular disease (CVD), but our study only observed changes in blood lipids, not CVD. Further studies are needed to confirm the association between BPA and CVD.

5. Conclusion

Cross-sectionally, higher BPA exposure is associated with a higher prevalence of low-HDL-cholesterolemia. Longitudinally, the baseline serum BPA level was an independent risk

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factor for the five-year incidence of low-HDL-cholesterolemia. There was no longitudinal relationship between baseline BPA exposure and high-LDL-cholesterolemia incidence. The results of our research need to be verified by further prospective and large-sample studies.

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Role of authors

Ruolin Li conducted the data analysis and wrote the manuscript. Shumin Yang applied for funding and oversaw the data collection. Rufei Gao designed the study, assisted with the data collection, and contributed to the writing and editing of the manuscript. Yin Deng, Jiahuan Liu, Chao Yuan, Qingmei Yao, Xinke Lv, Kanran Wang, Xiaoqi Ye took part in the experiments and assisted with the data collection. Jinbo Hu and Bin Peng provided statistical expertise, edited the manuscript and directed the study. Jinbo Hu and Aijun Chen applied for funding, and is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Declarations of interest

The authors declare no conflicts of interest.

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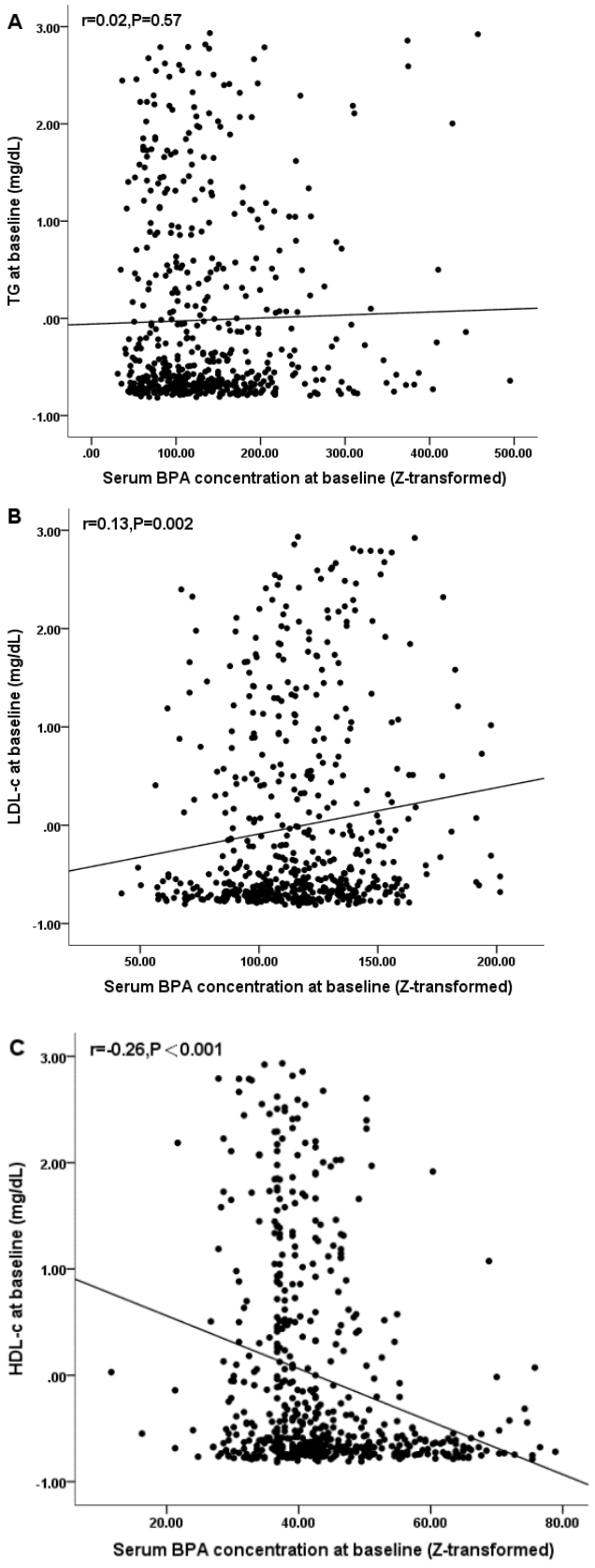

Fig. 1 Simple correlation analysis of the blood lipid levels with serum BPA concentration.
TG triglyceride; LDL-c low-density lipoprotein cholesterol; HDL-c high-density lipoprotein

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cholesterol; BPA bisphenol A.

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Table 1 Baseline characteristics of subjects by tertiles of serum bisphenol A

	Participants n=574	BPA tertiles			
		Low (0.17±0.07) n=191	Median (0.61±0.30) n=191	High (3.67±1.59) n=192	P-value
Women, n (%)	224 (39.0)	76 (39.8%)	70 (36.6%)	78 (40.6%)	0.702
age (years)	62.0±10.8	61.6±10.7	62.1±10.6	62.3±11.1	0.179
WC (cm)	82.8±8.9	82.3±9.7	82.5±8.1	83.7±9.0	0.276
BMI (kg/m2)	24.3±3.0	24.3±3.1	24.3±2.9	24.3±3.0	0.843
SBP (mm/Hg)	126.2±16.2	123.1±15.1*+	127.0±16.2*	128.4±17.0+	0.004
DBP (mm/Hg)	78.9±9.0	77.7±9.1+	79.0±8.5	80.1±9.3+	0.030
Cr (μmoI/L)	82.5±20.4	83.5±22.2	82.7±20.9	81.5±17.9	0.642
TC（mg/dL）	182.2±31.7	182.4±30.5	187.1±31.0#	177.1±33.0#	0.003
TG（mg/dL）	136.8±75.5	133.3±70.1	138.8±79.2	138.2±77.2	0.918
LDL-c(mg/dL)	115.3±26.7	108.1±24.4*+	118.2±27.4*	119.5±26.9+	<0.001
HDL-c(mg/dL)	43.2±10.2	46.2±11.7*+	43.8±9.9*#	39.5±7.5#+	<0.001
FPG (mmol/L)	4.7±1.2	4.7±1.4	4.6±1.2	4.8±1.1	<0.001
2hPG (mmol/L)	6.0±2.6	6.4±2.9+	6.1±2.5	5.7±2.2+	0.003
T2DM, n (%)	130(22.6%)	52 (27.2%)+	46 (24.1%)	32 (16.7%)+	0.040
Hypertension, n (%)	277(48.3%)	85 (44.5%)+	102 (53.4%)	110 (57.3%)+	0.037
Family history of HT, n (%)	204(35.5%)	81 (42.4%)	61 (31.9%)	62 (32.3%)	0.052
Physical activity					
Level 1, n (%)	117(20.4%)	30 (15.7%)	41 (21.5%)	46 (24.0%)	0.287
Level 2, n (%)	88(15.3%)	31 (16.2%)	32 (16.7%)	25 (13.0%)	
Level 3, n (%)	141(24.6%)	55 (28.8%)	46 (24.1%)	40 (20.8%)	
Level 4, n (%)	228(39.7%)	75 (39.3%)	72 (37.7%)	81 (42.2%)	
Smoking (%)	125(21.8%)	35 (18.3%)	46 (24.1%)	44 (22.9%)	0.354
Dyslipidemia (%)	367(63.9%)	88 (46.1%)*+	126 (66.0%)*#	153 (80.0%)#+	<0.001

Data are mean ± SD or %. WC waist circumference; BMI body mass index; BPA bisphenol A; SBP systolic blood pressure; DBP diastolic blood pressure; Cr creatinine; TC total cholesterol; TG triglyceride; LDL-c low-density lipoprotein cholesterol; HDL-c high-density lipoprotein cholesterol; FPG fasting plasma glucose; 2hPG 2-h plasma glucose in oral glucose tolerance test; T2DM type 2 diabetes mellitus; Family history of HT family history of hypertension; Physical activity level 1 was almost no exercise, level 2 was 2–3 times per week, level 3 was 3–5 times per week, level 4 was more than 5 times per week. *P<0.05: low tertiles vs. median tertiles; # P<0.05: median tertiles vs. high tertiles; + P<0.05: low tertiles vs. high tertiles.
BPA concentration: for low tertilee is 0.17±0.07ng/ml, for median tertilee is 0.61±0.30ng/ml, for high tertilee is 3.67±1.59ng/ml.

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Table 2 Multiple Linear Regression of circulating levels of LDL-c and HDL-c: cross-sectional analyses

	LDL-c(n=574)		HDL-c(n=574)	
	β	**P**	**β**	**P**
Z-BPA(per-SD change)	0.13	0.002	-0.28	＜0.001
Gender（female/male）	0.17	＜0.001	0.20	＜0.001
age	0.14	0.002	-0.15	0.001
BMI (kg/m2)	1.20	0.002	-0.17	＜0.001
hypertension（Yes/No）	0.05	0.249	0.01	0.789
T2DM（Yes/No）	0.02	0.716	0.03	0.443
smoking（Yes/No）	0.08	0.080	0.04	0.382

LDL-c low-density lipoprotein cholesterol; HDL-c high-density lipoprotein cholesterol; BMI body mass index; BPA bisphenol A; T2DM type 2 diabetes mellitus

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Table 3 Multivariable analyses for binary logistic regression of 5-year incident high-LDL-cholesterolemia, low-HDL-cholesterolemia, hypertriglyceridemia and dyslipidemia according to Z-BPA (per-SD change).

	Per-SD increment of BPA	
	Crude	Adjusted
Cross-sectional (n=574)		
High-LDL-cholesterolemia	1.16(0.94,1.43)	1.16(0.92,1.45)
Low-HDL-cholesterolemia	1.74(1.45,2.09)*	1.80(1.48,2.18)*
Hypertriglyceridemia	0.95(0.79,1.14)	0.94(0.78,1.13)
Dyslipidemia	1.77(1.43,2.20)*	1.77(1.41,2.22)*
Prospective		
High-LDL-cholesterolemia (n=468)	0.08(0.00,4.53)	0.07(0.00,5.00)
Low-HDL-cholesterolemia (n=310)	1.98(1.18,3.32)*	2.76(1.21,6.29)*
Hypertriglyceridemia (n=376)	0.93(0.70,1.22)	0.96(0.72,1.27)
Dyslipidemia (n=203)	1.06(0.71,1.60)	0.92(0.58,1.45)

Adjusted for age, sex, BMI, FPG, SBP, serum Cr, smoking, family history of hypertension, the frequency of exercise.

High-LDL-cholesterolemia was defined as LDL-c≥140 mg/dL; Low-HDL-cholesterolemia was defined as HDL-c<40 mg/dL; hypertriglyceridemia was defined as TG≥150 mg/dL; Dyslipidemia was defined as High-LDL-cholesterolemia or Low-HDL-cholesterolemia or Hypertriglyceridemia. *P<0.05.

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