**Name of Journal:** *World Journal of Diabetes*

**Manuscript NO:** 76315

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Cohort Study***

**Association between urinary concentrations of bisphenol A substitutes and diabetes in adults**

Moreno-Gómez-Toledano R *et al*. Urinary BPA substitutes and diabetes

Rafael Moreno-Gómez-Toledano, Esperanza Vélez-Vélez, María I Arenas, Marta Saura, Ricardo J Bosch

**Rafael Moreno-Gómez-Toledano, Ricardo J Bosch, Marta Saura,** Universidad de Alcalá, Department of Biological Systems/Physiology Unit, Alcalá de Henares 28871, Spain

**Esperanza Vélez-Vélez,** Fundación Jiménez Díaz School of Nursing, Jiménez Díaz Foundation, Autonomous University of Madrid, Madrid 28040, Spain

**María I Arenas,** Universidad de Alcalá, Department of Biomedicine and Biotechnology,Alcalá de Henares 28871, Spain

**Marta Saura,** Centro de Investigación en Red de Enfermedades Cardiovasculares, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid 28034, Spain

**Author contributions:** Moreno-Gómez-Toledano R contributed to the conceptualization and writing of original draft; Moreno-Gómez-Toledano R, Vélez-Vélez E, Arenas MI, Saura M, and Bosch RJ contributed to the data curation, and manuscript writing, review, and editing; Moreno-Gómez-Toledano R and Vélez-Vélez E contributed to the formal analysis and methodology; Saura M and Bosch RJ contributed to the funding acquisition and project administration; Moreno-Gómez-Toledano R, Vélez-Vélez E, Arenas MI, Saura M, and Bosch RJ contributed to the investigation; all authors have read and agreed to the published version of the manuscript.

**Supported by** the Instituto de Salud Carlos III, No. PI15/02139; and Comunidad Autónoma de Madrid, No. B2017-BMD-3686.

**Corresponding author: Rafael Moreno-Gómez-Toledano, PhD, Associate Research Scientist,** Universidad de Alcalá, Department of Biological Systems/Physiology Unit, Campus Universitario - C/19, Av. de Madrid, Alcalá de Henares 28871, Spain. rafael.moreno@uah.es

**Received:** March 11, 2022

**Revised:** April 26, 2022

**Accepted: June 22, 2022**

**Published online:**

**Abstract**

BACKGROUND

Due to new restrictions on the use of bisphenol A (BPA), industries are beginning to replace it with derived molecules such as bisphenol S and F (BPS and BPF). There is extensive evidence in the academic literature on the potential health effects of BPA, which is known to be a diabetogenic molecule. However, there are few publications related to new compounds derived from BPA.

AIM

To perform an epidemiological study of urinary BPS and BPF in the American National Health and Nutrition Examination Survey (NHANES) cohort, and analyze their possible relationship with diabetes mellitus.

METHODS

NHANES datasets from 2013 to 2016 were used due to the urinary BPF and BPS availability. Data from 3658 adults were analyzed to perform regression analysis exploring the possible relationship between BPA-derived compounds and diabetes.

RESULTS

Descriptive statistics, linear regression modeling, and logistic regression analysis revealed a significant relationship between urinary BPS, but not BPF, and diabetes risk. Additionally, a relationship was observed between both compounds and hypertension and a slight relationship between BPF and dyslipidemia.

CONCLUSION

In the present study, a strong relationship between urinary BPS, not BPF, and diabetes risk has been determined. BPA substitute molecules do not exempt the population from potential health risks.

**Key Words:** Bisphenol S; Bisphenol F; Diabetes mellitus; National Health and Nutrition Examination Survey; Urine

Moreno-Gómez-Toledano R, Vélez-Vélez E, Arenas MI, Saura M, Bosch RJ. Association between urinary concentrations of bisphenol A substitutes and diabetes in adults. *World J Diabetes* 2022; In press

**Core Tip:** Molecules derived from bisphenol A (increasing use in the plastic industry and the production of heat-sensitive tickets) could be related to pathologies such as diabetes (bisphenol S) and hypertension (bisphenol S and F).

**INTRODUCTION**

In the last decades, the demand and production of plastic polymers have increased substantially. Both its production and recycling involve the release of pollutants, xenobiotic compounds that should not be found in the air, rivers, or the human population[1,2]. One of the most important, due to its wide distribution and variety of biological effects, is bisphenol A (BPA)[3-6]. The European Chemicals Agency has recently included BPA within the Candidate List of substances of very high concern due to its properties as an endocrine disruptor and its potentially harmful effect on reproduction[7]. Furthermore, the European Union has restricted the use of this substance in thermal paper due to its potential danger to the health of exposed workers[8].

Therefore, the need to seek alternatives to BPA is a fact of vital importance for modern industry. Currently, two known compounds are bisphenol S (BPS) and bisphenol F (BPF), which can already be found in BPA-free packaging and thermal tickets regulated by European legislation[9,10]. The use of these derivatives does not imply a reduction in possible adverse effects *per se*; it only indicates the use of new materials whose safety has not yet been tested. Comparative studies between BPA substitutes have shown that both BPF and BPS are as hormonally active as BPA[9], so they could also be included in the category of endocrine disruptors.

Diabetes mellitus (DM) and its associated complications are a medical catastrophe of global dimensions[11]. The number of people affected has risen from 108 million in 1980[12] to almost 500 million today[13]. The latest estimates suggest that it could rise to 578 million in 2030 and 700 million in 2045[13]. Risk causes for the disease include a combination of genetic and metabolic factors. There are non-modifiable factors, such as ethnicity or age, and modifying factors, such as diet, obesity, or smoking[14]. The multiplicity of factors that influence the development of the disease implies that environmental pollutants could also affect it. There is evidence that BPA exposure correlates with the risk of developing DM[15].

However, new alternative compounds to BPA have only been used in modern industry for a short time. For this reason, few academic publications study its possible relationship with diabetes. The first pieces of evidence have been detected in a cellular experimental model[16], in males (but not females) of a murine experimental model[17], and in human cohorts from China[18,19] and France[20]. However, it has not yet been studied in one of the world's largest urinary bisphenol cohorts, the American National Health and Nutrition Examination Survey (NHANES). Studies in this cohort have demonstrated the presence of BPF and BPS in urine, observing positive and statistically significant relationships with disorders such as asthma[21], obesity[22-24], or depression[25]. Obesity is closely related to diabetes[26-28], so studying its relationship with new environmental pollutants is coherent and necessary. The present work aimed to correlate, for the first time in the NHANES cohort, diabetes with the urinary concentration of BPA substitutes using regression models.

**MATERIALS AND METHODS**

***NHANES 2013-2016 population***

The NHANES datasets from 2013 to 2016 were used in the present statistical model due to the urinary BPF and BPS availability. In the first phase, the data of all the study participants were extracted through the official website of the Centers for Disease Control and Prevention[29] (accessed December 01, 2021), obtaining 20146 individuals. Subsequently, the individuals with available BPS and BPF were selected, obtaining 5333 subjects, of which 3699 were adults (over 18 years of age). Data from 3658 patients could be used for regression models (complete data). Subsequently, two classifications were made: Group 1 was performed with individuals with and without diabetes. Groups 2 and 3 were performed by analyzing the individuals based on the concentration of urinary phenols (BPS for group 2 and BPF for group 3).

All individuals whose doctor had diagnosed them with diabetes, those taking blood glucose medication, and individuals with a fasting glucose value ≥ 126 mg/dL or hemoglobin A1c ≥ 6.5% were included in the diabetic group. The individuals classified according to the concentration of phenols were divided into four quartiles for BPS and BPF (Q1-Q4). BPS and BPF values were corrected for urinary creatinine to normalize variations due to hydration or glomerular filtration capacity[30].

Binary logistic regression models were corrected for factors such as age, sex, body mass index (BMI), smoking, hypertension, or dyslipidemia. All those patients diagnosed by their doctor, those with medication for hypertension, and individuals with systolic pressure ≥ 140 mmHg or systolic ≥ 90 mmHg were considered hypertensive. The patients with dyslipidemia were those with diagnosed cholesterol disorders, with prescribed medication or fasting total cholesterol ≥ 240 mg/dL[31]. For smoking, all individuals who answered affirmatively to the question “have you smoked more than 100 cigarettes in your life?” or individuals with a serum cotinine value greater than 10 mg/dL[32] were included.

***Statistical analysis***

The IBM SPSS Statistics 27 program was used for the statistical analyses to carry out linear regression and logistic regression analyses, and the GraphPad Prism 7.0 program was used for basic descriptive statistics and comparative analysis. In the comparative analysis of the diabetes subgroup, the Mann-Whitney test was used. In the case of classification based on the phenol quartile, the Kruskal-Wallis test was used. The linear regression analysis used the R-squared coefficient of determination to define the percentage of change in the dependent variable affected by the independent variable. The ANOVA test was used to validate the statistical significance of the coefficient. Finally, the β coefficients and their statistical significance were calculated.

Since the diabetes variable is dichotomous, a binary logistic regression model was used. BPF and BPS values were analyzed with the corresponding correction with urinary creatinine, using their logarithmic transformation to normalize the non-parametric distribution. Three different regression analyzes were performed for each parameter: individual (1), corrected for age, sex, and BMI (2), and corrected for the above parameters and smoking, hypertension, and dyslipidemia (3).

In the study of groups 2 and 3, a multinomial logistic regression model was used. As in the previous statistical model, age, sex, BMI, smoking, hypertension, and dyslipidemia were also included. In all cases, those results whose *P* value was less than 0.05 were interpreted as statistically significant.

**RESULTS**

***General data***

Descriptive statistical analyses showed, in addition to the expected differences related to blood glucose, interesting changes in BPS levels, significantly higher in diabetic patients. However, the BPF values did not show significant variations. In addition, diabetic patients had higher age, BMI, and systolic pressure and lower total cholesterol (Table 1).

Descriptive analyses of group 2 (distributed according to BPS quartile) showed that individuals with a higher concentration of BPS (Q4) had a significant increase in BMI, fasting glucose, and BPF than individuals with a lower level of BPS (Q1) (Table 2). In addition, the percentages showed a positive and dose-dependent relationship between the BPA quartile and the number of patients with diabetes, hypertension, and dyslipidemia. Interestingly, the percentage of men showed a negative trend with urinary BPS concentration, and a positive trend was observed between the percentage of individuals with diabetes, hypertension, or dyslipidemia, and urinary BPS concentration.

On the other hand, the descriptive analyses of group 3 (distributed according to the BPF quartile) showed significant age differences (in quartiles 2, 3, and 4), BMI (Q2 and Q3), and cotinine (the quartile 4 had a significantly higher concentration than the other three quartiles) (Table 3). In this group, no significant differences were observed in the parameters related to diabetes, but an interesting positive relationship was observed in the percentage of individuals with hypertension.

***Simple linear regression***

Linear regression analyses were performed using fasting glucose and hemoglobin A1c (HbA1c) values to explore the relationship between diabetes and phenols. As shown in Table 4, the results were significant in the BPS group, while BPF did not show a statistical relationship with these parameters.

***Binary logistic regression***

The subsequent binomial logistic regression analysis performed on the dichotomous dependent variable diabetes confirmed the data observed in the linear regression (Table 5). Thus, it was observed that the urinary concentration of BPS, both individually and corrected for other factors, was an independent factor related to diabetes mellitus. However, this relationship could not be determined in the urinary concentration of BPF.

***Multinomial logistic regression***

This statistical analysis model showed a significant relationship between diabetes and BPS, but not BPF (Table 6). However, statistically significant data were only observed in the first two models (individual and corrected for sex, age, and BMI). Although it did not become significant when corrected for all the parameters, the resulting *P* value was 0.063.

Interestingly, in the BPS study, Q4 individuals showed a positive and significant relationship with gender, with an odds ratio (OR) (95%CI) of 1.94 (1.61-2.35) for women. An important relationship was also observed in the risk of suffering hypertension, with an OR of 1.26 (1.01-1.57). In the BPF study, the same significant relationship was observed in gender, with an OR of 2.13 (1.75-2.58) for women. Finally, a positive relationship was observed with smoking [OR of 1.78 (1.47-2.17)] and slightly negative with the BMI [0.98 (0.97-0.998)].

***Complementary study of significant pathologies in regression models***

Due to the results observed in the regression models and the trends observed in the descriptive statistics, a binomial logistic regression model was established, using hypertension or dyslipidemia as the dependent variable, in order to relate the risk of suffering from any of them depending on the concentration of urinary phenols. As shown in Table 7, urinary BPS is an independent factor related to hypertension. BPF, on the other hand, showed a statistically significant relationship when analyzed individually with both hypertension and dyslipidemia. This relationship held when correcting for age, sex, and BMI for hypertension, but not for dyslipidemia. Finally, no significant relationship was determined after correction for the rest of the parameters.

**DISCUSSION**

In the present work, it has been demonstrated, for the first time in the NHANES cohort, that BPS, but not BPF, is related to diabetes. The academic literature includes few publications that explore the BPS-diabetes or BPF-diabetes paradigm. There are only three relevant epidemiological studies; two studied type 2 diabetes[18,20], and the remaining investigated gestational diabetes[19].

Duan *et al*[18] considered that all individuals with fasting glucose ≥ 7.0 mmol/L or HbA1c ≥ 6.5% had type 2 diabetes mellitus. After performing the logistic regression analysis, they determined an OR (95%CI) of 1.73 (1.37-2.18) for the urinary BPS, analogous to the results observed in this study.

Rancière *et al*[20] conducted a longitudinal study analyzing the cases of type 2 diabetes developed over 9 years in the DESIR cohort. Due to the low rate of detection of urinary BPS (less than 15%), the statistical model was established comparing individuals with detectable levels of BPS with those in whom the compound had not been detected, obtaining a higher (significant) risk of developing type 2 diabetes in those individuals with detectable levels of BPS. The detection rate in the NHANES cohort was 57.1% and 88.4% for BPF and BPS, respectively[21]. The results also support and reaffirm those obtained in the present work, although the difference in the detection ratio is very striking. Völkel *et al*[33,34] exclusively quantified BPS-glucuronide, the main metabolized form, according to human pharmacokinetic models. In the case of the NHANES cohort, the total concentration of bisphenol was analyzed after previously deconjugating the metabolized forms (glucuronide and sulfate) with Helix pomatiaenzymes.

Lastly, Zhang *et al*[19] analyzed BPS and BPF in a cohort of Chinese pregnant women to study their possible relationship with gestational diabetes mellitus. Interestingly, quantitative analyses detected BPS and BPF in most urine samples from pregnant women (greater than 90% in both cases). However, the regression models did not show significant relationships with either compound. They only determined a slight but significant increase in glucose related to urinary BPS concentration. Finally, when studying the relationship between blood glucose and urinary BPS according to fetal sex, they observed that the relationship was more significant in the case of female fetuses.

The present study determined that there was a significant relationship between urinary BPS and diabetes. However, such a relationship was not observed with urinary BPF. From a molecular point of view, it is interesting to note that BPF, like BPA, has carbon and hydrogen atoms, while BPS also contains sulfur atoms[19]. There is conflicting evidence in the academic literature between BPA and diabetes. Thus, some studies observed a positive and significant relationship with diabetes mellitus[35,36] or prediabetes[37], while others did not find a significant relationship[38]. In addition, there are even works, such as that by Wang *et al*[39], in which they determined that pregnant women with higher levels of urinary BPA had a lower risk of developing gestational diabetes.

Interestingly, both BPS and BPF (like BPA) have been shown to have pro-estrogenic and anti-androgenic activity[40]. In pancreatic cell cultures, it has been observed that both BPS and BPF can negatively affect insulin secretion and ion channels through a signaling mechanism that includes estrogen receptor beta[16]. A recent animal study conducted by Qiu *et al*[41] observed that BPF and BPS produced similar effects on the immune system in zebrafish. In an experimental non-obese diabetic mouse model, it has been observed that BPS could negatively affect glucose homeostasis in males, while a protective effect was observed in females[17]. From a mechanistic point of view, bisphenols have the potential to affect the development of diabetes through different pathways. In addition to the classical estrogen receptors (ER-α, ER-β, and G protein-coupled receptor 30), BPA has been shown to have increased binding capacity to the estrogen-related receptor (ERR-γ)[43]. ERR-γ is important in diabetes since it plays an essential role in correctly maturing pancreatic β cells[44] and insulin secretion[45]. This receptor also plays a vital role in coordinating metabolic and endocrine signals, regulating hepatic glucose metabolism[46]. Previous work by our group demonstrated that this receptor participates in the loss of podocyte adhesion induced by BPA and is directly related to diabetic nephropathy[3]. On the other hand, it has been observed that both BPA and BPS can affect insulin cell signaling in skeletal muscle and adipose tissue (reducing the expression of insulin receptor substrate 1 and Akt phosphorylation)[43].

The linear regression model of the present work showed very significant values only with the BPS. However, the *R*-squared value was low (0.005) despite being significant. This data implies that the relationship between both variables is low; urinary BPS could only explain a tiny part of diabetes cases. Subsequent binomial and multinomial logistic regression models confirmed and reinforced the relationship between BPS and diabetes while ruling out the statistical relationship with urinary BPF. Nowadays, the vision of “one factor-one disease” could be considered obsolete. Numerous pathologies, such as diabetes, cannot be explained by the action of a single element since they are multifactorial. Therefore, the main idea extracted from the results is that BPS is an environmental factor related to diabetes.

On the other hand, complementary studies on hypertension and dyslipidemia have shown interesting evidence. First, both derived compounds show interesting significant relationships with the risk of hypertension, especially BPS. As with diabetes, few works study the relationship between BPS or BPF and these diseases. Jiang *et al*[42] found a positive and significant relationship between individuals with higher levels of urinary BPS, but not BPF, with hypertension. On the other hand, the works of Liu *et al*[22] and Jacobson *et al*[24] found a significant relationship between urinary BPF[22] or both phenolic derivatives[24] and obesity in children and adolescents.

Due to the differences observed in the risks of predisposition to diseases, it could be stated that the compounds derived from BPA (despite having similar hormonal activity) could act on different cell signaling mechanisms, promoting the development or progression of different diseases.

**CONCLUSION**

The present study has determined a strong relationship between urinary BPS, not BPF, and diabetes risk. In the case of hypertension, both molecules could be involved in pathophysiological mechanisms, which, in the case of dyslipidemia, would be exclusive to BPF. Future studies will be necessary to delve into the paradigm and explore the relationship of the new BPA-derived molecules with other related diseases, such as kidney disease. BPA substitute molecules do not exempt the population from potential health risks.

**ARTICLE HIGHLIGHTS**

***Research background***

New restrictions on the use of bisphenol A (BPA) have conditioned the use of new derivative compounds by the plastics industry. The small amount of evidence for its possible effects on human health shows its need, especially in diseases such as diabetes, whose incidence has increased substantially in recent years.

***Research motivation***

The study of the urinary excretion of the new bisphenols and their possible relationship with human health is of particular importance. The present work aimed to provide new evidence that supports the need for restriction in using new molecules derived from BPA.

***Research objectives***

The work's objective was to analyze the relationship between urinary bisphenols and diabetes in one of the largest global cohorts, National Health and Nutrition Examination Survey (NHANES). The possible results could support the need to explore the signaling pathways involved in the pancreatic pathophysiology potentially induced by this class of molecules.

***Research methods***

By applying descriptive statistics, simple linear regressions, and logistic regression models, this study aimed to analyze the data from the NHANES cohort in a novel way in a context that has been little studied in the academic literature.

***Research results***

After using all the tools and statistical models, the results have consistently pointed to bisphenol S as a risk factor for diabetes, excluding bisphenol F. On the other hand, the relationships observed with hypertension and dyslipidemia maintain the need to evaluate both molecules in the human health context.

***Research conclusions***

In a novel way in the NHANES cohort, the present study has shown that exposure to new bisphenols is directly related to diabetes.

***Research perspectives***

Future research should explore the causal relationship through longitudinal studies and evaluate the potential deleterious effects on other pathologies, such as kidney disease.

**REFERENCES**

1 **Vandenberg LN**, Hauser R, Marcus M, Olea N, Welshons WV. Human exposure to bisphenol A (BPA). *Reprod Toxicol* 2007; **24**: 139-177 [PMID: 17825522 DOI: 10.1016/j.reprotox.2007.07.010]

2 **Vandenberg LN**, Chahoud I, Heindel JJ, Padmanabhan V, Paumgartten FJ, Schoenfelder G. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. *Environ Health Perspect* 2010; **118**: 1055-1070 [PMID: 20338858 DOI: 10.1289/ehp.0901716]

3 **Moreno-Gómez-Toledano R**, Arenas MI, González-Martínez C, Olea-Herrero N, Reventún P, Di Nunzio M, Sánchez-Esteban S, Arilla-Ferreiro E, Saura M, Bosch RJ. Bisphenol A impaired cell adhesion by altering the expression of adhesion and cytoskeleton proteins on human podocytes. *Sci Rep* 2020; **10**: 16638 [PMID: 33024228 DOI: 10.1038/s41598-020-73636-6]

4 **Moreno-Gómez-Toledano R**, Arenas MI, Muñoz-Moreno C, Olea-Herrero N, Reventun P, Izquierdo-Lahuerta A, Antón-Cornejo A, González-Santander M, Zaragoza C, Saura M, Bosch RJ. Comparison of the renal effects of bisphenol A in mice with and without experimental diabetes. Role of sexual dimorphism. *Biochim Biophys Acta Mol Basis Dis* 2022; **1868**: 166296 [PMID: 34718120 DOI: 10.1016/j.bbadis.2021.166296]

5 **Reventun P**, Sanchez-Esteban S, Cook A, Cuadrado I, Roza C, Moreno-Gomez-Toledano R, Muñoz C, Zaragoza C, Bosch RJ, Saura M. Bisphenol A induces coronary endothelial cell necroptosis by activating RIP3/CamKII dependent pathway. *Sci Rep* 2020; **10**: 4190 [PMID: 32144343 DOI: 10.1038/s41598-020-61014-1]

6 **Moreno-Gómez-Toledano R**, Sánchez-Esteban S, Cook A, Mínguez-Moratinos M, Ramírez-Carracedo R, Reventún P, Delgado-Marín M, Bosch RJ, Saura M. Bisphenol A Induces Accelerated Cell Aging in Murine Endothelium. *Biomolecules* 2021; **11** [PMID: 34680063 DOI: 10.3390/biom11101429]

7 **European Chemical Agency (ECHA)**. Candidate List of Substances of Very High Concern for Authorisation. 2014 [DOI: 10.1016/b978-0-12-386454-3.00547-9]

8 **Comisión Europea**. Reglamento (UE) 2016/2235 De La Comisión de 12 de diciembre de 2016. Diario Oficial de la Unión Europea (2016). [cited 2021 Nov 24]. Available from: https://www.boe.es/doue/2016/337/L00003-00005.pdf

9 **Rochester JR**, Bolden AL. Bisphenol S and F: A Systematic Review and Comparison of the Hormonal Activity of Bisphenol A Substitutes. *Environ Health Perspect* 2015; **123**: 643-650 [PMID: 25775505 DOI: 10.1289/ehp.1408989]

10 **Skledar DG**, Schmidt J, Fic A, Klopčič I, Trontelj J, Dolenc MS, Finel M, Mašič LP. Influence of metabolism on endocrine activities of bisphenol S. *Chemosphere* 2016; **157**: 152-159 [PMID: 27213244 DOI: 10.1016/j.chemosphere.2016.05.027]

11 **Ritz E**, Rychlík I, Locatelli F, Halimi S. End-stage renal failure in type 2 diabetes: A medical catastrophe of worldwide dimensions. *Am J Kidney Dis* 1999; **34**: 795-808 [PMID: 10561134 DOI: 10.1016/S0272-6386(99)70035-1]

12 **NCD Risk Factor Collaboration (NCD-RisC)**. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016; **387**: 1513-1530 [PMID: 27061677 DOI: 10.1016/S0140-6736(16)00618-8]

13 **Saeedi P**, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R; IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract* 2019; **157**: 107843 [PMID: 31518657 DOI: 10.1016/j.diabres.2019.107843]

14 **Glovaci D**, Fan W, Wong ND. Epidemiology of Diabetes Mellitus and Cardiovascular Disease. *Curr Cardiol Rep* 2019; **21**: 21 [PMID: 30828746 DOI: 10.1007/s11886-019-1107-y]

15 **Hwang S**, Lim JE, Choi Y, Jee SH. Bisphenol A exposure and type 2 diabetes mellitus risk: a meta-analysis. *BMC Endocr Disord* 2018; **18**: 81 [PMID: 30400886 DOI: 10.1186/s12902-018-0310-y]

16 **Marroqui L**, Martinez-Pinna J, Castellano-Muñoz M, Dos Santos RS, Medina-Gali RM, Soriano S, Quesada I, Gustafsson JA, Encinar JA, Nadal A. Bisphenol-S and Bisphenol-F alter mouse pancreatic β-cell ion channel expression and activity and insulin release through an estrogen receptor ERβ mediated pathway. *Chemosphere* 2021; **265**: 129051 [PMID: 33250229 DOI: 10.1016/j.chemosphere.2020.129051]

17 **Xu J**, Huang G, Guo TL. Bisphenol S Modulates Type 1 Diabetes Development in Non-Obese Diabetic (NOD) Mice with Diet- and Sex-Related Effects. *Toxics* 2019; **7** [PMID: 31234578 DOI: 10.3390/toxics7020035]

18 **Duan Y**, Yao Y, Wang B, Han L, Wang L, Sun H, Chen L. Association of urinary concentrations of bisphenols with type 2 diabetes mellitus: A case-control study. *Environ Pollut* 2018; **243**: 1719-1726 [PMID: 30408859 DOI: 10.1016/j.envpol.2018.09.093]

19 **Zhang W**, Xia W, Liu W, Li X, Hu J, Zhang B, Xu S, Zhou Y, Li J, Cai Z, Li Y. Exposure to Bisphenol a Substitutes and Gestational Diabetes Mellitus: A Prospective Cohort Study in China. *Front Endocrinol (Lausanne)* 2019; **10**: 262 [PMID: 31114544 DOI: 10.3389/fendo.2019.00262]

20 **Rancière F**, Botton J, Slama R, Lacroix MZ, Debrauwer L, Charles MA, Roussel R, Balkau B, Magliano DJ; D.E.S.I.R. Study Group. Exposure to Bisphenol A and Bisphenol S and Incident Type 2 Diabetes: A Case-Cohort Study in the French Cohort D.E.S.I.R. *Environ Health Perspect* 2019; **127**: 107013 [PMID: 31663775 DOI: 10.1289/EHP5159]

21 **Mendy A**, Salo PM, Wilkerson J, Feinstein L, Ferguson KK, Fessler MB, Thorne PS, Zeldin DC. Association of urinary levels of bisphenols F and S used as bisphenol A substitutes with asthma and hay fever outcomes. *Environ Res* 2020; **183**: 108944 [PMID: 31911000 DOI: 10.1016/j.envres.2019.108944]

22 **Liu B**, Lehmler HJ, Sun Y, Xu G, Sun Q, Snetselaar LG, Wallace RB, Bao W. Association of Bisphenol A and Its Substitutes, Bisphenol F and Bisphenol S, with Obesity in United States Children and Adolescents. *Diabetes Metab J* 2019; **43**: 59-75 [PMID: 30793552 DOI: 10.4093/dmj.2018.0045]

23 **Liu B**, Lehmler HJ, Sun Y, Xu G, Liu Y, Zong G, Sun Q, Hu FB, Wallace RB, Bao W. Bisphenol A substitutes and obesity in US adults: analysis of a population-based, cross-sectional study. *Lancet Planet Health* 2017; **1**: e114-e122 [PMID: 29308453 DOI: 10.1016/S2542-5196(17)30049-9]

24 **Jacobson MH**, Woodward M, Bao W, Liu B, Trasande L. Urinary Bisphenols and Obesity Prevalence Among U.S. Children and Adolescents. *J Endocr Soc* 2019; **3**: 1715-1726 [PMID: 31528831 DOI: 10.1210/js.2019-00201]

25 **Hao K**, Luo J, Sun J, Ge H, Wang Z. Associations of urinary bisphenol A and its alternatives bisphenol S and F concentrations with depressive symptoms among adults. *Chemosphere* 2021; **279**: 130573 [PMID: 33878692 DOI: 10.1016/j.chemosphere.2021.130573]

26 **Maggio CA**, Pi-Sunyer FX. Obesity and type 2 diabetes. *Endocrinol Metab Clin North Am* 2003; **32**: 805-822, viii [PMID: 14711063 DOI: 10.1016/s0889-8529(03)00071-9]

27 **Polsky S**, Ellis SL. Obesity, insulin resistance, and type 1 diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes* 2015; **22**: 277-282 [PMID: 26087341 DOI: 10.1097/MED.0000000000000170]

28 **Riobó Serván P**, Moreno Ruiz I. [Nutrition in chronic kidney disease]. *Nutr Hosp* 2019; **36**: 63-69 [PMID: 31368337 DOI: 10.20960/nh.02812]

29 **Centers for Disease Control and Prevention (CDC)**. National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey (NHANES). (2021). [cited 2021 Dec 1]. Available from: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx

30 **Mage DT**, Allen RH, Kodali A. Creatinine corrections for estimating children's and adult's pesticide intake doses in equilibrium with urinary pesticide and creatinine concentrations. *J Expo Sci Environ Epidemiol* 2008; **18**: 360-368 [PMID: 17878925 DOI: 10.1038/sj.jes.7500614]

31 **Moon S**, Yu SH, Lee CB, Park YJ, Yoo HJ, Kim DS. Effects of bisphenol A on cardiovascular disease: An epidemiological study using National Health and Nutrition Examination Survey 2003-2016 and meta-analysis. *Sci Total Environ* 2021; **763**: 142941 [PMID: 33158523 DOI: 10.1016/j.scitotenv.2020.142941]

32 **Pirkle JL**, Flegal KM, Bernert JT, Brody DJ, Etzel RA, Maurer KR. Exposure of the US population to environmental tobacco smoke: the Third National Health and Nutrition Examination Survey, 1988 to 1991. *JAMA* 1996; **275**: 1233-1240 [PMID: 8601954 DOI: 10.1001/jama.1996.03530400021033]

33 **Völkel W**, Colnot T, Csanády GA, Filser JG, Dekant W. Metabolism and kinetics of bisphenol a in humans at low doses following oral administration. *Chem Res Toxicol* 2002; **15**: 1281-1287 [PMID: 12387626 DOI: 10.1021/tx025548t]

34 **Völkel W**, Bittner N, Dekant W. Quantitation of bisphenol A and bisphenol A glucuronide in biological samples by high performance liquid chromatography-tandem mass spectrometry. *Drug Metab Dispos* 2005; **33**: 1748-1757 [PMID: 16103135 DOI: 10.1124/dmd.105.005454]

35 **Shankar A**, Teppala S. Relationship between urinary bisphenol A levels and diabetes mellitus. *J Clin Endocrinol Metab* 2011; **96**: 3822-3826 [PMID: 21956417 DOI: 10.1210/jc.2011-1682]

36 **Tosirisuk N**, Sakorn N, Jantarat C, Nosoongnoen W, Aroonpakmongkol S, Supornsilchai V. Increased bisphenol A levels in Thai children and adolescents with type 1 diabetes mellitus. *Pediatr Int* 2021; **64**: e14944 [PMID: 34342913 DOI: 10.1111/ped.14944]

37 **Sabanayagam C**, Teppala S, Shankar A. Relationship between urinary bisphenol A levels and prediabetes among subjects free of diabetes. *Acta Diabetol* 2013; **50**: 625-631 [PMID: 23636267 DOI: 10.1007/s00592-013-0472-z]

38 **İnce T**, Balcı A, Yalçın SS, Özkemahlı G, Erkekoglu P, Kocer-Gumusel B, Yurdakök K. Urinary bisphenol-A levels in children with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2018; **31**: 829-836 [PMID: 29975667 DOI: 10.1515/jpem-2018-0141]

39 **Wang X**, Wang X, Chen Q, Luo ZC, Zhao S, Wang W, Zhang HJ, Zhang J, Ouyang F. Urinary Bisphenol A Concentration and Gestational Diabetes Mellitus in Chinese Women. *Epidemiology* 2017; **28** Suppl 1: S41-S47 [PMID: 29028674 DOI: 10.1097/EDE.0000000000000730]

40 **Park C**, Song H, Choi J, Sim S, Kojima H, Park J, Iida M, Lee Y. The mixture effects of bisphenol derivatives on estrogen receptor and androgen receptor. *Environ Pollut* 2020; **260**: 114036 [PMID: 31995776 DOI: 10.1016/j.envpol.2020.114036]

41 **Qiu W**, Shao H, Lei P, Zheng C, Qiu C, Yang M, Zheng Y. Immunotoxicity of bisphenol S and F are similar to that of bisphenol A during zebrafish early development. *Chemosphere* 2018; **194**: 1-8 [PMID: 29195089 DOI: 10.1016/j.chemosphere.2017.11.125]

42 **Jiang S**, Liu H, Zhou S, Zhang X, Peng C, Zhou H, Tong Y, Lu Q. Association of bisphenol A and its alternatives bisphenol S and F exposure with hypertension and blood pressure: A cross-sectional study in China. *Environ Pollut* 2020; **257**: 113639 [PMID: 31796315 DOI: 10.1016/j.envpol.2019.113639]

43 **Ahmed F**, Pereira MJ, Aguer C. Bisphenols and the Development of Type 2 Diabetes: The Role of the Skeletal Muscle and Adipose Tissue. *Environ* 2021; **8**: 35 [DOI: 10.3390/ENVIRONMENTS8040035]

44 **Yoshihara E**, Wei Z, Lin CS, Fang S, Ahmadian M, Kida Y, Tseng T, Dai Y, Yu RT, Liddle C, Atkins AR, Downes M, Evans RM. ERRγ Is Required for the Metabolic Maturation of Therapeutically Functional Glucose-Responsive β Cells. *Cell Metab* 2016; **23**: 622-634 [PMID: 27076077 DOI: 10.1016/j.cmet.2016.03.005]

45 **Lei Z**, JunHui L, PeiFeng L. Candidate genes mediated by estrogen-related receptor γ in pancreatic β cells. *J Biochem Mol Toxicol* 2019; **33**: e22390 [PMID: 31478280 DOI: 10.1002/jbt.22390]

46 **Kim DK**, Choi HS. Emerging role of the orphan nuclear receptor estrogen-related receptor gamma in liver metabolic diseases. *Liver Res* 2019; **3**: 99-105 [DOI: 10.1016/j.livres.2019.03.001]

**Footnotes**

**Institutional review board statement:** The study was reviewed and approved for publication by our Institutional Reviewer.

**Conflict-of-interest statement:** 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.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** March 11, 2022

**First decision:** April 17, 2022

**Article in press:**

**Specialty type:** Endocrinology and metabolism

**Country/Territory of origin:** Spain

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** He Z, China; Rojas A, Chile **S-Editor:** Zhang H **L-Editor:** Wang TQ **P-Editor:** Zhang H

**Table 1 Descriptive statistics of main variables analyzed in individuals of group 1 (diabetes)**

|  |  |  |
| --- | --- | --- |
|  | **Non-diabetic** | **Diabetic** |
| *n* | 3017 | 641 |
| Age | 41.11 (40.48-41.75) | 58.33 (57.15-59.53)d |
| Gender, % of men | 46.6 | 51 |
| BMI, kg/m2 | 27.82 (27.6-28.04) | 31.4 (30.86-31.94)d |
| Fasting glucose, mg/dL | 98.08 (97.56-98.6) | 149.6 (144.4-154.9)d |
| HbA1c, % | 5.41 (5.40-5.43) | 7.26 (7.14-7.39)d |
| Cotinine, serum ng/mL | 0.28 (0.24-0.31) | 0.18 (0.13-0.24)a |
| Smoker, % | 42.5 | 50.2 |
| Systolic blood pressure, mmHg | 121 (120.4-121.6) | 130.2 (128.7-131.7)d |
| Diastolic blood pressure, mmHg | 68.86 (68.42-69.31) | 68.21 (67.17-69.26) |
| Hypertension, % | 36.1 | 71.9 |
| Dyslipidemia, % | 35 | 66.6 |
| Total cholesterol, mg/dL | 187.4 (186-188.9) | 180.7 (177.2-184.2)c |
| Bisphenol F, µg/g creatinine | 0.41 (0.39-0.43) | 0.43 (0.38-0.48) |
| Bisphenol S, µg/g creatinine | 0.5 (0.48-0.52) | 0.59 (0.53-0.64)b |

a*P* < 0.05.

b*P* < 0.01.

c*P* < 0.001.

d*P* < 0.0001.

The results are expressed as percentages (%) or as geometric mean (95%CI). BMI: Body mass index; HbA1c: Hemoglobin A1c.

**Table 2 Descriptive statistics of main variables analyzed in individuals of group 2 (****bisphenol S)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **BPS quartile** | **Q1** | **Q2** | **Q3** | **Q4** |
| *n* | 915 | 911 | 894 | 938 |
| Age | 42.88 (41.65-44.14) | 42.42 (41.22-43.65) | 44.5 (43.32-45.72) | 45.8 (43.89-46.3)d |
| Gender, % of men | 56.3 | 49.7 | 42.8 | 40.6 |
| BMI, kg/m2 | 27.76 (27.36-28.17) | 28.41 (27.99-28.83) | 28.94 (28.51-29.38)c | 28.57 (28.15-29)a |
| Diabetes mellitus, % | 15.3 | 16.6 | 18.1 | 20 |
| Fasting glucose, mg/dL | 103.7 (101.8-105.8) | 104.5 (102.4-106.6) | 108.2 (105.5-111) | 108.8 (106.3-111.5)a |
| HbA1c, % | 5.62 (5.57-5.68) | 5.66 (5.61-5.72) | 5.75 (5.69-5.81) | 5.78 (5.71-5.85) |
| Smoker, % | 43.6 | 44.8 | 42.4 | 44.5 |
| Cotinine, serum ng/mL | 0.24 (0.19-0.32) | 0.27 (0.21-0.35) | 0.24 (0.18-0.31) | 0.27 (0.21-0.35) |
| Hypertension, % | 39 | 40.6 | 43.4 | 46.3 |
| Systolic blood pressure, mmHg | 120.6 (119.5-121.7) | 123.1 (122-124.2) | 122.5 (121.4-123.7) | 123.9 (122.7-125.1) |
| Diastolic blood pressure, mmHg | 68.31 (67.5-69.13) | 69.36 (68.52-70.21) | 69.18 (68.37-69.99) | 68.18 (67.37-69) |
| Dyslipidemia, % | 39.3 | 40.6 | 40.8 | 41.5 |
| Total cholesterol, mg/dL | 184.3 (131.6-187) | 184.7 (182-187.3) | 187.7 (184.9-190.5) | 188.3 (185.7-190. 9) |
| Bisphenol F, µg/g creatinine | 0.37 (0.34-0.41) | 0.43 (0.39-0.47)a | 0.41 (0.38-0.45) | 0.45 (0.41-0.49)b |

a*P* < 0.05, significant differences with respect to group Q1.

b*P* < 0.01, significant differences with respect to group Q1.

c*P* < 0.001, significant differences with respect to group Q1.

d*P* < 0.05, significant differences between Q2 and Q4.

The results are expressed as percentages (%) or as geometric mean (95%CI). BMI: Body mass index; HbA1c: Hemoglobin A1c; BPS: Bisphenol S; BPF: Bisphenol F.

**Table 3 Descriptive statistics of main variables analyzed in individuals of group 3 (****bisphenol F)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **BPF quartile** | **Q1** | **Q2** | **Q3** | **Q4** |
| *n* | 912 | 912 | 922 | 912 |
| Age | 41.22 (40.04-42.42) | 44.81 (43.59-46.06)c | 45.22 (44.02-46.46)d | 43.69 (42.5-44.92)a |
| Gender, % of men | 58.2 | 44.5 | 43.7 | 43 |
| BMI, kg/m2 | 29.04 (28.61-29.48) | 28.01 (27.6-28.43)b | 28.04 (27.63-28.45)b | 28.59 (28.16-29.02) |
| Diabetes mellitus, % | 17.1 | 19.7 | 16.4 | 16.9 |
| Fasting glucose, mg/dL | 108.3 (105.9-110.7) | 106.2 (103.9-108.6) | 104.7 (102.6-106.9) | 105.6 (5.63-5.75) |
| HbA1c, % | 5.7 (5.64-5.75) | 5.74 (5.68-5.81) | 5.69 (5.63-5.75) | 5.69 (5.63-5.75) |
| Smoker, % | 38.6 | 40.9 | 46.4 | 49.3 |
| Cotinine, serum ng/mL | 0.18 (0.14-0.23) | 0.19 (0.15-0.25) | 0.29 (0.22-0.38) | 0.43 (0.33-0.57)cef |
| Hypertension, % | 39.7 | 42 | 43.3 | 44.4 |
| Systolic blood pressure, mmHg | 121.9 (120.9-123.1) | 122.9 (121.8-124.1) | 123 (121.8-124.1) | 122.3 (121.1-123.5) |
| Diastolic blood pressure, mmHg | 68.73 (67.93-69.53) | 68.53 (67.76-69.31) | 68.79 (67.94-69.64) | 68.95 (68.1-69.82) |
| Dyslipidemia, % | 37.6 | 41 | 43.4 | 40.2 |
| Total cholesterol, mg/dL | 185.3 (182.2-187.9) | 186.9 (184.1-189.8) | 186.7 (184.1-189.4) | 185-9 (183.3-188.6) |
| BPS, µg/g creatinine | 0.48 (0.44-0.51) | 0.5 (0.46-0.54) | 0.55 (0.51-0.59) | 0.54 (0.50-0.58) |

a*P* < 0.05, significant differences with respect to group Q1.

b*P* < 0.01, significant differences with respect to group Q1.

c*P* < 0.001, significant differences with respect to group Q1.

d*P* < 0.0001, significant differences with respect to group Q1.

e*P* < 0.05, significant differences between Q2 and Q4.

f*P* < 0.05, significant differences between Q3 and Q4.

The results are expressed as percentages (%) or as geometric mean (95%CI). BMI: Body mass index; HbA1c: Hemoglobin A1c; BPS: Bisphenol S; BPF: Bisphenol F.

**Table 4 Simple linear regression with hemoglobin A1c and fasting glucose**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **HbA1c** | | | **Fasting glucose** | | |
| Variable | Adjusted *R*2 | β0 | β | Adjusted *R*2 | β0 | β |
| 1BPS | 0.005d | 5.835d | 0.069d | 0.006c | 111.69d | 2.48d |
| 1BPF | 0.000 | 5.795 | 0.006 | 0.000 | 109.65 | -0.39 |

c*P* < 0.001.

d*P* < 0.0001.

1Log transformed.

HbA1c: Hemoglobin A1c; BPS: Bisphenol S; BPF: Bisphenol F.

**Table 5 Association between phenols and diabetes**

|  |  |  |
| --- | --- | --- |
|  | **Diabetes** | |
| Variable | OR (95%CI) | *P* value |
| 1BPS (1) | 1.115 (1.038-1.196) | 0.003 |
| 1BPS (2) | 1.109 (1.026-1.198) | 0.009 |
| 1BPS (3) | 1.099 (1.016-1.188) | 0.018 |
| 1BPF (1) | 1.020 (0.961-1.083) | 0.513 |
| 1BPF (2) | 1.005 (0.941-1.072) | 0.890 |
| 1BPF (3) | 0.991 (0.928-1.059) | 0.795 |

1Log-transformed.

(1) Individual; (2) Corrected for age, sex, and body mass index; (3) Corrected for the above parameters and smoking, hypertension, and dyslipidemia. OR: Odds ratio; BPS: Bisphenol S; BPF: Bisphenol F.

**Table 6 Association between diabetes and** **bisphenol S or F quartile**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Q1** | **Q2** | **Q3** | **Q4** |
| Variable | Ref. | OR (95% CI) | OR (95%CI) | OR (95%CI) |
| 1Diabetes (1) | Ref. | 1.1 (0.86-1.41) | 1.23 (0.96-1.57) | 1.39 (1.09-1.77)c |
| 1Diabetes (2) | Ref. | 1.11 (0.85-1.46) | 1.14 (0.87-1.48) | 1.32 (1.01-1.71)a |
| 1Diabetes (3) | Ref. | 1.09 (0.83-1.43) | 1.12 (0.86-1.47) | 1.28 (0.99-1.67) |
| 2Diabetes (1) | Ref. | 1.19 (0.94-1.51) | 0.95 (0.74-1.21) | 0.98 (0.77-1.26) |
| 2Diabetes (2) | Ref. | 1.16 (0.90-1.51) | 0.88 (0.68-1.15) | 0.94 (0.72-1.23) |
| 2Diabetes (3) | Ref. | 1.17 (0.90-1.52) | 0.86 (0.66-1.13) | 0.92 (0.70-1.20) |

a*P* < 0.05.

c*P* < 0.001.

1Bisphenol S (group 2).

2Bisphenol F (group 3).

(1) Individual; (2) Corrected for age, sex, and body mass index; (3) Corrected for the above parameters and smoking, hypertension, and dyslipidemia. OR: Odds ratio.

**Table 7 Association between hypertension or dyslipidemia and bisphenol S or F**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Hypertension** | | **Dyslipidemia** | |
| Variable | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| 1BPS (1) | 1.12 (1.06-1.18) | 0.000 | 0.99 (0.99-1.11) | 0.099 |
| 1BPS (2) | 1.09 (1.02-1.17) | 0.007 | 1.02 (0.95-1.08) | 0.607 |
| 1BPS (3) | 1.08 (1.01-1.16) | 0.017 | 0.99 (0.937-1.065) | 0.980 |
| 1BPF (1) | 1.07 (1.02-1.12) | 0.005 | 1.05 (1.005-1.1) | 0.03 |
| 1BPF (2) | 1.06 (1.001-1.12) | 0.044 | 1.04 (0.98-1.1) | 0.168 |
| 1BPF (3) | 1.04 (0.99-1.11) | 0.136 | 1.03 (0.98-1.09) | 0.274 |

1Log-transformed.

(1) Individual; (2) Corrected for age, sex, and body mass index; (3) Corrected for the above parameters and smoking, hypertension, and dyslipidemia. OR: Odds ratio.