

Article

Independent Associations Between Urinary Bisphenols and Vitamin D Deficiency: Findings from NHANES Study

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Abstract

Plastic pollution is one of the leading global problems of modern society. The growing demand for and production of plastic polymers has caused bisphenol A (BPA) and its emergent substitute molecules bisphenol S and F (BPS and BPF) to be present in water, food, and soil worldwide, exposing humans to endocrine disruptors. Exposure to these compounds has been associated with pathologies such as diabetes, obesity, hypertension, and psychiatric disorders. Interestingly, hypovitaminosis D (or low 25(OH)D) is also associated with this class of diseases. Therefore, the present work, for the first time, explores the relationship patterns between urinary bisphenols (BPs) and low 25(OH)D in a large general cohort (NHANES 13–16). Descriptive statistical analyses, comparative analyses, linear regressions, and binomial and multinomial logistic regressions were performed. Descriptive and comparative analysis, and simple linear regressions, showed different trends between BPs, and binomial logistic regressions showed that only BPS is a risk factor of low 25(OH)D, independently of age, BMI, gender, diabetes, dyslipidemia, smoking, and vitamin supplements consumption; odds ratio (95% confidence interval) of 1.10 (1.04–1.17). The different trend patterns observed in urinary bisphenols show that, despite being structurally similar molecules and potential analogs, they may affect the body in different ways. From an integrated perspective, this could represent an even greater potential threat than that posed by BPA alone. Future integrated studies will be required to further explore and clarify this emerging paradigm.



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1. Introduction

The constant growth in the demand for and production of plastic polymers has caused a significant pollution problem worldwide. Their production, disposal, and recycling suppose their increasing presence in different ecosystems [1]. Water, air, and soil contamination endanger all trophic levels of the ecosystem, which ultimately means chronic human exposure to particles and molecules released by plastics, usually identified as endocrine disruptors [2–5]. One of the main elements studied by the scientific community, due to its ubiquitous distribution and its innumerable potential harmful effects on health, is bisphenol A (BPA) [6]. BPA is related to reproductive [7,8] and psychiatric disorders, obesity [9], diabetes [10], kidney disease [11], cardiovascular disease [12], and even disturbances in embryonic development [13,14].

Currently, scientific evidence is producing a paradigm shift, motivating government institutions to promote legislative restrictions on the use of BPA. For this reason, companies are replacing BPA with molecules with similar properties, such as bisphenol F and S (BPS and BPF, respectively) [15,16]. However, both have structural similarities with BPA, which probably gives them the potential to act as endocrine disruptors [15]. Their only difference is in the inter-phenolic linker: $C(CH_3)_2$ for BPA; CH_2 for BPF; SO_2 for BPS [17]. There is evidence in the academic literature that both substitute molecules are as hormonally active as BPA and, therefore, can act as endocrine disruptors [15]. Certain similarities in the effects caused by these compounds have been reported in some cell and animal models [18–21].

Despite this, no law regulates its use due to the scant amount of evidence that explores its potential effects on human health. Consequently, BPS and BPF have already been detected in various parts of the world [2,22,23] and human biological fluids [24–28].

Parallel to the environmental problem of endocrine disruptors, there has been an alarming growth in the prevalence of chronic diseases and clinical disorders in recent decades. Vitamin D (or 25-hydroxyvitamin D, 25(OH)D) is a prohormone obtained via skin synthesis (UVB-induced) and diet (vitamin D₂ and D₃) [29]. Both forms are hydroxylated in the liver to 25(OH)D, then in the kidney to active calcitriol [29–31]. Serum 25(OH)D is the best indicator of vitamin D status due to its stability and longer half-life [31–33].

Vitamin D deficiency has become the most common clinical disorder worldwide. In the academic literature, levels above 50 nmol/L of 25(OH)D are considered to meet the vitamin requirements of most of the population [29,34,35]. Recent studies have determined a prevalence of vitamin D deficiency (serum 25(OH)D values less than 50 nmol/L or 20 ng/mL) of 24%, 37%, and 40% in the USA, Canada, and Europe, respectively [36]. Values below 30 nmol/L or 12 ng/mL are considered a severe deficiency, and prevalence rates of 5.9%, 7.4%, and 13% have been determined in the USA, Canada, and Europe [36]. It is interesting to note that the high prevalence of vitamin D deficiency has been detected in all types of population groups, regardless of the country's latitude or level of development. This problem can be exceptionally high in girls and women from the Middle East [37].

Severe vitamin D deficiency is associated with an increased risk of mortality, infections, and many other pathologies. Moderate deficiency has been associated with bone metabolism [36,38,39], insulin resistance [40,41], obesity [42–44], as well as hypertension, cancer, and even psychiatric disorders [45,46].

There are currently no academic publications that explore the relationship between the new BPA substitute molecules and vitamin D. However, the published works on BPA, whose results suggest its relationship with this prohormone [47–50], show the urgent need to carry out the present study. To develop it, one of the main global cohorts of urinary BPS and BPF, the NHANES (National Health and Nutrition Examination Survey) cohort, will be analyzed, and its possible relationship with 25(OH)D deficiency will be explored.

2. Materials and Methods

2.1. Study Population (NHANES 13–16)

Datasets from 2013 to 2014 and 2015 to 2016 were used due to BPF and urinary BPS availability. Firstly, all the information relevant to the study context was downloaded from the official NHANES cohort website [51]. Once all the data were unified according to the patient code, 20,146 individuals were obtained. Of these, all those with urinary bisphenols (BPs) and vitamin D values were selected, obtaining a total of 4968 individuals. After classifying them according to age, 3572 adults were obtained (Figure 1). Subsequently, subclassifications were made based on vitamin D status:

- Dichotomous classification: subdivided into healthy (total vitamin D values greater than 50 nmol/L) and hypovitaminosis (HV, subjects with values less than 50 nmol/L) groups.

- Classification according to the degree of vitamin D deficiency: subdivided into healthy, moderate deficiency (MD, vitamin D values between 30 and 50 nmol/L), and severe deficiency (SD, <30 nmol/L) groups.
- Risk of bias: The variables were reanalyzed in a new subgroup in which all those individuals who took any vitamin D supplement were eliminated. For this, the files related to the intake of dietary supplements (NHANES Dietary Data [52]) were used.

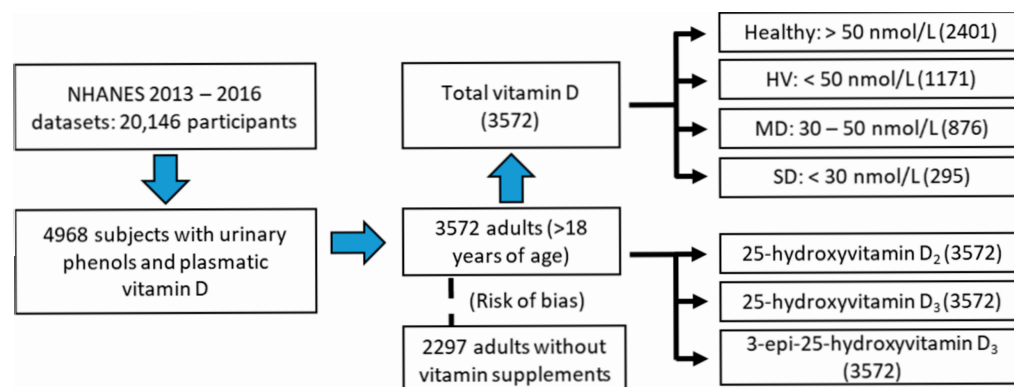


Figure 1. Schematic representation of the selection and grouping process of the data extracted from the NHANES 13–16 cohort. Abbreviations: HV, hypovitaminosis; MD, moderate deficiency; SD, severe deficiency. Note that the number of subjects analyzed in the main vitamin D analysis was 3572 subjects, and that all had quantified levels of vitamin D₂, D₃, and epi-D₃. However, the second subgroup analyzed, the subjects who did not take vitamin supplements, corresponds to 2297 subjects.

2.2. Covariates and Corrections

The quantitative variables used to correct the logistic models, age and body mass index (BMI), were obtained directly from the NHANES datasets, as well as the sex of the individuals (dichotomous qualitative variable [0, female; 1, male]). For the rest of the dichotomous covariates, the following classification criteria were used:

- Diabetes (dichotomous variable [0, healthy; 1, diseased]): Diabetics were all those individuals diagnosed by a doctor, those taking blood glucose medication (NHANES questionnaires [53]), and all subjects with values of fasting glucose ≥ 126 mg/dL or hemoglobin A1c $\geq 6.5\%$.
- Chronic kidney disease (CKD): Firstly, the estimated glomerular filtration rate (eGFR) was calculated using the two usual formulas for clinical use (Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI, and Modification of Diet in Renal Disease, MDRD-4) [54–56]. Subsequently, all those individuals with eGFR less than 60 mL/min/1.73 m² were included [57,58].
- Albuminuria: All albumin-to-creatinine ratio (ACR) values greater than 30 mg albumin/g creatinine were considered albuminuria.
- Hypertension: Patients diagnosed by their doctor, those taking medication for hypertension, and individuals with systolic pressure ≥ 140 mmHg or systolic ≥ 90 mmHg were considered hypertensive.
- Dyslipidemia: Patients with diagnosed cholesterol disorders, with prescribed medication or fasting total cholesterol ≥ 240 mg/dL.
- Smoking: All individuals who answered affirmatively to the question “have you smoked more than 100 cigarettes in your life?” or individuals with serum cotinine levels > 10 mg/dL [59] were included.

The urine samples used in the NHANES cohort study were spot urine samples. Due to the impossibility of obtaining the diuresis value in 24 h, the urinary BPs were corrected

by the urinary creatinine value ($\mu\text{g BPs/g creatinine}$) to avoid errors associated with the variation in the glomerular filtration capacity.

2.3. Statistical Analysis

GraphPad Prism 7.0 software (GraphPad Software Inc., San Diego, CA, USA) was used for descriptive statistics, comparative analysis, and graphs. The Mann–Whitney test was used to compare the healthy vs. hypovitaminosis groups. In the case of the comparison between the groups healthy vs. moderate deficiency vs. severe deficiency, Kruskal–Wallis followed by Dunn’s test was used. Quantitative variables were expressed as geometric mean (95% confidence interval) (GM (95% CI)).

IBM SPSS Statistics for Windows software, version 27 (IBM Corp., Armonk, NY, USA), was used to perform binomial and multinomial logistic regression analyses. Three different analyses were performed in each regression model: individual (1), corrected for age, sex, and BMI (2), corrected for the above parameters, and diabetes, CKD, albuminuria, hypertension, dyslipidemia, and smoking (3). Results were expressed as an odds ratio, OR (95% CI).

Urinary BP values were corrected with their corresponding urinary creatinine. Due to the skewed distribution of urinary bisphenol concentrations, natural log-transformation ($\ln$) was applied to normalize the data and meet the assumptions required for regression analyses. Finally, the data were reanalyzed using individuals who did not take vitamin D supplements to avoid a variable that could alter the results. Those results whose p -value was ≤ 0.05 were interpreted as statistically significant in all cases.

3. Results

3.1. Analysis of Total Vitamin D (Dichotomous and Multinomial Vitamin D Status)

3.1.1. Descriptive Statistics

Firstly, a descriptive analysis of the variables included in the study was performed. Table 1 shows that vitamin D deficiency is associated with younger age and a higher body mass index, both in severe and moderate deficiency. As expected, the severely deficient group showed a higher percentage of diabetic and albuminuric individuals. However, the low percentage of kidney patients suggests a counterintuitive relationship between kidney function and vitamin D status.

In the quantitative analysis of urinary bisphenols, we observed distinct and divergent patterns of association with vitamin D deficiency for each compound. Specifically, urinary BPA levels showed no statistically significant differences between individuals with or without vitamin D deficiency, suggesting a neutral association in our sample. Conversely, BPF concentrations were significantly lower in individuals with vitamin D deficiency, while BPS levels were significantly higher in the same group. These opposite trends—reduction in BPF and elevation in BPS—suggest potential differences in the biological behavior, metabolism, or tissue affinity of these BPA substitutes, despite their structural similarities.

As illustrated in Figure 2, the relationship between each urinary bisphenol and serum 25(OH)D appears compound-specific. The unchanged levels of BPA contrast with the divergent directions observed for BPF and BPS, supporting the hypothesis that these substitutes may not be interchangeable in terms of biological activity or health impact. This differential behavior underscores the importance of independently evaluating the health effects of each bisphenol analog, rather than assuming class-wide similarities.

Table 1. Descriptive statistics according to vitamin D status.

	Healthy	HV	MD	SD
N	2401 (67.22%)	1171 (32.78%)	876 (24.52%)	295 (8.26%)
Age	46.27 (45.49–47.06)	39.45 (38.53–40.4) ^d	39.4 (38.32–40.51) ^d	39.61 (37.84–41.47) ^d
Gender, % of men	47.5	46.7	47.4	44.7
BMI, kg/m ²	27.92 (27.68–28.16)	29.54 (29.12–29.96) ^d	29.33 (28.85–29.81) ^d	30.18 (29.29–31.1) ^d
CKD, %	10.9	4.9	4.2	6.8
DM, %	17.8	17.6	16.4	21
Dyslipidemia, %	45.8	31.7	32.9	28.1
Hypertension, %	44.6	38.7	36.9	44.1
Smokers, %	44.1	43.2	40.4	51.5
Albuminuria, %	11.6	13.2	11.6	18
ACR, mg/g	9.65 (9.23–10.1)	10.37 (9.67–11.13)	9.63 (8.93–10.39)	12.92 (10.99–15.2) ^{b,#}
BPA, µg/g creat.	1.17 (1.13–1.22)	1.16 (1.1–1.22)	1.15 (1.08–1.22)	1.18 (1.06–1.32)
BPF, µg/g creat.	0.44 (0.42–0.47)	0.37 (0.34–0.4) ^d	0.37 (0.33–0.4) ^d	0.36 (0.31–0.42)
BPS, µg/g creat.	0.49 (0.47–0.52)	0.56 (0.52–0.6) ^b	0.55 (0.51–0.6)	0.59 (0.52–0.69) ^a

Results are expressed as a percentage or geometric mean (95% confidence interval). Note that the HV group includes both the MD and SD categories. Comparisons between healthy and HV were performed using the Mann–Whitney test. For comparisons among healthy, MD, and SD groups, the Kruskal–Wallis test followed by Dunn’s post hoc test was used. ^a $p \leq 0.05$, ^b $p \leq 0.01$, ^d $p \leq 0.0001$ compared to the healthy group. [#] $p \leq 0.05$ compared to the MD group. Abbreviations: HV, hypovitaminosis (<50 nmol/L); MD, moderate deficiency (30–50 nmol/L); SD, severe deficiency (<30 nmol/L); BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; ACR, albumin-to-creatinine ratio; BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S; Creat., creatinine.

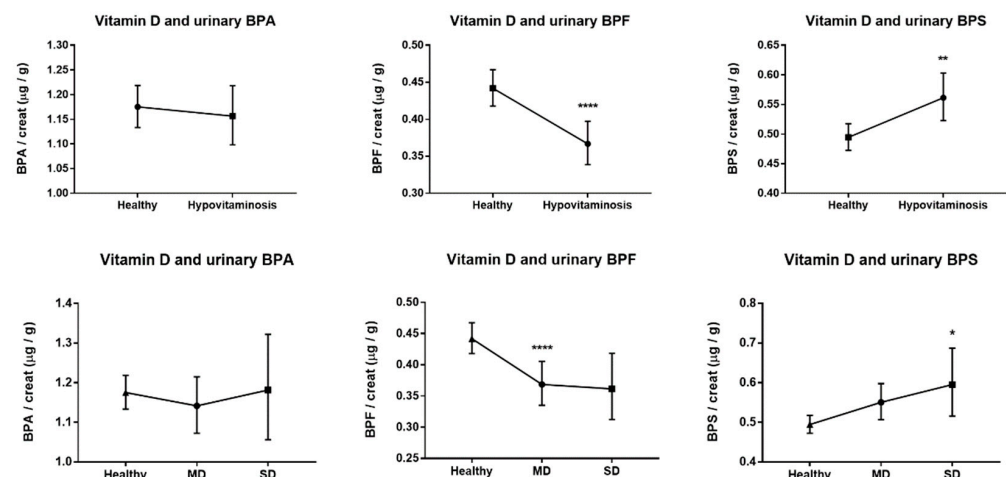


Figure 2. Variation in urinary bisphenol concentrations according to vitamin D status. Each compound shows a distinct pattern. Data are presented as geometric means (95% CI) due to non-parametric distribution. Mann–Whitney test was used for comparisons between healthy and HV groups. Kruskal–Wallis test followed by Dunn’s post hoc test was used for comparisons among healthy, MD, and SD groups. * $p \leq 0.05$; ** $p \leq 0.01$; **** $p \leq 0.0001$. Abbreviations: MD, moderate deficiency (30–50 nmol/L); SD, severe deficiency (<30 nmol/L).

3.1.2. Binomial and Multinomial Logistic Regression

Logistic regression analyses confirmed the trends described in the previous analyses, showing a significant relationship between urinary BPS and the risk of vitamin D deficiency. The logistic regression models indicate that a one-unit logarithmic increase in urinary BPS concentration is associated with a significantly increased risk of hypovitaminosis D. Thus, for each increase of one log unit of urinary BPS, an OR (95% CI) of 1.104 (1.038–1.175) was observed for hypovitaminosis D, 1.094 (1.022–1.171) for moderate deficiency, and 1.133 (1.021–1.257) for severe deficiency (Tables 2 and 3). Consequently, the results showed that urinary BPS is an independent risk factor for vitamin D deficiency. On the contrary, urinary BPF showed an inverse relationship, confirming the existence of potential differ-

ences in the mechanism of action associated with the new BPA substitute compounds (Tables 2 and 3). BPA, however, has not shown significant results in any of the statistical analyses carried out.

Table 2. Binomial logistic regression with vitamin D status as the dichotomous dependent variable (healthy–hypovitaminosis).

	Analysis	OR (95% CI)	p-Value
BPA, µg/g creat. ¹	1	0.98 (0.91–1.06)	0.602
	2	0.99 (0.91–1.07)	0.747
	3	0.98 (0.91–1.07)	0.699
BPF, µg/g creat. ¹	1	0.91 (0.86–0.95)	0.000
	2	0.92 (0.87–0.97)	0.001
	3	0.92 (0.87–0.97)	0.001
BPS, µg/g creat. ¹	1	1.09 (1.03–1.16)	0.002
	2	1.11 (1.05–1.18)	0.001
	3	1.10 (1.04–1.17)	0.002

Three models were applied as follows: (1) unadjusted, (2) adjusted for age, sex, and BMI, and (3) fully adjusted for age, sex, BMI, diabetes, CKD, albuminuria, hypertension, dyslipidemia, and smoking. Abbreviations: OR, odds ratio; CI, confidence interval; BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S; Creat., creatinine. ¹ log-transformed.

Table 3. Multinomial logistic regression with vitamin D as the dependent variable (healthy–moderate deficiency–severe deficiency).

Analysis		Healthy		Moderate Deficiency		Severe Deficiency	
		OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
BPA, µg/g creat. ¹	1	REF	-	0.97 (0.89–1.06)	0.498	1.01 (0.88–1.15)	0.928
	2	REF	-	0.98 (0.90–1.07)	0.645	1.01 (0.88–1.16)	0.895
	3	REF	-	0.98 (0.90–1.08)	0.719	0.99 (0.86–1.13)	0.839
BPF, µg/g creat. ¹	1	REF	-	0.91 (0.86–0.96)	0.001	0.90 (0.82–0.98)	0.021
	2	REF	-	0.92 (0.87–0.98)	0.005	0.91 (0.83–0.99)	0.039
	3	REF	-	0.92 (0.87–0.98)	0.009	0.89 (0.81–0.98)	0.015
BPS, µg/g creat. ¹	1	REF	-	1.08 (1.01–1.15)	0.020	1.14 (1.03–1.26)	0.010
	2	REF	-	1.10 (1.03–1.18)	0.006	1.15 (1.04–1.28)	0.006
	3	REF	-	1.09 (1.02–1.17)	0.009	1.13 (1.02–1.26)	0.019

Three models were applied as follows: (1) unadjusted, (2) adjusted for age, sex, and BMI, and (3) fully adjusted for age, sex, BMI, diabetes, CKD, albuminuria, hypertension, dyslipidemia, and smoking. Abbreviations: OR, odds ratio; CI, confidence interval; BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S; Creat., creatinine. ¹ log-transformed.

The binomial logistic regression model also showed interesting results in the covariates used. Thus, it was observed that increased BMI, diabetes, and albuminuria are risk factors related to hypovitaminosis D, with an OR (95% CI) of 1.03 (1.02–1.05), 1.29 (1.05–1.60), and 1.39 (1.11–1.75), respectively. However, significant negative relationships were also observed, such as age, kidney disease, and dyslipidemia, with an OR (95% CI) of 0.98 (0.97–0.98), 0.61 (0.44–0.84), and 0.69 (0.58–0.82), respectively.

Furthermore, the multinomial logistic regression model showed similar results with age, BMI, and dyslipidemia in both the moderate and severe deficiency groups. In the case of kidney disease, the negative relationship was only significant in the group with moderate deficiency. In the severe deficiency group, a significant OR (95% CI) of 1.57 (1.11–2.22) for diabetes, 1.8 (1.27–2.56) for albuminuria, and 1.5 (1.11–2.02) for hypertension was observed.

3.2. Supplementary Analysis of Vitamin D Metabolites

The central axis of this work has been developed on 25(OH)D (the sum of 25(OH)D₂ and D₃). It is accepted that it is the marker of vitamin D status due to its higher presence and half-life [31–33]. However, to delve into the effects of urinary BPs, their combined linear relationship with the vitamin D metabolites was explored.

As seen in Table 4, the positive relationship observed between 25(OH)D and urinary BPF only coincides with the relationship shown by 25(OH)D₃, which means that changes related to vitamin D status are only linked with vitamin D₃. In the case of urinary BPS, a significantly negative relationship is observed for both 25(OH)D₃ and its epimer (epi-25(OH)D₃).

Table 4. Linear regression between vitamin D metabolites and urinary bisphenol levels.

Dependent Variable	BPA, µg/g Creat. ¹		BPF, µg/g Creat. ¹		BPS, µg/g Creat. ¹	
	β	p-Value	β	p-Value	β	p-Value
Total (25(OH)D ₂ + 25(OH)D ₃), nmol/L	0.000	0.978	0.060	0.000	−0.051	0.000
25(OH)D ₂ , nmol/L	0.007	0.683	0.009	0.610	0.006	0.730
25(OH)D ₃ , nmol/L	−0.004	0.809	0.057	0.001	−0.055	0.001
epi-25(OH)D ₃ , nmol/L	0.005	0.778	0.030	0.076	−0.038	0.023

Abbreviations: BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S; Creat., creatinine; 25(OH)D, 25-hydroxyvitamin D. ¹ log-transformed.

3.3. Risk of Bias: Exclusion of Vitamin D Supplements

Finally, data from all subjects not taking any vitamin D-related vitamin supplements were reanalyzed. Firstly, descriptive statistics showed the same trends with urinary BPs, and the same patterns detected in the covariates analyzed. Furthermore, comparative analyses showed significant changes in the same parameters (Supplementary Table S1).

Similarly, Supplementary Figure S1 shows the same relationships described in the statistical model of the entire cohort. Urinary BPA shows no significant patterns or trends. The BPF and the BPS show the same inverse patterns as in the main study.

Binomial logistic regression analysis also showed the same patterns observed in the general model, with an OR (95% CI) of 0.99 (0.90–1.09), 0.90 (0.85–0.96), and 1.09 (1.01–1.17) for BPA, BPF, and BPS, respectively. Age, sex, and BMI also showed significant results, showing the same trend as the general model. However, an interesting difference with the general model was observed, a higher risk of hypovitaminosis D in women, with an OR (95% CI) of 1.26 (1.05–1.50).

Multinomial logistic regression analysis of moderate deficiency only showed significant results with BPF, age, BMI, and kidney disease, analogous to the general model. However, the *p*-value for sex was 0.058, with an OR (95% CI) of 1.21 (0.99–1.47) for women. In the case of severe deficiency, sex was significant, with an OR (95% CI) of 1.41 (1.07–1.87). Finally, smokers had a higher risk of severe vitamin D deficiency, with an OR (95% CI) of 1.44 (1.09–1.90).

4. Discussion

In the present study, the existence of significant relationships between the new BPA substitute compounds and vitamin D deficiency has been evidenced for the first time. Despite their high structural homology, the inverse relationship patterns observed between BPS and BPF have confirmed their potential differential risks on human health.

The BPs analyzed in this work are similar in their two phenolic rings at a structural level. However, significant differences between these compounds could help explain the risks observed in the present retrospective study. Firstly, Danzl et al. [60] showed that BPS could not be degraded in the marine environment, contrary to BPA and BPF. Secondly, Gayraud et al. [61] found that the bioavailability of BPS was 250 times greater than that of BPA in a porcine model. In addition, in the same work, they showed that the plasma clearance of BPS was 3.5 times lower than BPA, analogous to the results described by Grandin et al. [62] in a bovine model. Hercog et al. [63] observed that BPA and BPF, but not BPS, were genotoxic in a liver cell line. Kaimal et al. [64] found that the administration of relatively low doses of BPF could cause abortions in rats, an effect that was not seen after treatment with BPS. It has also been reported that BPS has a lower cytotoxic capacity than BPA in human tubular cells [65] and BPA and BPF in the cardiovascular context [66].

Although *in vitro* and *in vivo* studies have suggested that BPS may exhibit lower cytotoxicity than BPA and other analogs, emerging evidence points to potential endocrine-disrupting and genotoxic effects of BPS. For instance, Frenzilli et al. [67] demonstrated that both BPA and BPS can induce endocrine and chromosomal alterations in brown trout, raising concerns about genotoxicity. Moreover, Marroquí et al. [18] showed that BPS and BPF can disrupt pancreatic β -cell ion channel expression, activity, and insulin release in mice via an estrogen receptor β -mediated pathway. These findings underscore the need for further investigation into the endocrine and metabolic consequences of BPS exposure, especially in sensitive populations.

Previous work by our team has shown that BPA can affect the renal and vascular systems, promoting podocyte damage in mice [68], affecting the structural integrity of the human podocyte [69], and inducing kidney damage analogous to that observed in diabetic nephropathy [70], promoting increased blood pressure [12], and generating endothelial dysfunction through mechanisms of cell death by necroptosis [71] and cell senescence [72]. During the development of the experimental models, we found interesting indications that pointed to angiotensin II (Ang II) as one of the mediators of the nephro-vascular pathology induced by BPA. There is an essential negative interaction between Ang II and the nephroprotective protein Klotho, whose downregulation is associated with increased circulating levels of fibroblast growth factor 23 (FGF23) [73]. In CKD, the increase in FGF-23 is associated with a compensatory mechanism for phosphate retention and with the inhibition of the renal enzyme 1α -hydroxylase, which consequently reduces the levels of active vitamin D (calcitriol) [32]. Finally, the alteration in the circulating calcitriol levels will induce the reduction in the intestinal capacity for calcium absorption [74]. Interestingly, there is evidence in the literature that the administration of BPA can affect the intestinal capacity for calcium absorption [75,76].

In this way, it shows the possible relationship between bisphenol and calcitriol. Epidemiological publications on the BPA–vitamin D paradigm have determined some interesting associations. Erden et al. [49] observed a negative relationship between serum BPA and 25(OH)D in a group of 128 subjects, in whom there were 43 healthy and 85 with obstructive sleep apnea syndrome (OSAS). Brandie et al. [48] found a negative relationship between urinary BPA and serum levels of 25(OH)D and 1,25(OH)D in a cohort of 299 elderly Italians. Johns et al. [47] analyzed data from the 2005–2010 NHANES cohort and found that in women only, an interquartile range increase in urinary BPA was associated with -3.71% (95% CI, -6.41 , -1.02) in 25(OH)D. Their subsequent study in pregnant women [50] showed a non-significant association between BPA and 25(OH)D. However, they did detect an association with the risk of vitamin D deficiency.

It is interesting to note that the results of this study have not shown any significant relationship between urinary BPA and vitamin D in any of the analyses carried out. However,

significant relationships with BPA substitute molecules have been detected. Currently, no academic publications explore the possible relationship between emerging BPs and vitamin D in a large general population cohort. This shows the novelty of this study, in which a differential effect has been detected for the first time.

Descriptive statistics and linear regression analysis have shown the first indications of this differential effect, showing completely different patterns between them. Subsequently, binomial and multinomial logistic regression models have confirmed that BPS is a risk factor for vitamin D deficiency, independent of other covariates, such as age, BMI, sex, diabetes, kidney disease, hypertension, dyslipidemia, or smoking. The analysis and evidence have shown the inexistence of a significant association between BPA and 25(OH)D. However, the inverse patterns between BPA substitute BPs have shown that, despite the structural homology, there are potential differential risks on human health. This fact reaffirms the need to strengthen research and limit their use by industry.

Previous work by our group evidenced a relationship between new BPA substitute molecules excreted in the urine of the general population with various metabolic and cardiovascular pathologies, including diabetes, heart disease, hypertension, and renal dysfunction. Epidemiological analyses have shown associations between urinary concentrations of these compounds and an increased risk of diabetes in the adult population [77,78]. Additionally, combined exposure to BPA and its substitutes has been associated with a higher incidence of renal, cardiovascular diseases, and adverse effects on vascular endothelium [79,80]; these findings reinforce the idea that BPA substitutes, despite being presented as safer alternatives, may exert harmful biological effects similar to or different from those of BPA itself. The current results, showing differential associations between BPS, BPF, and vitamin D deficiency, align with this growing body of evidence and underscore the urgent need for broader studies addressing the systemic health impacts of these molecules.

The analysis of vitamin D metabolites has shown that vitamin D₃ is precisely the one that is related to substitute BPs, with no significant relationships being observed with vitamin D₂. D₃ is synthesized through ultraviolet radiation that strikes the skin, which transforms 7-dehydrocholesterol into cholecalciferol or vitamin D₃, or through the consumption of certain foods, such as egg yolks and oily fish. For its part, vitamin D₂ is acquired through the diet [29–31]. Considering that both vitamins have a common entry into the body (diet) and a differential entry (skin), the idea that BPS could affect the synthesis of this vitamin through the skin is consistent.

On the other hand, the analysis of serum vitamin D includes the quantitative study of 25(OH)D, that is, 25(OH)D₂ + 25(OH)D₃, the forms hydroxylated by the liver but still inactive. The analysis of these metabolites is carried out due to their high half-life in the body (13–15 days), unlike calcitriol (hours) [33]. Another possibility suggested by the results is that BPS exposure could affect the hepatic metabolism of 25(OH)D₃, thus affecting 25(OH)D status independently of renal function. Moreover, recent studies suggest that BPS may interfere directly with hepatic function, which is essential for the conversion of vitamin D into its circulating form, 25(OH)D₃. Experimental models in mice have shown that BPS exposure alters hepatic mitochondrial dynamics, induces endoplasmic reticulum stress, and disrupts lipid and glucose metabolism, especially under obesogenic conditions [81]. Additionally, BPS promotes hepatic steatosis by upregulating monocarboxylate transporter 1 (MCT1) and impairing the mitochondrial respiratory system [82]. A third study has revealed that BPS blocks hepatic autophagy via a PPAR α –EP300–mTORC1 signaling axis, leading to lipid accumulation and the progression of NAFLD [83]. These findings provide plausible mechanistic support for the idea that BPS may impair hepatic vitamin D hydroxylation, contributing to lower serum 25(OH)D₃ levels even independently of renal function. However, further studies are needed to confirm this mechanism in humans.

The results have identified counterintuitive patterns between vitamin D status and eGFR, which this phenomenon could explain. There is evidence in the academic literature that identifies the same patterns between 25(OH)D and kidney function. The works of Teumer et al. [84] and Geng et al. [85] detected a negative association between serum 25(OH)D and kidney function in six cohorts and the NHANES cohort, respectively. Moore et al. [86] found that patients with the highest eGFR had the lowest 25(OH)D levels. Finally, Priyadarshini et al. [87] determined that most of their CKD patients had normal vitamin D levels. The authors argued that the intake of vitamin supplements was a possible cause of the phenomenon. However, the present work eliminated this possibility by excluding all those individuals who take supplements. Future epidemiological studies should incorporate PTH values due to their relationship with active vitamin D, calcium metabolism, and renal function.

Finally, the analysis of individuals who do not consume vitamin supplements has reaffirmed the relationships between urinary BPs and vitamin D. However, the supplementary analysis has shown interesting relationships between the sex of individuals and tobacco consumption associated with vitamin D status. In this case, the reanalysis of the data has shown that the consumption of vitamin supplements could mask specific associations of great relevance for the study. Sex could play an essential role in vitamin D metabolism, which would mean that the effect of BPS in this context could be more relevant for women. The percentage of women in the healthy group was 44.9%, while the severe deficiency group was 53.3% in the analysis of subjects without vitamin supplements. In the entire cohort, 52.5% of women were in the healthy group, and 55.3% were in the severe deficiency group. The consumption of vitamin supplements masked the relationship with sex in the corrected logistic models. It should be considered in future studies related to the object of study of this work.

The possible relationship between sex, smoking, and vitamin D is an interesting topic derived from the results of the present study. It is important to note that it has been documented that sex may be a differentiating element in vitamin D levels due to biological differences. For instance, sex hormones such as estrogen can modulate the activity of the hydroxylase enzymes responsible for vitamin D activation, and variations in body composition also play a role [88]. Regarding tobacco use, regular tobacco users have been reported to have lower vitamin D levels. In the recent meta-analysis conducted by Yang's team, the authors suggest that smoking could affect vitamin D metabolism by different mechanisms, from increased skin aging to the expression of inflammatory mediators or even PTH inhibition [89].

A recent study by Brennan et al. [90] analyzed the relationship between bisphenol exposure and vitamin D levels in a small cohort of 57 women, evaluating correlations between the concentrations of BPA, BPS, and the combined measure (Σ BPs) with serum 25(OH)D. Their results did not reveal statistically significant associations. While this study is an important initial step, several methodological aspects differentiate it from our approach. Firstly, the limited sample size considerably restricts the statistical power, making it difficult to detect subtle associations. In contrast, our study leverages a large, representative population sample from NHANES, which includes both sexes and a broad age range. Moreover, rather than simple correlation analyses, we applied multivariate logistic regression models adjusted for relevant covariates to evaluate the risk of vitamin D deficiency across bisphenol exposure levels. This approach allowed us to uncover associations not previously identified, supporting the notion that BPS exposure may represent a potential risk factor for vitamin D deficiency in the general population.

In the present study, individuals under 18 years of age were excluded due to methodological considerations. Childhood and adolescence are characterized by significant physi-

ological variability, including growth, puberty, and unique dietary patterns, which strongly influence vitamin D metabolism and endocrine responses. These age-related factors, along with the widespread use of pediatric vitamin D supplementation, may act as confounders in studies evaluating environmental exposures. Moreover, bisphenol exposure patterns may differ substantially in minors compared to adults, both in intensity and source. Although not included in this analysis, this group represents a population of high interest and vulnerability. Future studies should specifically address the potential effects of bisphenols on vitamin D status in children and adolescents, as this remains an open question in environmental health research.

The lack of a significant association between urinary BPA concentrations and vitamin D status in this study contrasts with the findings observed for BPS. This difference may be partially explained by the distinct pharmacokinetic profiles of these compounds. BPA is known to have a short half-life and is rapidly metabolized and excreted through urine within a few hours of exposure. Therefore, urinary BPA levels primarily reflect recent exposure and may not accurately represent bioavailable concentrations or a long-term internal dose. This could lead to a potential underestimation of its biological effects in cross-sectional studies such as this one. On the other hand, BPA substitutes like BPS may exhibit different absorption, metabolism, or retention patterns, potentially resulting in a greater cumulative effect or prolonged interaction with vitamin D metabolism pathways. Moreover, the vitamin D biomarker used in this study—25-hydroxyvitamin D—is a stable circulating precursor with a long half-life, and it reflects the combined influence of multiple physiological and environmental factors over time. These temporal mismatches in the kinetics of BPA and vitamin D may also explain the absence of a statistically significant relationship.

Furthermore, retrospective cohort studies do not allow us to identify causal relationships but to identify patterns of relationship or association independent of the effect of other covariates. Future longitudinal studies, accompanied by cellular and animal models, exploring the relationship between BPS and vitamin D will be necessary to confirm the results of this manuscript. There are epidemiological studies that have linked BPA substitute molecules with pathologies such as diabetes [91,92], obesity [93–95], hypertension [96], and depression [97]. Similarly, vitamin D deficiency has been associated with changes in bone metabolism, diabetes, obesity, hypertension, psychiatric disorders, and even cancer [39–46]. Therefore, the idea that vitamin D deficiency could be a risk factor associated with BPS is consistent, helping to explain the global associations described in the literature.

5. Conclusions

This study has identified new and relevant associations between BPS exposure and vitamin D deficiency. BPS is a molecule of growing industrial use, and human exposure is expected to increase unless regulatory frameworks are updated. Although BPS has been considered a potentially less toxic alternative to BPA, emerging evidence—including our findings—suggests that it may still exert significant biological effects, particularly as an endocrine disruptor. Considering these results, and given the precautionary principle in public health, regulatory agencies should critically assess the widespread use of BPA substitutes until their safety is clearly established through longitudinal and mechanistic studies.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/greenhealth1020010/s1>, Figure S1: Variation in urinary bisphenol concentrations according to vitamin D status in participants not taking vitamin D-related supplements; Table S1: Descriptive statistics of vitamin D status among individuals not taking vitamin D-related supplements.

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