Nutrition, Metabolism & Cardiovascular Diseases (xxxx) xxx, xxx

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Bisphenol A and cardiometabolic risk in adolescents: Data from the Generation XXI cohort

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Received 3 July 2023; received in revised form 12 December 2023; accepted 8 January 2024
Handling Editor: A. Siani
Available online ■ ■ ■

KEYWORDS
Bisphenol A;
Cardiometabolic risk;
Endocrine disruptors;
Food packaging;
Adolescents

Abstract *Background and aims:* Bisphenol A (BPA), an endocrine disruptor widely used in food contact materials, has been linked to a worse health profile. This study intends to estimate the association between BPA exposure and cardiometabolic patterns at adolescence.
Methods and results: Data from the Portuguese population-based birth cohort Generation XXI at the age of 13 were used (n = 2386 providing 3-day food diaries and fasting blood samples). BPA exposure was measured in 24-h urine from a subsample (n = 206) and then predicted in all participants using a random forest method and considering dietary intake from diaries. Three cardiometabolic patterns were identified (normal, modified lipid profile and higher cardiometabolic risk) using a probabilistic Gaussian mixture model. Multinomial regression models were applied to associate BPA exposure (lower, medium, higher) and cardiometabolic patterns, adjusting for confounders. The median BPA exposure was 1532 ng/d, corresponding to 29.4 ng/kg/d. Adolescents higher exposed to BPA (compared to medium and lower levels) had higher BMI z-score (kg/m^2) (0.68 vs. 0.39 and 0.52, respectively; p = 0.008), higher levels of body fat (kg) (16.3 vs. 13.8 and 14.6, respectively; p = 0.002), waist circumference (76.2 vs. 73.7 and 74.9, respectively; p = 0.026), insulinemia (ug/mL) (14.1 vs. 12.7 and 13.1, respectively; p = 0.039) and triglyceridemia (mg/dL) (72.7 vs. 66.1 and 66.5, respectively; p = 0.030). After adjustment, a significant association between higher BPA and a higher cardiometabolic risk pattern was observed (OR: 2.55; 95%CI: 1.41, 4.63).
Conclusion: Higher BPA exposure was associated with a higher cardiometabolic risk pattern in adolescents, evidencing the role of food contaminants in health.

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https://doi.org/10.1016/j.numecd.2024.01.007

Please cite this article as: Magalhães V et al., Bisphenol A and cardiometabolic risk in adolescents: Data from the Generation XXI cohort, Nutrition, Metabolism & Cardiovascular Diseases, https://doi.org/10.1016/j.numecd.2024.01.007

1. Introduction

Bisphenol A (BPA) is used as a monomer in the manufacture of polycarbonates and epoxy resins: polycarbonates are used in food contact materials such as reusable beverage bottles, infant feeding bottles, tableware and storage containers, while epoxy resins are used in protective linings for food and beverage cans and vats [1]. BPA was first synthesized in 1891, and its endocrine-disrupting effects have been described since 1936 [2]. The proposed mechanisms of BPA-induced multi-organ toxicity involve disruption of the neuroendocrine system, inhibition of enzymes, modulation of immune and inflammatory responses, and genotoxic and epigenetic mechanisms [3]. The main route of exposure to BPA is food, as it is contaminated by the migration of BPA from packaging during processing or storage [4]. A population-wide exposure to BPA was suggested in a systematic review and meta-analysis that included fifteen studies (28,353 participants) [5], in which BPA was detected in more than 90 % of participants. A negative effect of this compound has been mainly described during critical exposure windows such as pregnancy, neonatal period and early childhood [6,7]. BPA was also found ubiquitously in almost all urine samples from the German Environmental Survey for Children and Adolescents 2014–2017 [8]. Adolescence may also be a critical period for the action of endocrine disruptors, since several hormonal changes take place.

Some systematic reviews with meta-analysis have been carried out pointing to the harmful effect of BPA on obesity [9–11], diabetes [12] and other cardiovascular diseases [13] in both children and adults. Nevertheless, the literature on dietary BPA exposure highlights the need for more studies in young populations and considering specifically BPA from food intake. Although current studies generally support the influence of BPA on metabolic pathways, further evidence can be obtained through studies with larger sample sizes and daily representative urine BPA measurements compared to single urine spots. The assessment of BPA in 24h-urine accurately reflect daily exposure [14], but it is difficult to apply in large epidemiological studies due to the higher cost in relation to a point, in addition to requiring greater commitment from individuals. Studies using different statistical approaches to estimate BPA exposure in larger samples using urine biomarkers collected subsamples would be of great interest. Thus, the present study aimed to explore the association between exposure to BPA and cardiometabolic patterns in adolescents from a population-based cohort, using an innovative methodology of exposure estimation.

2. Methods

2.1. Study design and participants

Data from 13-year follow-up of the population-based birth cohort Generation XXI (G21) were used, with details published previously [15]. Briefly, between April 2005 and August 2006, mothers and their newborns were recruited from five level III maternity hospitals in the metropolitan area of Porto, Portugal. At that time, these maternity hospitals contributed 91.6 % of deliveries to the eligible population. Mothers were invited to participate 24–72 h after delivery, of which 91 % accepted, with the participation of 8495 mothers and 8647 children. Follow-up of the entire cohort was performed at 4y (participation: 86 %), 7y (participation: 80 %), 10y (participation: 75 %) and 13y (participation: 54 % - follow-up interrupted in March 2020 due to issues related to the COVID-19 pandemic).

G21 was approved by the University of Porto Medical School/S. João Hospital Centre Ethics Committee. Written informed consent was obtained for all participants and signed by the legal representatives of the children.

The present analysis used a cross-sectional approach, including data from 2386 adolescents who completed food diaries and collected blood samples at the 13-years follow-up.

2.2. Data collection

At the baseline and each follow-up evaluation, trained interviewers collected data using structured questionnaires that covered information on sociodemographic, clinical and behavioral characteristics, objective anthropometric measurements and biochemical blood analysis.

In the current study, sociodemographic variables included the sex and exact age of the adolescents and maternal age and education at the baseline. A dichotomous question about practice of regular leisure and sports activities assessed adolescents' physical activity. Dietary exposures and cardiometabolic outcomes are described in detail below.

2.3. Dietary variables

As previously stated, participants were asked to complete a 3-day food diary (two weekdays and one weekend day, non-consecutive) [16]. Adolescents, supported by their parents, provided a detailed description of each food and drink consumed, including the packaging material, the cooking preparation, recipes and place of consumption, whenever possible. In relation to the prepared dishes, instructions were given to provide recipe details namely ingredients and cooking methods. Oral and written instructions were given for correctly using the food diary and quantifying food portions. Participants were taught how to use household measures and standard units to quantify the food portions. Adolescents were instructed to follow their usual diet and to ask for the help of parents or other caregivers if they had any doubts. During the face-to-face interview, the fieldwork team was responsible for receiving and checking the completeness of the food diaries. If a food diary was found to be incomplete, participants were asked to mail a new report later. Posteriorly trained nutritionists directly handled the information in the eAT24 module of the You eAt&Move e-platform developed for the National Food, Nutrition and Physical Activity Survey (IAN-AF) 2015–2016 [17]. The eAT24 integrates the FoodEx2 classification and description

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system proposed by the European Food Safety Authority (EFSA) [18] and the Portuguese food composition table [19], resulting in a total of 1777 food items. Foods were grouped in food groups and sub-groups, according to nutritional similarities, source and packaging material. The eAT24 also includes several food quantification methods, such as an electronic picture book [20], household measures, standard units, volume, weight, and default portion. Dietary data collected using the eAT24 software was previously validated in a subsample of adults using urinary biomarkers [21].

2.4. Estimation of exposure to BPA

A convenience subsample of 206 adolescents was asked to collect urine for 24 h on a later day as close as possible to the interview. All procedures were explained orally and in writing, and the necessary material was made available (including a BPA-free plastic container). Total BPA was measured using a validated gas chromatography method coupled with mass spectrometry [22]. The method's detection and quantification limits were 0.03 ng/mL and 0.1 ng/mL, respectively. The exposure of the total sample to BPA was estimated from the subsample data. A random forest method was used, which allowed estimation of exposure to BPA for the total sample, combining food consumption information (food groups and foods reported with packaging materials - in grams) with BPA measured in 24-h urine of a subsample. This method shown the best performance when compared to other methodologies of assessing BPA at the population level, as previously described [23]. The correlation between the estimated exposure using the random forest method and the urinary excretion was 0.979, 95%CI: 0.972; 0.984. To handle the possible overfitting of the model, a 5-fold cross-validation was performed, obtaining a new correlation of 0.168.

In addition to the continuous data, three categories of exposure to BPA were created, whose cutoff points were based on the sample distribution of the predicted value of BPA: "lower exposure" if below 1200 ng/day (n = 172, 7.2 %), "medium exposure" if between 1200 and 2000 ng/day (n = 2068, 86.7 %), and "higher exposure" if above 2000 ng/day (n = 146, 6.1 %).

The characterization of the random forest model predictors, in the subsample that collected urine and in the total sample, is detailed in Supplementary Table 1. The results followed the same trend, and the expected gain in statistical power was achieved when using the total sample.

2.5. Cardiometabolic outcomes

Under standard procedures, anthropometric measurements were performed with subjects in light clothing and barefoot after 12 h of fasting. Body weight was measured to the nearest 0.1 kg using a digital scale (SECA, Columbia, USA) and height to the nearest centimetre using a wall stadiometer (SECA, Hamburg, Germany). Adolescents' BMI was classified according to age- and sex-specific WHO BMI standard z-scores [24]. Tetrapolar bioelectric impedance analysis was performed (Akern BIA 101 Anniversary, Florence, Italy). Fat-free mass was determined using the Schaefer et al. equation, and fat mass was derived accordingly [25]. Waist circumference was ascertained as the midway between the lower limit of the rib cage and the iliac crest to the nearest centimetre.

Blood pressure (BP) was measured with an automatic upper arm blood pressure monitor (Omron®) placed over the brachial artery pulse. Two systolic (SBP) and diastolic (DBP) BP measurements were taken, separated by at least 5 min, after a 10-min rest. The mean was calculated if the difference between the measurements was <5 mmHg for SBP or DBP. A third measurement was taken if the difference was larger than 5 mmHg, and the mean of the two closest values was used.

In participants who accepted, a blood sample was collected on the morning of the assessment after a 12-h overnight fast. Serum analysis was conducted at the Clinical Pathology Department of the Hospital of São João, Porto, Portugal. Glucose was measured using an UV enzymatic assay (hexokinase method), and insulin using an electrochemiluminescence immunoassay. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) [26] was used as a marker of insulin resistance. Triglycerides [27], total cholesterol and high-density lipoprotein-cholesterol (HDL cholesterol) were measured using enzymatic colorimetric assays. The low-density lipoprotein-cholesterol (LDL cholesterol) was obtained by the difference using the Friedewald formula.

2.6. Statistical analysis

Student's *t*-test or the analysis of variance (ANOVA) were used to assess differences in means, while Chi-Square or McNemar was used to compare proportions.

To estimate adjusted means and respective 95 % confidence intervals (95%CI) for the cardiometabolic indicators by BPA exposure categories (lower, medium, and higher exposure), the analysis of covariance (ANCOVA) was used. The means were adjusted for sex, maternal age, maternal educational level, physical activity and total energy intake.

Cardiometabolic patterns were identified using the probabilistic Gaussian mixture model, including waist circumference, glucose, insulin, total and HDL cholesterol, triglycerides and systolic and diastolic blood pressure. To define the appropriate number of clusters, the Bayesian Information Criterion was used.

Multinomial regression models were applied to evaluate the relation between BPA exposure (lower, medium, higher) and cardiometabolic patterns. The first model was adjusted for sex, the second model was additionally adjusted for maternal age and maternal education, and the third was further adjusted for physical activity and energy intake.

Missing data were treated as completely at random.

A significance level of 0.05 was considered. Statistical analyses were conducted using R software [28], version 3.6.1 for *Windows*.

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3. Results

The comparison of the main characteristics between the subsample that collected 24h urine and the remaining sample is presented in Table 1. In general, similarities were observed, although a greater proportion of males and a higher fat-free mass mean were found in the subsample.

Table 2 describes the total sample characteristics by exposure categories to BPA. The group with the highest exposure to BPA includes a higher proportion of males (63.0 %). A higher energy intake was also observed in this group (2116 ± 474 kcal; medium exposure: 1802 ± 416 kcal; lower exposure: 1664 ± 457 kcal). No significant differences were observed regarding maternal education or regular practice of leisure or sports activities. Overall, the median exposure to BPA of 13 years of age adolescents was 1532 ng/d, corresponding to 29.4 ng/kg/d.

Table 3 describes the different cardiometabolic parameters according to the categories of BPA exposure. The mean results according to the three categories were not linear; however, the highest values were observed for participants in the higher BPA exposure category. After adjusting for sex, maternal age, maternal education level, physical activity and energy intake, a significantly higher BMI z-score was found in the group with higher exposure to BPA than in the medium and lower exposure groups (0.68 vs. 0.39 and 0.52, respectively; p = 0.008). Also, a greater fat mass was observed in this group (16.3 kg vs. 13.8 kg and 14.6 kg, respectively; p = 0.002), as well as a greater waist circumference (76.2 cm vs. 73.7 cm and 74.9 cm, respectively; p = 0.026). Furthermore, a significantly higher free fat mass was found (40.6 kg vs. 38.8 kg and 38.5 kg, respectively; p = 0.001). Regarding analytics, a higher level of insulin was observed among those with higher BPA exposure compared to the medium and lower exposure group (14.1 μg/mL vs. 12.7 μg/mL and 13.1 μg/mL, respectively; p = 0.039) and the same was observed to triglycerides (72.7 mg/dL vs. 66.1 mg/dL and 66.5 mg/dL, respectively; p = 0.030). Supplementary Table 2 shows the relationship between the categories of BPA exposure and cardiometabolic indicators in the subsample that collected urine, showing similar trends in the estimations despite the lower statistical power. This also support the good quality of the predictive model of BPA assessment.

Through clustering, eight solutions were obtained. Four had less than 200 individuals in each cluster, and one had an unclear interpretation, so it was decided to stick with three solutions. The three cardiometabolic patterns

Table 1 Characteristics of the subsample with valid 24-h urine and the remaining sample.

		Subsample (n = 206)	Remaining sample (n = 2180)	p-value
Predicted Bisphenol A	ng/d, median (IQR)	1568 (886)	1512 (302)	**0.040**
	ng/kg/d, median (IQR)	29.2 (16.8)	29.5 (10.6)	0.570
Sex	Female, n (%)	89 (43.2)	1101 (50.5)	**0.045**
	Male, n (%)	117 (56.8)	1079 (49.5)	
Maternal education (years), mean (sd)		11.8 (4.5)	11.3 (4.3)	0.136
Regular leisure and sports activities	No, n (%)	74 (35.9)	863 (40.0)	0.136
	Yes, n (%)	132 (64.1)	1296 (60.0)	
Body Mass Index z-score[a]	≤1, n (%)	136 (66.3)	1460 (67.5)	0.256
	>1, n (%)	69 (33.7)	704 (32.5)	
Fat Mass (kg), mean (sd)		14.9 (9.1)	13.9 (8.8)	0.146
Fat Mass (%), mean (sd)		25.0 (11.1)	24.7 (11.9)	0.725
Free Fat Mass (kg), mean (sd)		41.4 (6.8)	38.8 (6.2)	**< 0.001**
Energy intake, kcal/day, mean (sd)		1835 (418)	1809 (432)	0.395

sd: standard deviation, IQR: interquartile range.
Bold denotes statistical significance.
[a] Body Mass Index z-score ≤1 includes underweight and normal weight, >1 includes overweight and obesity adolescents.

Table 2 Characterization of the sample (n = 2386) by exposure categories to bisphenol A.

		Total	Lower exposure n = 172 (7.2 %)	Medium exposure n = 2068 (86.7 %)	Higher exposure n = 146 (6.1 %)	p-value
Predicted Bisphenol A (ng/d), median (IQR)		1532 (334)	1121 (118)	1535 (285)	2182 (297)	**< 0.001**
Predicted Bisphenol A (ng/kg/d), median (IQR)		29.4 (11.0)	20.2 (6.6)	29.7 (10.2)	43.7 (14.3)	**< 0.001**
Sex	Female, n (%)	1190 (49.9)	105 (61.0)	1031 (49.9)	54 (37.0)	**< 0.001**
	Male, n (%)	1196 (50.1)	67 (39.0)	1037 (50.1)	92 (63.0)	
Maternal age (years), mean (sd)		11.3 (4.5)	11.0 (4.2)	11.4 (4.4)	11.4 (4.6)	0.491
Maternal education (years), mean (sd)		11.4 (4.4)	11.1 (4.3)	11.4 (4.4)	11.0 (4.5)	0.430
Regular leisure physical activity	No, n (%)	937 (39.6)	72 (42.1)	817 (39.9)	48 (32.9)	0.190
	Yes, n (%)	1428 (60.4)	99 (57.9)	1231 (60.1)	98 (67.1)	
Energy intake (kcal/day), mean (sd)		1811 (431)	1664 (457)	1802 (416)	2116 (474)	**< 0.001**

Lower exposure: <1200 ng/d; Medium Exposure: ≥1200 and < 2000 ng/d; Higher exposure: ≥2000 ng/d.
sd: standard deviation, IQR: interquartile range.
Bold denotes statistical significance.

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Table 3 Cardiometabolic indicators according to the categories of exposure to bisphenol A.

		Crude				Adjusted[a]			
Variables, mean (sd)	n	Lower exposure	Medium exposure	Higher exposure	p-value	Lower exposure	Medium exposure	Higher exposure	p-value
Body mass index z-score	2386	0.60 (1.18)	0.41 (1.17)	0.54 (1.20)	**0.050**	0.52 (0.34; 0.69)	0.39 (0.34; 0.44)	0.68 (0.49; 0.87)	**0.008**
Fat Mass (kg)	2379	15.7 (10.0)	13.8 (8.7)	14.6 (10.0)	**0.019**	14.6 (13.4; 15.9)	13.8 (13.4; 14.2)	16.3 (14.9; 17.7)	**0.002**
Fat Mass (%)	2379	26.7 (12.8)	24.6 (11.7)	24.4 (11.7)	0.079	25.1 (23.5; 26.8)	24.6 (24.1; 25.1)	26.8 (25.0; 28.7)	0.059
Free Fat Mass (kg)	2379	39.1 (6.2)	38.8 (6.2)	41.2 (6.8)	**< 0.001**	39.5 (38.6; 40.4)	38.8 (38.5; 39)	40.6 (39.6; 41.6)	**0.001**
Waist circumference (cm)	2382	75.5 (10.2)	73.7 (9.8)	75.2 (10.8)	**0.021**	74.9 (73.4; 76.3)	73.7 (73.2; 74.1)	76.2 (74.6; 77.8)	**0.026**
Glucose (mg/dL)	2380	88.6 (7.3)	89.0 (9.7)	88.4 (5.9)	0.738	89.1 (87.6; 90.5)	89.0 (88.6; 89.4)	88.2 (86.7; 89.8)	0.623
Insulin (ug/mL)	2350	13.4 (7.8)	12.6 (6.3)	13.4 (7.1)	0.143	13.1 (12.2; 14.1)	12.7 (12.4; 13.0)	14.1 (13; 15.2)	**0.039**
HOMA-IR	2350	2.96 (1.87)	2.79 (1.48)	2.95 (1.65)	0.194	2.9 (2.7; 3.2)	2.8 (2.7; 2.9)	3.1 (2.8; 3.3)	0.075
Total cholesterol (mg/dL)	2380	150.8 (31.1)	148.2 (25.8)	147.2 (28.2)	0.402	149.6 (145.7; 153.6)	148.0 (146.9; 149.2)	149.2 (144.8; 153.5)	0.676
LDL cholesterol (mg/dL)	2339	87.4 (24.6)	84.1 (20.8)	84.1 (21.9)	0.143	86.8 (83.6; 90.0)	84.0 (83.1; 85.0)	85.9 (82.3; 89.4)	0.189
HDL cholesterol (mg/dL)	2381	50.9 (10.6)	51.6 (9.6)	50.2 (9.6)	0.147	50.8 (49.3; 52.2)	51.5 (51.1; 52.0)	49.9 (48.3; 51.4)	0.086
Triglycerides (mg/dL)	2381	67.7 (29.0)	66.2 (28.7)	70.6 (31.1)	0.174	66.5 (62.2; 70.9)	66.1 (64.8; 67.4)	72.7 (68.0; 77.4)	**0.030**
Systolic blood pressure (mmHg)	2383	112.1 (10.5)	111.9 (10.3)	112.6 (10.3)	0.701	112.3 (110.8; 113.9)	111.9 (111.4; 112.3)	112.5 (110.8; 114.2)	0.676
Diastolic blood pressure (mmHg)	2383	69.7 (8.7)	69.7 (8.8)	69.0 (9.4)	0.640	69.5 (68.2; 70.9)	69.7 (69.3; 70.1)	69.4 (68.0; 70.9)	0.910

Lower exposure: <1200 ng/d; Medium Exposure: ≥1200 and < 2000 ng/d; Higher exposure: ≥2000 ng/d.
sd: standard deviation, LDL cholesterol: low-density lipoprotein-cholesterol, HDL cholesterol: high-density lipoprotein-cholesterol.
Bold denotes statistical significance.
[a] Adjusted for sex, maternal age, maternal education (increase of 5 years), regular leisure and sports activities (no/yes) and total energy intake (kcal).

identified were then classified as normal (n = 1256), modified lipid profile (n = 917) and higher cardiometabolic risk (n = 170). As evidenced in Table 4, the pattern of higher cardiometabolic risk presents values higher than the overall mean in almost all studied analytical parameters, especially for waist circumference, serum insulin and triglycerides and, also has a lower value for HDL cholesterol. The modified lipid profile pattern shows higher mean values of total cholesterol, HDL cholesterol as well as triglycerides, while the defined normal cardiometabolic risk pattern shows values closer to the overall mean in all parameters.

In the multinomial regression model (Table 5), considering the group with medium exposure to BPA and the normal cardiometabolic risk pattern as reference categories, and after adjustment for confounders, an association was observed only between the group with the higher exposure to BPA and the pattern of higher cardiometabolic risk (OR: 2.55; 95%CI: 1.41, 4.63 – model 3).

4. Discussion

The present study estimated and described BPA exposure among adolescents and found an association between higher exposure and higher cardiometabolic risk pattern. This study found a median exposure to BPA of 1532 ng/d corresponding to 29.4 ng/kg/d, far above the tolerable daily intake (TDI) recently proposed by EFSA (0.2 ng/kg/d) [29]. In children from six European member states, higher values of BPA in the first-morning urine were observed in Slovenia (41.4 ng/kg/d), and lower levels were found in Sweden (32.6 ng/kg/d) [30]. Despite being above the EFSA

Table 4 Characterization of the cardiometabolic patterns identified by the Gaussian mixture model (n = 2343).

Variables, *mean (sd)*	Overall n = 2343	Normal cardiometabolic risk n = 1256	Modified lipid profile n = 917	Higher cardiometabolic risk n = 170	p-value
Waist circumference (cm)	73.9 (9.8)	75.1 (9.1)	69.7 (7.1)	87.2 (12.8)	**< 0.001**
Glucose (mg/dL)	88.9 (9.4)	88.8 (6.5)	87.7 (5.5)	96.3 (26.3)	**< 0.001**
Insulin (ug/mL)	12.7 (6.5)	12.2 (5.3)	11.1 (4.0)	25.2 (10.7)	**< 0.001**
Total cholesterol (mg/dL)	148.3 (26.3)	139.4 (20.6)	158.6 (28.4)	158.3 (28.8)	**< 0.001**
HDL cholesterol (mg/dL)	51.5 (9.7)	50.1 (8.1)	54.1 (11.1)	48.1 (8.7)	**< 0.001**
Triglycerides (mg/dL)	66.4 (28.8)	51.5 (12.8)	78.6 (23.4)	111.5 (53.1)	**< 0.001**
Systolic blood pressure (mmHg)	111.9 (10.3)	113.0 (10.7)	109.4 (9.2)	118.0 (10.1)	**< 0.001**
Diastolic blood pressure (mmHg)	69.6 (8.7)	69.7 (9.3)	68.5 (7.3)	74.6 (9.7)	**< 0.001**

sd: standard deviation, LDL cholesterol: low-density lipoprotein-cholesterol, HDL cholesterol: high-density lipoprotein-cholesterol.
Bold denotes statistical significance.

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Table 5 Relationship between exposure to bisphenol A and cardiometabolic patterns (n = 2343; reference: normal cardiometabolic risk).

	Modified lipid profile			Higher cardiometabolic risk		
	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
Lower exposure	0.87 (0.62; 1.22)	0.88 (0.62; 1.25)	0.89 (0.63; 1.26)	1.68 (0.99; 2.85)	1.65 (0.96,2.85)	1.44 (0.82; 2.53)
Medium exposure	Ref	Ref	Ref	Ref	Ref	Ref
Higher exposure	1.17 (0.81; 1.68)	1.17 (0.81; 1.69)	1.12 (0.77; 1.63)	**1.92 (1.08;3.41)**	**1.91 (1.07;3.40)**	**2.55 (1.41;4.63)**

Lower exposure: <1200 ng/d; Medium Exposure: ≥1200 and < 2000 ng/d; Higher exposure: ≥2000 ng/d.
OR (95%CI): Odds ratio (95% confidence interval).
Model 1: Adjusted for sex.
Model 2: Model 1 further adjusted for maternal age and maternal education (increase of 5 years).
Model 3: Model 2 further adjusted for regular leisure physical activity (no/yes) and total energy intake (kcal).
Bold denotes statistical significance.

limit and this being a concern, Portugal has a lower BPA exposure to that reported in the aforementioned study carried out a few years earlier. It should be noted that there are differences in urine collection methods and spot samples may be more concentrated resulting in a higher BPA measurement. Furthermore, the current risk assessment methodology deserves to be discussed given that for some exposures, in particular for BPA, non-monotonic dose response curves (in which the curve sign changes, i.e., in the form of U or inverted U) have been demonstrated [31]. Thus, predicting "safe" low doses from high dose exposures has been questioned - small doses can have more harmful effects than the higher doses, and this makes it more challenging to define the dose limit "safe" pathways. This also conditions the study of its modes of action, having been recently proposed the study of the placenta together with the umbilical arteries and veins to clarify the pregnancy exposome and the adverse outcomes related to the cardiovascular health of the mother and the newborn [32].

The ban on the use of BPA in food-related products for children in many countries began in 2009. It is described that, since then, BPA exposure has evidently decreased in this age group. In contrast, the corresponding intake in the adult population continued to increase [33], probably related to the nutritional transition that has been taking place with higher choices for packaged and ready-to-eat foods. Using data from US participants older than 6 years from the 2009–2016 National Health and Nutrition Survey (urinary measurements and a 24-h food recall), a higher intake of minimally processed foods was associated with lower concentrations of BPA but only in adults [34]. In Spain, it has been shown that girls with overweight/obesity showed a higher cardiometabolic risk of increased dietary exposure to BPA in comparison with girls with a lower BMI [35], which may be related to higher energy consumption in individuals with overweight and probably higher consumption of ultra-processed foods. In another study carried out in the G21, increased consumption of unprocessed or minimally processed foods at 7 years of age showed a favourable effect on later children's cardiometabolic health (lower body weight, body fat, waist circumference, blood pressure and insulin serum levels) at 10 years [36].

These relationships should not be dissociated from each country's dietary pattern and the specific food contributions to BPA exposure. An overview of the literature shows a lower concentration of BPA and its analogues detected in foodstuffs in Northern Europe compared to Southern Europe [37], the region in which canned meat and vegetables have been named as the most significant sources of BPA. In Portugal, a previous work that used the traditional method of estimating exposure by crossing the occurrence of BPA (literature and analysis of Portuguese samples) with consumption, identified milk as a relevant contributor because it is widely consumed [38]. An overestimation cannot be excluded since BPA was not detected in the analyzed milk samples and the value of the limit of quantification of the method for milk was assumed (0.2 ng/mL) instead of zero. However, other authors [39] already warned about milk as a food vehicle and the need to establish concrete regulations in food production and packaging, which we emphasize. It should be noted that soft drinks were the main contributor to BPA in adolescents [38]. Contamination of soft drinks by BPA has previously been described as a risk to children's health in Italy [40].

The current work identified a relationship between the exposure to BPA and a higher BMI, body fat and fat-free mass. The results of a recent systematic review [10] also showed that the relatively high exposure group to BPA had 1.6 higher odds of childhood obesity than the relatively low exposure group. Furthermore, in a neighboring Spanish cross-sectional study, a positive association was observed between dietary exposure to total bisphenols and BPA estimated by food frequency questionnaires with overweight/obesity in adolescent girls [35]. BPA concentrations from spot urine samples of around three hundred peripubertal boys from the Environment and Childhood (INMA) cohort in Granada (Spain) were associated with higher BMI z-score, greater likelihood of overweight/obesity, higher values of the waist-to-height ratio, higher cardiometabolic risk of abdominal obesity, but not to body fat mass percentage [41]. On the other hand, a study in Dutch school-age children found no statistical significant detect associations between bisphenol urinary concentrations, body fat measures, and cardiovascular risk factors [42]. The associations we found are probably related to the

Please cite this article as: Magalhães V et al., Bisphenol A and cardiometabolic risk in adolescents: Data from the Generation XXI cohort, Nutrition, Metabolism & Cardiovascular Diseases, https://doi.org/10.1016/j.numecd.2024.01.007

larger sample size and the specificity of bioimpedance compared to other types of anthropometric measurements most often used. Furthermore, obesity is often reflected in increments in all body compartments, not only fat mass, and this phenomenon may be even more evident in adolescents who have not yet completed their development.

The present study also found a relationship between a higher exposure to BPA and higher levels of serum insulin and triglycerides. In a Spanish birth cohort [43], prenatal exposures to both phthalate and phenol metabolites were weakly associated with cardiometabolic health at 11 years of age. The authors point out possible errors in exposure measurement and reduced variability in cardiovascular measurements at early ages that may have conditioned the ability to draw strong conclusions. In Chinese children as young as 2 years old [44], blood pressure was higher in the girls whose mothers had higher prenatal levels of BPA, while a higher serum glucose level was seen in boys with medium maternal prenatal exposure to BPA. No associations were found between prenatal BPA and infant BMI, skinfolds, serum lipids or insulin, probably also due to young age.

In a systematic review and meta-analysis [45], mainly including studies in adults, the concentration of BPA in urine or serum was not correlated with total cholesterol or LDL, but it was correlated with gender, WC, HDL, age, and BMI. A BMI-modifying effect was observed on the associations between exposure to BPA and TGs in young adults in a study that found cardiometabolic effects of BPA on the lipid profile [46].

Animal experiments suggest that BPA could potentially induce lipid abnormalities via interaction with members of the nuclear receptor superfamily (including steroid hormone receptors, thyroid hormone receptors and others), affecting circadian rhythms, and regulating the expression of signals belonging to the endocannabinoid system, leading to a notable increase in lipid accumulation [47]. Indeed, the risk of suspected non-alcoholic fatty liver disease increased in participants in higher quartiles of BPA exposure [48]. This condition encompasses a relevant component of insulin resistance. Exposure to bisphenols was previously positively associated with oxidative stress, insulin resistance, and endothelial dysfunction in children [49].

It is estimated that the association of BPA with diseases, particularly obesity and coronary heart disease, has a relevant impact on health costs, which could be minimized by replacing it by tested potential substitutes [50]. However, the safety of BPA analogues must be thoroughly studied as the reported data are generally inconsistent and unsatisfactory, particularly with regard to the cardiovascular system [51]. A recent review on the effects of BPA substitutes in the prenatal period and on the cardiovascular system concluded that they can affect maternal and fetal health in animal and human models as well as induce the same type of health problems, although possibly through different mechanisms. The authors of the aforementioned work recommend that epidemiological studies and studies in animal models continue in order to understand whether replacing BPA with its analogues is beneficial or even leads to more adverse health effects [52]. A preliminary analysis of the data on BPA analogues (BPAF, BPAP, BPB, BPE, BPF, BPP, BPS, BPZ) in the biological samples of this study showed that BPF was detected only in 7.5 % of the samples, BPE in only 6.6 % and BPB in 5.8 % with lower concentrations; all other types of bisphenol analyzed were even less detected - data not shown. The low sample size and variability were not sufficient to perform any analysis with these BPA analogues. Thus, assuming the precautionary principle, consuming of fresh and unpackaged food should continue to be promoted to the detriment of plastic containing packaged foods.

Several strengths and limitations in the present study deserve to be discussed. Due to the exhaustive and systematic data collected in the G21 cohort it was possible to study a range of cardiometabolic outcomes suspected of being influenced by BPA and using a clustering approach. It was also possible to consider the adjustment for several confounding factors. Urine is the preferred matrix for measuring total internal BPA exposure, as BPA has a short half-life and is quickly excreted [53], and most published studies have evaluated BPA in urine spot samples. The existence of 24-h urine in the present study in a subsample was fundamental to perform a random forest model in order to estimate BPA exposure to the remaining sample, allowing a study with greater power. A cross-validation was performed to handle and reduce the possible overfitting of these models. The model also benefits from the detailed food data from 3-day food diaries, including information on food packaging, and with adequate representation of all week and weekend days, reducing the likelihood of bias on exposure assessment. However, we cannot exclude error reports by adolescents, as their knowledge of brands and packaging description may be lower, which we tried to minimize by asking for parents' assistance. Finally, it is not expected that relevant metabolic deviations will be observed during adolescence, which could constitute a limitation in finding associations. The aggregation of the cardiometabolic indicators into clusters enabled us to identify a group of adolescents globally with the main cardiometabolic parameters above the average. Despite that, the direction of the associations between BPA and cardiometabolic risk factors and patterns cannot be guaranteed in the current design due to its cross-sectional nature although reverse causality is not expected. It is recommended that this analysis be replicated at older ages and with a longitudinal approach.

Funding

G21 was funded by the Health Operational Programme – Saúde XXI, Community Support Framework III and the Regional Department of the Ministry of Health. It was supported by the Calouste Gulbenkian Foundation, by FEDER from the Operational Programme Factors of Competitiveness – COMPETE and through national funding from the Foundation for Science and Technology – FCT (Portuguese Ministry of Education and Science).

This article is a result of the project FOCAcCIa: Exposure to food additives and contaminants from food processing and packaging: Defining patterns and their effects on adiposity and cognitive function from childhood to adolescence (POCI-01-0145-FEDER-031949).

This study was financed by national funds through FCT, I.P., under the projects UIDB/04750/2020 and LA/P/0064/2020. VM benefited from an FCT individual doctoral grant (SFRH/BD/143747/2019). SAC also benefited from an FCT individual doctoral grant (UI/BD/150785/2020). SCu acknowledges FCT for 2022.07841.CEECIND/CP1724/CT0014 contract.

Acknowledgments

The authors gratefully acknowledge the participants enrolled in the Generation XXI cohort for their kindness and all research team members for their enthusiasm. We are also very grateful to Flávia Mello for her role and technical dedication in the laboratory analysis of bisphenols.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2024.01.007.

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