Bisphenol-A in the European Prospective Investigation into Cancer and Nutrition cohort in Spain: Levels at recruitment and associated dietary factors

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ABSTRACT

Bisphenol A (BPA) is considered an endocrine disruptor and it is present in numerous products of daily use. The aim of this study was to analyze serum BPA concentrations in a subcohort of the Spanish European Prospective Investigation into Cancer and Nutrition (EPIC), as well as to identify potential predictors of the exposure. The population consisted on 3553 subjects from 4 EPIC-Spain centres and BPA levels were measured in serum samples by UHPLC-MS/MS. Almost 70% of the participants showed detectable BPA values (> 0.2 ng/ml), with a geometric mean of 1.19 ng/ml (95% CI: 1.12–1.25). By sex, detectable percentages were similar ($p = 0.56$) but with higher serum levels in men (1.27 vs 1.11 ng/ml, $p = 0.01$). Based on the adjusted regression models, a 50 g/day increase in the consumption of added fats and oils were associated with 43% lower BPA serum levels, while sugar and confectionary was associated with 25% higher levels of serum BPA. We evidenced differential exposure levels by province, sex and age, but not by anthropometric or lifestyle characteristics. Further investigation is needed to understand the influence of diet in BPA exposure.

1. Introduction

Bisphenol A (BPA) is an industrial chemical that was first developed in the 1890s and is now one of the highest-volume chemicals produced worldwide, with an output of 372,000 tons in 2012 (Mcgroup, 2013).

BPA is a synthetic oestrogen that is widely used in the manufacture of polymers and epoxy resins, polycarbonates and polysulphones plastics. It is also used as an additive in polyvinyl chloride (PVC), acrylonitrile butadiene styrene (ABS), and polystyrene (Hahladakis et al., 2018; Rezg et al., 2014) and is part of a great variety of everyday products such as

food packaging, medical and dental devices, CDs and DVDs, inks and toners. Its ubiquity means that the general population is frequently and inadvertently exposed to this compound (Geens et al., 2012a; Vandenberg et al., 2010).

BPA is considered a non-persistent chemical, i.e., it is eliminated from the organism (half-life in humans: 7–8 h)), despite the constant level of human exposure (vom Saal and Hughes, 2005). It is estimated that over 90% of the population in the US, Europe and Asia is exposed to BPA, with detectable levels in urine (> 0.4 ng/ml) (Hormann et al., 2014; Liao and Kannan, 2012; Vandenberg et al., 2010, 2009). BPA has also been detected in the serum of the general population and in pregnant women in the placenta, breast milk and amniotic fluid (Bloom et al., 2011; Fénichel et al., 2012; Fujimoto et al., 2011; Prins et al., 2011; Ye et al., 2013). Humans are exposed to BPA through several routes: food (orally), occupation (inhalation) and contact (dermal) via plastic-type materials and medical devices (Geens et al., 2012a; Vandenberg et al., 2013). However, the main exposure route is through diet, as many forms of food packaging such as tins and plastic wrap contain BPA, which migrates towards the food consumed, especially with heat (Ćwiek-Ludwicka, 2015; Geens et al., 2012a; Grumetto et al., 2008; Hahladakis et al., 2018; Huang et al., 2017; López-Cervantes and Paseiro-Losada, 2003).

Once absorbed in the intestine, BPA is readily glucuro-conjugated or sulpho-conjugated in the liver, until it is finally excreted in urine (Niwa et al., 2001). BPA concentrations in biological matrices are commonly expressed as the sum of conjugated and unconjugated BPA (total BPA), but also as free BPA, which is considered the biologically active form (Calafat et al., 2013).

BPA is known to be an endocrine disruptor, which means it has the ability to interfere with the production, secretion, transport, action, function and elimination of natural hormones, even at very low doses (Dickerson and Gore, 2007). Recent laboratory studies have reported an oestrogenic potential of BPA in experimental animals (Acevedo et al., 2013; Betancourt et al., 2012; Castro et al., 2013; Mandrup et al., 2016; Wu et al., 2011). However, it can also act as an anti-oestrogen by competing with the endogenous hormone 17-beta oestradiol (Rochester, 2013). Studies have shown that environmental exposure to BPA could play a role in cancer, insulin resistance, and obesity (Artacho-Cordón et al., 2018; Keri et al., 2007; Rezg et al., 2014). However, its potential effects on human health remain controversial due to the lack of large prospective studies in this respect.

In 2015, increasing concerns about the potential health effects of BPA exposure led the European Food Safety Authority (EFSA) to reduce the tolerable daily intake of BPA from 50 to 4 µg/kg per day and this recommendation will be reviewed in 2020 (Ćwiek-Ludwicka, 2015). Moreover, the General Court of the European Union recently confirmed the inclusion of Bisphenol A as a substance of very high concern (General Court of the European Union, 2019).

In Spain, some studies have assessed BPA exposure in different populations and biological tissues (Supplementary Material Table 1). There are several studies assessing BPA in urine samples in children and their mothers, in human milk or in hospitalised patients (Artacho-Cordón et al., 2018; Dualde et al., 2019; Martínez et al., 2017; Mustieles et al., 2018; Perez-Lobato et al., 2016), as well as in adult population (González et al., 2019). To our knowledge, therefore, this could one of the first studies assessing exposure to BPA among the adult general population and its possible determinants in Spain.

The aim of the present study is to characterise the exposure to BPA in a sub-cohort of the Spanish European Prospective Investigation into Cancer and Nutrition (EPIC) cohort by an analysis of serum BPA concentrations as well as to identify the potential dietary determinants of exposure.

2. Methods

2.1. Study design

This cross-sectional study was conducted of a sub-cohort of EPIC-Spain. EPIC is a prospective multi-centre cohort study undertaken to investigate the relationship between diet, lifestyles and cancer. It involves 23 research centres in ten European countries, with five centres in Spain: Asturias, Granada, Murcia, Navarra and Gipuzkoa (González et al., 2004). The study participants reported information about their dietary, lifestyle, reproductive and anthropometric factors at baseline.

2.2. Study population

In the EPIC-Spain study, a total of 41,446 participants aged 29–69 years were enrolled between 1992 and 1996 in five provinces of Spain. The majority (60%) of these participants were recruited from blood donors and the study population included a broad range of socio-economic and educational levels. At recruitment, a fasting blood sample was obtained from each participant. Signed informed consent was obtained in every case and the study was approved by the Ethics Committee of the Bellvitge Hospital (Barcelona).

A sub-cohort of 1000 participants from each centre was selected using stratified random sampling by sex and age, excluding persons with chronic disease. In our sub-cohort, 90% of the participants provided a fasting blood sample at recruitment, extracted between 6 am and 11 a.m. The remaining 10% of the samples did not have the fasting status. However, we can generalize and assume most of our samples were taken during the mornings and in fasting conditions. After excluding the samples considered inadequate (insufficient serum volume, or decayed serum sample during chemical analysis), the final study population analysed consisted of a sub-cohort of 3553 participants from the four EPIC-Spain centres (807 from Granada, 934 from Murcia, 903 from Navarra and 909 from Gipuzkoa). The characteristics of our sample regarding the rest of the EPIC-Spain cohort were similar for the variables included in the study, except for the distribution by sex and age that was deliberately different due to the stratified sample design used to extract the sample (Supplementary Material Table 2).

2.2.1. Assessment of diet and lifestyle variables

Information on lifestyle and other health-related factors was obtained by an interviewer-administered questionnaire at baseline. All interviewers had received appropriate training for this task.

Information on the usual diet over the last twelve months was collected by means of an interviewer-administered computerised version of a dietary history questionnaire that had been previously validated in Spain (EPIC group of Spain, 1997; "Relative validity and reproducibility of a diet history questionnaire in Spain. II. Nutrients. EPIC Group of Spain. European Prospective Investigation into Cancer and Nutrition.," 1997). The questionnaire was structured by meals and included a list of 662 common foods and recipes from each region. Recipes were broken down into simple foods, and the frequency of consumption of foods and recipes consumed at least twice a month was recorded and classified into 16 food groups.

Measurements of height, weight, and hip and waist circumferences were taken at recruitment using standardised procedures (Riboli et al., 2003). The questionnaire included items on educational level, history of previous illnesses, history of tobacco use, physical activity, occupation and reproductive history (Riboli et al., 2003). The participants were classified into three categories by body mass index (BMI): < 25 kg/m², $25-< 30$ kg/m², ≥ 30 kg/m². Educational level was classified according to five categories: none, primary school, secondary school, technical or vocational training and university degree. Smoking status was summarised in three categories: never smoked, former smoker and current smoker. Information on the domains of physical activity was compiled taking seasonal variation into account. A simple four-level

physical activity index (inactive, moderately inactive, moderately active and active) was derived and validated by combining occupational and recreational activity (Wareham et al., 2003). Total energy intake was analysed as a continuous variable in kcal/day.

The variable 'consumption of ultra-processed foods' was defined as the percentage of calories provided by ultra-processed foods to the daily energy intake. Each item on the food database was independently classified in one of the four categories of the NOVA classification (supplementary material): unprocessed or minimally processed foods (group 1, e.g. natural foods like fruits), culinary ingredients (group 2, e.g. oil), processed foods (group 3, e.g. canned fish) and ultra-processed foods (group 4, e.g. soft drinks) (Supplementary Material 3). Discrepancies over classification were resolved through literature research and expert consultation. The variable was calculated using the total energy contribution to daily energy intake from foods classified as ultra-processed, and divided into quartiles of consumption (Crino et al., 2017; Monteiro et al., 2018).

2.3. Sample collection and chemical analyses

Blood samples were drawn from each participant at recruitment. The samples were then centrifuged, and aliquots of plasma, serum, red blood cells and buffy coat in 0.5 mL straws were stored in liquid nitrogen (-196 °C).

BPA levels were quantified in serum samples using two of 0.5 mL straws, in an adaptation of a previously-validated methodology (Vela-Soria et al., 2014). In brief, BPA was analysed by dispersive liquid–liquid micro-extraction (DLLME) and ultra-high performance liquid chromatography with tandem mass spectrometry detection (UHPLC-MS/MS). Samples were thawed completely at room temperature, centrifuged at 2600 g for 10 min and 0.75 mL was extracted for analysis. In order to determine total BPA (free plus conjugated) in serum, each sample was spiked with 50 μL of enzyme solution (β-glucuronidase/sulphatase) and incubated at 37 °C for 24 h. The treated serum was placed in a 15 mL screw-cap glass tube and spiked with 30 μL of the surrogate standard solution (1.25 mg/L of BPA-d16). The serum was then diluted to 10.0 mL with 5% NaCl aqueous solution (w/v) and the pH was adjusted to 2.0. Next, 0.75 mL of acetone and 0.75 mL of trichloromethane were mixed and injected rapidly into the aqueous sample with a syringe. After manual shaking, centrifugation and evaporation of the extract, the residue was dissolved with 100 μL of a mixture consisting of water (0.1% ammonia)/acetonitrile (0.1% ammonia), 70:30 (v/v), and finally 10 μL was injected into the LC system. Limit of detection (LOD) was 0.2 ng/ml. Values below LOD were assigned the LOD divided by the square root of 2.

2.4. Statistical analysis

The BPA levels were transformed using natural logarithms to smooth their strong asymmetric distribution and to assure compliance with the normality assumption of the residuals in the regression analyses. Geometric means and 95% confidence intervals of the BPA levels (in ng/ml) were calculated overall and according to centre, sex, age group, educational level, body mass index, physical activity, smoker status and total energy intake. The differences in the BPA levels across the categories of the potential associated variables were assessed by mixed-effect Tobit regression. Tobit regression is suitable to estimate linear relationships between variables when there is either left- or right-censoring in the dependent variable, as happens in the case of BPA levels with a minimum detection limit. On the other hand, mixed-effect models, including a random effect at center level, allow to model the non-independence in data for the clustering of individuals in the same province of residence. Univariate models were generated with each variable as a predictor, and finally a multivariate model including all the study variables was adjusted to identify the independent effect of each variable. The exponential of the regression coefficient minus one

multiplied by 100 corresponded to the percentage of change in BPA levels for a given category of a variable relative to the reference category (Barrera-Gomez et al., 2015).

The variable identifying the centre was included in the regression model using the effect coding approach (Te Grotenhuis et al., 2017), so that the coefficient for each centre compared its BPA average level with the overall mean. This approach avoids the need to choose a reference category, which would not be meaningful in this case and would force us to omit the result for one of the centres.

For the diet analysis, 63 subjects who presented extreme data in this respect (extremely low or extremely high consumption of energy) were discarded. Thus, 3490 participants were finally analysed. Mixed-effect Tobit regression models were used to assess the association of each food group intake with BPA levels, and in these models the centre was included as a random effect, thus controlling for the correlation between participants from the same geographic area. The intake of individual food groups was previously adjusted for total energy intake by the residual regression method (Willett and Stampfer, 1986).

The models were adjusted using three strategies: A) unadjusted with a random effect for the centre; B) adjusted for sex and age with a random effect for the centre; C) adjusted for sex, age, and intake of all foods groups with a random effect for the centre.

Statistical analysis was conducted with Stata v14 (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

3. Results

In our study population, the average age of the participants was 53 years (range 30–69), and 49% were men. At baseline, 50.4% of them had overweight and almost 60% had never smoked (Table 1). Differences between centres were observed in all the participants' characteristics, including the percentage of energy intake obtained from ultra-processed foods (highest in Murcia and Navarra) and the mean energy intake (Kcal/day) (Table 1).

Of the 3553 samples analysed, 2476 (69.7%) had detectable BPA values, with a geometric mean of 1.19 ng/ml (95% CI: 1.12–1.25) (Table 2). There were significant differences in BPA concentrations according to the centre, with the highest concentrations in Granada (1.83 ng/ml; 95% CI: 1.64 to 2.04) and the lowest in Gipuzkoa (0.67 ng/ml; 95% CI: 0.61 to 0.75). The adjusted regression analysis revealed that the participants from Granada and Navarra had, respectively, 84% and 34% significantly higher levels of BPA in serum than the overall sample, while the levels of those from Gipuzkoa were 56% lower than the mean. The levels recorded in the participants from Murcia did not vary significantly from the overall average (Table 2).

By sex, the detectable BPA values were similar (about 70%), although they were lower in women (unadjusted geometric mean 1.11 vs 1.27 ng/ml, respectively), and 32% lower according to the adjusted models (Table 2). Comparison of age groups revealed an inverted V shape, with higher values in the central age group (1.31 ng/dl for the participants aged 45–54 years). Those aged 45–49 and 50–54 years had 35% and 34% significantly higher levels of BPA, respectively, than the younger age-group (< 45), but those older than 55 years had similar levels to those of the participants who were younger than 45 years (Table 2). No significant associations were observed between BPA levels and BMI, educational level, physical activity or smoking status. However, the former smokers had 19% lower levels than the never-smokers, and the participants with a university education had 24% lower levels than those with no formal education. Regarding the energy obtained from ultra-processed food, the participants in the second and third tertiles presented 9% and 20% higher levels of BPA, respectively, than those in the first tertile. A borderline significant negative association was observed between total energy intake and BPA levels (Table 2).

Based on the adjusted Tobit regression models for diet, a 50 g/day increase in the intake of added fats and oils (fats used for seasoning or cooking, such as olive oil, sunflower oil or butter) was associated with a

Table 1
Characteristics at recruitment of EPIC sub-cohort participants by center.

N (%)	Total	Gipuzkoa	Granada	Murcia	Navarra	p
	3553 (100)	909 (25.6)	807 (22.7)	934 (26.3)	903 (25.4)	
Sex						0.65
Male	1728 (48.6)	437 (48.1)	407 (50.4)	455 (48.7)	429 (47.5)	
Female	1825 (51.4)	472 (51.9)	400 (49.6)	479 (51.3)	474 (52.5)	
Age						0.02
< 45	679 (19.1)	163 (17.9)	178 (22.1)	187 (20.0)	151 (16.7)	
45–49	572 (16.1)	149 (16.4)	109 (13.5)	141 (15.1)	173 (19.2)	
50–54	757 (21.3)	198 (21.8)	182 (22.6)	206 (22.1)	171 (18.9)	
55–59	687 (19.3)	170 (18.7)	147 (18.2)	176 (18.8)	194 (21.5)	
60+	858 (24.1)	229 (25.2)	191 (23.7)	224 (24.0)	214 (23.7)	
Education level						< 0.01
None	1405 (39.8)	266 (29.4)	376 (47.3)	479 (51.4)	284 (31.7)	
Primary school	1242 (35.2)	390 (43.1)	201 (25.3)	215 (23.1)	436 (48.7)	
Technical school	281 (7.9)	143 (15.8)	29 (3.6)	36 (3.9)	73 (8.2)	
Secondary school	206 (5.8)	51 (5.6)	54 (6.8)	47 (5.09)	54 (6.0)	
University	392 (11.1)	54 (6.0)	135 (17.0)	155 (16.6)	48 (5.4)	
BMI						< 0.01
< 25 kg/m2	650 (18.3)	236 (26.0)	110 (13.6)	147 (15.7)	157 (17.4)	
25- < 30 kg/m2	1789 (50.3)	488 (53.7)	398 (49.3)	462 (49.5)	441 (48.8)	
≥30 kg/m2	1114 (31.3)	185 (20.4)	299 (37.1)	325 (34.8)	305 (33.8)	
Smoke status						< 0.01
Never	2114 (59.5)	538 (59.2)	485 (60.1)	537 (57.5)	554 (61.4)	
Former	669 (18.8)	157 (17.3)	184 (22.8)	201 (21.5)	127 (14.1)	
Smoker	767 (21.59)	214 (23.5)	138 (17.1)	193 (20.7)	222 (24.6)	
Physical activity						< 0.01
Inactive	528 (14.9)	155 (17.1)	129 (16.0)	135 (14.5)	109 (12.1)	
Moderately inactive	807 (22.7)	181 (19.9)	186 (23.0)	240 (25.7)	200 (22.1)	
Moderately active	1909 (53.7)	462 (50.8)	447 (55.4)	481 (51.5)	519 (57.5)	
Active	309 (8.7)	111 (12.2)	45 (5.6)	78 (8.4)	75 (8.3)	
% energy from ultra-processed food[a]						0.03
Tertile 1 (0–16%)	1164 (33.4)	306 (34.3)	273 (34.1)	301 (32.9)	284 (32.2)	
Tertile 2 (16%–24.5%)	1163 (33.3)	318 (35.7)	280 (35.0)	288 (31.4)	277 (31.4)	
Tertile 3 (24.5%–79.6%)	1163 (33.3)	267 (30.0)	247 (30.9)	327 (35.7)	322 (36.5)	
Energy intake*						< 0.01
Mean (SD) – kcal/day	2211 (704.4)	2265 (671.0)	1979 (639.4)	2259 (728.4)	2314 (722.6)	

[a] On 3490 subjects with reliable dietary information.

43% lower level of serum BPA (95% CI: 0.36–0.89) (Table 3). This association was consistent in the three adjusted models. A positive association, borderline significant, was also observed between sugar and confectionery (honey, jam, chocolate, sweet bars, ice cream, etc.) and 25% higher levels of serum BPA (95% CI: 1.00–1.56), which was detected in adjusted model C (Table 3).

Analysis of individual oils showed that the strongest association of lower serum BPA levels was for mixed oils (51% lower levels (95% CI: 0.19–1.25) followed by sunflower oil (49% lower levels (95% CI: 0.28–0.96)) (Table 4). In our cohort, however, olive oil was the most commonly consumed source of fats, by 86.8% of participants, and was associated with a 35% lower serum BPA level (95% CI: 0.43–0.97) (Table 4).

4. Discussion

BPA was frequently detected in our study population. The highest levels were found in men recruited in Southern Spain (Granada). Serum concentrations in our participants (GM = 1.19 ng/mL) were somewhat lower (although of a similar order of magnitude) than those observed in other countries, such as (date of the collection of the serum sample): Japan 1998 (GM = 2.24 ng/ml), Japan 2004 (GM = 2.5 ng/ml), USA 2008 (GM = 5.9 ng/ml), Italy 2009 (GM = 2.91 ng/ml), China 2015 (GM = 9.73 ng/ml in working time ≤ 5 years and 27.18 ng/ml in working time > 5 years), China 2014 (GM = 1.50 ng/ml), Korea 2012 (GM = 1.56 ng/ml) and China 2015 (GM = 3.2 ng/ml) (Cobellis et al., 2009; Hiroi et al., 2004; Lee et al., 2018; Padmanabhan et al., 2008; Song et al., 2019; Yamada et al., 2002; Ye et al., 2017; Zhuang et al., 2015). However, several previous studies have reported lower concentrations than those found in our study population, including Thailand 2009 (GM = 0.34 ng/ml), Japan 2003 (GM = 0.46 ng/ml), Japan 2004 (GM = 1.17 ng/ml) (Aekplakorn et al., 2015; Kuroda et al., 2003; Takeuchi et al., 2004a) and Spain (GM = 0.58 ng/ml) (González et al., 2019). In order to compare different studies, the date of sampling should be taken into account, since most previous research has been performed on populations recruited years or decades after the study period corresponding to our cohort (1992–1996). Date of sampling is relevant because during the 90s plastic containers or canned food were less usual as they were during the following years up to date. Being food the main rout of BPA exposure, dietary habits have also been gradually changed to use pre-cooked meals more frequently. However, due to the increasing concern of BPA, some analogues have raised their use in substitution of BPA in the recent years and therefore it would be expected that in new exposure measures, BPA biological levels may be lower (Rochester and Bolden, 2015).

In our population, the main determinants of BPA serum levels were sex, recruitment centre, and diet. Regarding dietary predictors, sugar and confectionery consumption was positively associated with serum BPA levels and added fats and oils was negatively associated with BPA.

In our sub-cohort, the consumption of added fats and oils was mainly that of vegetable oils, particularly olive oil, which accounted for 70.4% of total added fats and oils consumed, and sunflower oil with 12.2%. These items, together with mixed and unspecified oils, constituted 93% of the consumption in this main group. In our opinion, it is difficult to assess the negative association between BPA levels and the consumption of olive oil, as information on olive oil packaging was lacking at the time of recruitment. Regarding packaging, a study of BPA in Mediterranean olive oil revealed higher BPA levels in samples stored

Table 2
Blood BPA levels (ng/ml) (percentage above the limit of detection (LOD) and geometric mean (GM) with 95% confidence interval) and exponentiated coefficients from Tobit regression models by participants' sociodemographic and life style characteristics.

Total	> LOD (%)	GM (ng/ml)	95% CI	Tobit univariate models		Tobit multivariate model	
				e^β	p	e^β	p
	69.7	1.19	1.12-1.25				
Centre							
Gipuzkoa	57.7	0.67	0.61-0.75	0.44	< 0.01	0.44	< 0.01
Granada	82.0	1.83	1.64-2.04	1.85	< 0.01	1.84	< 0.01
Murcia	69.7	1.10	0.99-1.22	0.91	0.19	0.92	0.22
Navarra	70.8	1.54	1.36-1.73	1.33	< 0.01	1.34	< 0.01
Sex							
Male	70.2	1.27	1.17-1.38	Ref.	–	Ref.	–
Female	69.2	1.11	1.03-1.20	0.85	0.05	0.68	0.00
Age group							
< 45	68.0	1.04	0.92-1.18	Ref.	–	Ref.	–
45–49	70.1	1.31	1.13-1.52	1.32	0.05	1.35	0.03
50–54	70.0	1.31	1.15-1.48	1.31	0.03	1.34	0.03
55–59	70.5	1.23	1.08-1.39	1.23	0.11	1.23	0.13
60+	69.8	1.10	0.98-1.23	1.08	0.52	1.09	0.52
Educational level							
None	71.1	1.24	1.14-1.36	Ref.	–	Ref.	–
Primary school	68.8	1.19	1.08-1.31	0.92	0.38	1.00	0.97
Technical school	65.8	0.98	0.80-1.20	0.72	0.04	0.96	0.79
Secondary school	72.3	1.26	1.00–1.59	1.03	0.86	1.02	0.92
University	69.1	1.09	0.92-1.29	0.84	0.22	0.76	0.07
BMI							
< 25 kg/m2	66.8	1.02	0.90- 1.16	Ref.	–	Ref.	–
25- < 30 kg/m2	70.3	1.21	1.12-1.31	1.25	0.04	1.04	0.74
≥30 kg/m2	70.4	1.25	1.13- 1.38	1.30	0.03	0.93	0.57
Physical activity							
Inactive	68.9	1.21	1.04-1.40	Ref.	–	Ref.	–
Moderately inactive	69.0	1.18	1.04-1.33	0.97	0.84	0.91	0.51
Moderately active	70.7	1.21	1.12-1.31	1.03	0.81	1.05	0.74
Active	66.7	1.03	0.85-1.25	0.81	0.24	0.98	0.91
Smoke status							
Never	70.7	1.23	1.14-1.32	Ref.	–	Ref.	–
Former	69.1	1.12	0.99-1.28	0.89	0.27	0.81	0.08
Smoker	67.4	1.12	0.99-1.27	0.87	0.16	0.84	0.13
% energy from ultra-processed food							
Tertile 1 (0–16%)	69.0	1.13	1.02-1.25	Ref.	–	Ref.	–
Tertile 2 (16%–24.5%)	69.9	1.18	1.07-1.31	1.06	0.54	1.09	0.41
Tertile 3 (24.5%–79.6%)	70.3	1.27	1.15-1.40	1.15	0.16	1.20	0.07
Energy intake (per an increment of 1000 kcaL/day)				0.92	0.15	0.87	0.07

in plastic vs. non-plastic packaging (B = 121.56, 95% CI 53.44–194.39, p value = 0.009) (Abou Omar et al., 2017). Similar findings were obtained in a study of canned tuna, where the levels of bisphenols detected were higher than the mean values for oil (Fattore et al., 2015). Some studies show that BPA is slightly lipophilic (Liao and Kannan, 2014; Oz and Seyyar, 2016). and one reported finding detectable BPA concentrations in 86.8% of the adipose tissue samples from an adult cohort (GraMo cohort) (Artacho-Cordón et al., 2018). Some chemical substances similar to BPA present a log of the octanol-water partition coefficient (Kow) for phenols and parabens ranging from 1 to 5; in consequence, they should be considered at least partially lipophilic compounds that would potentially be distributed in adipose tissues (Geens et al., 2012b). Therefore, because of their presence in food packaging, it seems reasonable to conclude that when there is an environmental release, such as the migration of BPA from different types of plastic packaging (Geens et al., 2012a; López-Cervantes and Paseiro-Losada, 2003; Rochester, 2013), (Geens et al., 2012a; López-Cervantes and Paseiro-Losada, 2003; Rochester, 2013), foods cooked with fats (which, in our country, generally means olive oil) would have lower

levels of BPA. Our results show that a 50 g/day increase in the consumption of added fats and oils is associated with 43% lower levels of BPA in serum. However, account should be taken of the lack of information about olive oil packaging in this respect when the study participants were recruited. Furthermore, the negative association observed between olive oil consumption and BPA serum levels might be due to biological mechanisms and/or hepatic metabolism. Thus, olive oil is expected to exert a protective effect related to liver metabolism, as shown by studies according to which olive oil phenols inhibit human hepatic microsomal activity (Stupans et al., 2000). Therefore, it could be hypothesised that olive oil could be playing a role in BPA metabolism and elimination. Also, it could be assumed that olive oil consumption and its protective effect against BPA could be reflecting a higher adherence to a Mediterranean diet. Mediterranean diet is inversely associated with BPA levels (Rivas et al., 2016) as it appear to represent less BPA migrating from food packaging and microwave containers (Rivas et al., 2016).

In our cohort, the intake of sugar and confectionery was positively associated with serum BPA levels. In this regard, Larsson et al. found higher levels of BPA in children who often ate chocolate and suggested this might reflect a more frequent consumption of foods contaminated from food wrapping materials (Larsson et al., 2014). In line with this view, as said before, Rivas et al. (2016) concluded in their dietary study that adherence to a Mediterranean diet (with very low or zero consumption of confectionery) was inversely associated with BPA levels in human matrices. However, evidence shows that BPA dietary exposure is more determined by food packaging than the food by itself. Therefore, this association could the reflecting some dietary habits more related to BPA exposure as people that consume more confectionary products may be consuming more canned foods, precooked meals or soft drinks, which are products related to BPA exposure (Cao et al., 2011, 2009; Schecter et al., 2010).

Our results also highlighted the existence of a positive association with ultra-processed food consumption. This relationship corroborates that found for sugar intake, as ultra-processed foods usually include high levels of sugars (Latasa et al., 2018; Martínez Steele et al., 2016; Neri et al., 2019). However, although sugar and confectionery products are usually wrapped in plastic, canned foods have also been shown to make a major dietary contribution to BPA levels (Oldring et al., 2014).

Overall our results suggest that dietary exposure to BPA goes beyond the individual food items, and might be affected by the different methods of cooking, packing or preparing food – which, in fact, could be the key route of exposure to BPA.

We found significant gender-related differences in exposure, with men having significantly higher levels of BPA in serum than the women in our study. Previous studies, too, have reported significantly higher BPA concentrations in male plasma than in that of females (Jin et al., 2018) (He et al., 2009). On the other hand, González et al. (2019) found BPA levels 2-fold higher in female workers (0.68 and 1.20 µg/L in men and women, respectively), but this difference did not reach the level of statistical significance (p < 0.05) and may be related to the different work place among gender in their study. However, other studies have found no significant differences in this respect (Santhi et al., 2012; Song et al., 2019). Gender differences in BPA levels could be explained through the mechanisms by which BPA is metabolised in the liver. Biologically, hepatic physiology differs by sex; men have more liver enzymes than women, (Uno et al., 2017), and so they should eliminate BPA faster. In fact, however, the men in our cohort had higher levels of BPA than the women. Accordingly, unmeasured variables, such as life habits, occupation or even biological reasons must be assumed to play a role in this context. The smoking habit, high androgen levels in blood and dietary habits are other possible explanations of the higher BPA concentrations observed in our male participants. In a related study, Takeuchi et al. (2004b) analysed the serum concentrations and the metabolism of BPA in rats, finding significantly higher concentrations in the males than in the females. These authors commented that the

Table 3

Exponentiated coefficients from mixed-effects Tobit regression models and 95% confidence intervals (95% CI).

Food groups (per 50 g/day energy-adjusted increase)	Model A			Model B			Model C		
	e^{β}	95% CI	p	e^{β}	95% CI	p	e^{β}	95% CI	p
Potatoes and other tubers	1.03	(0.95–1.12)	0.48	1.04	(0.96–1.13)	0.34	1.08	(0.99–1.18)	0.09
Vegetables	0.99	(0.96–1.02)	0.52	0.99	(0.96–1.02)	0.49	1.00	(0.97–1.03)	0.94
Legumes	1.00	(0.88–1.13)	0.99	0.98	(0.87–1.11)	0.75	0.99	(0.87–1.12)	0.85
Fruits, nuts and seeds	1.01	(0.99–1.03)	0.27	1.01	(0.99–1.03)	0.38	1.01	(0.99–1.03)	0.57
Dairy products	0.99	(0.97–1.01)	0.38	0.99	(0.97–1.02)	0.66	0.99	(0.96–1.01)	0.31
Cereals and derivatives	0.98	(0.92–1.03)	0.43	0.98	(0.92–1.03)	0.44	0.96	(0.90–1.02)	0.18
Meat and derivatives	0.97	(0.89–1.05)	0.44	0.97	(0.89–1.05)	0.43	0.96	(0.88–1.05)	0.37
Fish and seafood	1.09	(0.98–1.2)	0.10	1.07	(0.97–1.18)	0.18	1.08	(0.97–1.20)	0.15
Eggs and derivatives	0.84	(0.67–1.06)	0.14	0.83	(0.66–1.05)	0.12	0.83	(0.65–1.06)	0.13
Added fats and oils	0.65	(0.45–0.95)	0.02	0.65	(0.45–0.95)	0.03	0.57	(0.36–0.89)	0.01
Sugar and confectionery	1.17	(0.95–1.45)	0.15	1.20	(0.97–1.48)	0.10	1.25	(1.00–1.56)	0.05
Cakes and cookies	0.97	(0.88–1.07)	0.54	0.99	(0.89–1.09)	0.79	0.94	(0.84–1.06)	0.32
Non-alcoholic drinks	0.98	(0.96–1.00)	0.09	0.98	(0.96–1.01)	0.15	0.98	(0.95–1.00)	0.06
Alcoholic drinks	1.02	(1.00–1.04)	0.11	1.01	(0.99–1.04)	0.29	1.01	(0.98–1.03)	0.65
Condiments and sauces	1.20	(0.75–1.92)	0.45	1.22	(0.76–1.95)	0.41	1.30	(0.81–2.10)	0.27
Soups and broths	0.99	(0.94–1.04)	0.67	0.98	(0.93–1.04)	0.48	0.97	(0.92–1.03)	0.35

Model A: unadjusted, random effect at centre level.
Model B: adjusted for sex and age, random effect at centre level.
Model C: adjusted for sex, age, random effect at centre level, and all food groups.

Table 4

Exponentiated coefficients from mixed-effects Tobit regression models and 95% confidence intervals (95% CI) for components of the main food group "Added fats and oils" [a].

Food groups (per 50 g/day energy-adjusted increase)	Consumers (%)	Model C		
		e^{β}	95% CI	p
Oil not specified	18.4	0.80	(0.40–1.60)	0.53
Olive oil	86.8	0.65	(0.43–0.97)	0.04
Sunflower oil	23.6	0.51	(0.28–0.96)	0.04
Mixed oil	5.8	0.49	(0.19–1.25)	0.13
Butter	6.7	0.54	(0.07–4.04)	0.55
Margarine	22.7	0.85	(0.37–1.97)	0.70

[a] Food items with consumption in less than 5% of the sample have been omitted (soya oil, peanut oil, corn/maize oil, grape oil, rapeseed oil, safflower oil, walnut oil, other oils, deep frying fats, marine oils, other animal fats).

gender difference in serum BPA concentrations might be explained by differences in clearance, according to the resultant enzyme activities. In our own analysis, male participants have significantly higher levels of BPA in serum than female. In this regard, we constructed gender-adjusted models to study the association with added fats and oils and we observed that consumption of added fats and oils was inversely associated with serum BPA levels in women. However, when the study group was stratified by sex, this association was not observed in men. The protective effect of added fats and oils against BPA levels that we observed only in women could be interpreted as reflecting differences in vegetable oil consumption among the participants in our cohort, in which olive oil was consumed by more women than men (52.3% vs 47.7%, respectively; data not shown). Moreover, as stated above, olive oil could play a role in the hepatic metabolism and exert a protective effect (Stupans et al., 2000). Moreover, this metabolism differs between the sexes (Uno et al., 2017). On the other hand, and despite the differences observed, stratifying the participants by sex reduced the statistical power of our analysis and therefore we decided to combine both sexes in the dietary models constructed.

Age and BPA were positively associated in our cohort. However, an earlier study observed no significant age-related differences in blood BPA concentration in people living in Shanghai, China (He et al., 2009). Some publications have reported higher urinary levels of BPA in younger adults (Adoamnei et al., 2018; Artacho-Cordón et al., 2018), probably reflecting their greater consumption of bottled water (Engel

et al., 2014; Li et al., 2013) and food packaged in plastic containers (Nahar et al., 2012). Moreover, other studies have suggested that non-persistent pollutants such as BPA may not be completely excreted, and that a proportion may be stored in body compartments (Doerge et al., 2012; Stahlhut et al., 2009). In this respect, a pharmacokinetic study revealed that unconjugated BPA levels remained for up to 20 h in the adipose tissue, whereas serum concentrations were rapidly converted (< 5 h) into the non-oestrogenic BPA monoglucuronide-iso-form (Doerge et al., 2012).

Our study has some limitations, being one the design of our study, as being a cross-sectional study we may be overestimating or underestimating BPA exposure through time. Another limitation would be the type of dietary information compiled at recruitment, since no questions referred to the use or otherwise of precooked containers or meals, which at the time (the 1990s) were less common than today. It could be hypothesised that the packaging of food, together with its processing, preparation and cooking mechanism, could be even more important than the frequency of consumption alone. This would be especially true of the use of canned food and beverages, as BPA is part of the material from which these containers are manufactured. Moreover, the migration of BPA from canned foods and beverages has been established (Sungur et al., 2014) and its migration from canned foods has been recorded in infant products, canned fish and meat products, canned vegetables, canned soft drinks, coffee and sauces (Cao et al., 2009; Errico et al., 2014; Ferrer et al., 2011; González-Castro et al., 2011; Grumetto et al., 2008; Kang and Kondo, 2002; Sajiki et al., 2007). Another limitation of the present study might be the biological matrix where BPA was measured, as serum presents greater variability than urine as regards BPA exposure. Serum BPA concentrations can be relatively unstable, representing recent exposures (Calafat et al., 2013; LaKind et al., 2014). Its representativeness of long-term exposures can only be assumed when external, lifestyle and biological determinants of serum concentrations remain constant at a certain degree, which is unlikely in a cohort study with a long follow-up time. Some studies point out that, among the biomonitoring matrices, urine contains the highest BPA concentrations, followed by serum (Lee et al., 2018) which implies a greater capacity to detect levels of exposure and also an improved estimator of medium-term exposure. In this regard, Spanish cohort included members of local blood donor associations. Blood samples were taken in fasting conditions and they were aliquoted into blood plasma, blood serum, white blood cells and erythrocytes. In this study, we only had the one single sample per participant taken at

recruitment, and therefore we assumed BPA exposure to be similar through the follow-up period. The estimated exposure of the general population to BPA from canned food may reach a body burden of 9 μg/kg/day (Commission, 2002). However, BPA levels in the organism are not stable: levels are highest immediately following exposure and are not metabolised and excreted until seven or 8 h after incorporation into the body. Fortunately, BPA is rapidly conjugated and excreted by humans, due to its efficient glucuronidation (Völkel et al., 2002). Other pathways of BPA exposure include dust inhalation and dermal absorption, which can be a predominant source of occupational exposure in electronic waste recycling plants and production facilities of BPA-containing materials (Wang et al., 2015; Zhang et al., 2016). Finally in this respect, our study does not take occupational exposure into account, as the production facilities of BPA were not included in the EPIC questionnaire at recruitment.

On the other hand, our study also has a number of strengths. The population considered is large and well representative of exposure to BPA in the 1990s. This characteristic is valuable, enabling us to study possible associations between BPA exposure at recruitment and certain chronic illnesses currently present in the participants. In this respect, it is of notable importance that almost 70% of the study population had detectable levels of BPA. In addition, we identify certain determinants of exposure. Although the cohort was recruited during the 1990s, analysis of our study results reveals the temporal evolution of BPA levels, both by comparing our levels with those obtained for more recent populations and also by comparing them with the current levels in our cohort. Our research group is currently working to determine the possible long-term implications of the levels found and their temporal evolution, by following up the EPIC subcohort. We expect to find that in the updated measures of BPA exposure among our cohort, serum levels will be lower due to the extended use of BPA substitutes BPS and BPF (Rochester and Bolden, 2015). Moreover, we accomplished the objectives of this study as we measured BPA serum concentrations in our population at recruitment as well as we identified potential dietary determinants of the exposure. In this regard, food assessment of the diet of this study and its statistical management are some of the novelties of this study.

In conclusion, almost 70% of the study population had detectable levels of BPA, in a range similar to that found for other populations. We identify certain predictors of exposure, although this finding needs to be confirmed in further research. The historical characterisation of BPA exposure obtained in the present study represents a first step towards an assessment of the long-term implications of BPA exposure in the EPIC cohort. Further investigation is needed to understand the influence of diet on BPA exposure.

Ethics

This paper includes human samples for the investigation. All participants were informed at recruitment and they signed an informed consent. This study was approved by Ethics Committee of the Bellvitge Hospital (Barcelona).

CRediT authorship contribution statement

Elena Salamanca-Fernández: Writing - original draft, Data curation, Investigation, Writing - review & editing, Supervision. **Miguel Rodríguez-Barranco:** Methodology, Data curation, Formal analysis, Investigation, Software, Writing - review & editing, Supervision. **Juan Pedro Arrebola:** Writing - review & editing, Supervision. **Fernando Vela:** Formal analysis, Supervision. **Caridad Díaz:** Formal analysis, Supervision. **María Dolores Chirlaque:** Writing - review & editing, Supervision. **Sandra Colorado-Yohar:** Writing - review & editing, Supervision. **Ana Jiménez-Zabala:** Writing - review & editing, Supervision. **Amaia Irizar:** Writing - review & editing, Supervision. **Marcela Guevara:** Writing - review & editing, Supervision. **Eva Ardanaz:** Writing - review & editing, Supervision. **Luz María Iribarne-Durán:** Formal analysis, Supervision. **José Pérez del Palacio:** Formal analysis, Supervision. **Nicolás Olea:** Conceptualization, Funding acquisition, Writing - review & editing, Supervision. **Antonio Agudo:** Writing - review & editing, Supervision. **Maria-José Sánchez:** Conceptualization, Funding acquisition, Project administration, Supervision, Resources, Writing - review & editing.

Declaration of competing interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2019.109012.

Authorship statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in *Environmental Research*.

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