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Bisphenol A urinary level, its correlates, and association with cardiometabolic risks in Lebanese urban adults

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Abstract Bisphenol A (BPA) is an endocrine disruptor with multiple purported metabolic effects. This study aimed to measure BPA among Lebanese population, to identify its predictors, and to explore any link to metabolic disorders. A representative sample of 501 adults from Lebanon was recruited in a cross-sectional study. Urinary BPA was measured, and data were collected for anthropometric measurements, medical history, food intake, and laboratory markers of metabolic conditions. BPA data was divided into tertiles. A total of 89% of the subjects had detectable urinary BPA levels, with an overall mean of 3.67 ± 4.75 μg/L and a mean creatinine-adjusted BPA of 2.90 ± 4.79 μg/g. There was a significant positive association with female gender and older age for being in the highest BPA tertile. BPA level was linked to metabolic syndrome (MetS), obesity, type-2 diabetes (T2D), hypertension, and dyslipidemia. After adjustment, the trend remained for BPA in association with MetS and T2D. Though urinary BPA in the Lebanese population was higher in older women, the levels were similar to world-reported figures. Our results suggest a link with metabolic disorders but not at a significant level. These findings call for longitudinal and broader sample measurements.

Keywords BPA · Urine · Cardiometabolic · Lebanon · Predictors · Outcomes

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Introduction

The endocrine disruptor bisphenol A (BPA) has been the subject of intensive research over the past decade (Diamanti-Kandarakis et al. 2009). Initially developed as a synthetic estrogen, its physical properties, rather than its chemical properties, made it a prime element in

the plastic industry. Its use has grown extensively over the past 50 years in products such as linings/coatings, polycarbonate bottles, and containers. Due to its hardening properties, BPA has also made it into dental sealants (Chapin et al. 2008).

As an estrogen agonist, BPA interacts with both estrogen alpha and beta nuclear receptors to differing degrees and interferes with their natural expression, thus acting as an endocrine disruptor (Routledge et al. 2000; Alonso-Magdalena et al. 2012). Similarly, it is reported to interact with the thyroid hormone receptor (Iwamuro et al. 2006). There is ample evidence through in vitro and in vivo animal studies that ill effects on reproductive and metabolic functions occur as a result of this interference (vom Saal et al. 1998; Rubin et al. 2001; Chapin et al. 2008). Clinical studies in humans on metabolic effects have been mainly cross-sectional and have suggested a positive association of BPA with obesity, type-2 diabetes (T2D), metabolic syndrome (MetS), cardiovascular disease, and hypertension (Lang et al. 2008; Lind and Lind 2011; Silver et al. 2011; Shankar and Teppala 2012; Wang et al. 2012), although this has not been consistently observed (Ning et al. 2011; Olsen et al. 2012).

Human non-occupational exposure to BPA is thought to occur mainly through ingestion from BPA "leakage" from plastic containers into the food or beverage in direct contact (Chapin et al. 2008). Population studies have revealed detectable blood and urine levels of BPA across most studies from North America, Europe, and Eastern Asia) (Vandenberg et al. 2007; Chapin et al. 2008). One comparative study conducted over seven countries in Asia found comparable levels as well; however, Kuwait, the only country included from the Eastern Mediterranean Region (EMR), had the highest levels (Zhang et al. 2011).

Except for the above report, to date, there are no data on BPA exposure in countries of the EMR, although the region harbors one of the highest burdens of obesity and diabetes worldwide (Abuyassin and Laher 2016; Federation 2016) coupled with a lack of monitoring of contaminants in foods and beverages. In this respect, Lebanon, a small country of the EMR, is no different than most of its neighboring countries.

In response to the need for data that contribute towards characterizing the risk for the Lebanese population, the present study was conducted on a sample of Lebanese adults, mainly from the Greater Beirut area with the aim of (1) assessing urinary BPA levels; (2) investigating the association of urinary BPA levels with demographic, socioeconomic, and lifestyle factors; and (3) examining the association of urinary BPA levels with cardiometabolic risk factors, including obesity, T2D, hypertension, dyslipidemia, and MetS.

Materials and methods

We carried out a cross-sectional, community-based study on a representative sample of adult subjects residing in Greater Beirut area. The study was carried out at the American University of Beirut during the period between February and June 2014. This study was approved by the Institutional Review Board (IRB) of the American University of Beirut and all participants signed an informed consent form. All Lebanese adults (age > 18 years) were eligible for this study. Pregnant women, patients on dialysis, mentally disabled subjects, and those working in a plastic or any other chemical company were excluded.

Sampling strategy

A representative sample of Lebanese adults was selected based on a multistage probability sampling, where the strata were the districts of the Greater Beirut area. Within each district, neighborhoods, then households were randomly selected based on a systematic random sampling according to the estimated number of neighborhoods and households within each district. At the household level, a primary adult respondent was selected based on the most recent day of birth.

Data collection

Subjects who agreed to participate were instructed to present to the Department of Nutrition and Food Sciences, American University of Beirut, after a 10-h fast and to bring with them all the medications that they were taking at the time of the study. Data were collected through a one-to-one interview using a multicomponent questionnaire. Anthropometric and blood pressure measurements and blood and urine samples were also obtained. All interviews were conducted by well-trained staff to minimize interviewer and measurement errors. Other quality control measures, including pre-testing of the study instruments, equipment, and data collection

procedure and field monitoring of data collection, were applied.

The multicomponent questionnaire covered the following: (1) demographic and socioeconomic information including age, gender, area of residence, marital status, education, occupation, crowding index (Freedman 1975; Baum and Epstein 1978), and income per family; (2) lifestyle-related characteristics including smoking, alcohol, and coffee intake; (3) physical activity using the short version of the International Physical Activity Questionnaire (IPAQ 2004); and (4) medical history including coronary artery disease, hypertension, dyslipidemia, T2D, and any other chronic condition with duration and treatment when applicable.

Dietary assessment was also performed using an 80-item semi-quantitative Food Frequency Questionnaire (Millen and Morgan 1996; Nasreddine et al. 2006) which referred to the subjects' dietary intake over the previous year. The reported frequency of each food item and beverage was then converted to daily intake. The daily energy and macronutrient intake was computed using the food composition database of Nutritionist Pro™ software (Axxya Systems LCC 2016, Nutritionist Pro™ version 6.3.0. Stafford) and the food composition table of Middle-Eastern foods for local and traditional foods (Pellet and Shadarevian 1970).

Anthropometric measurements were taken using standardized protocols (Lee and Nieman 2007) and calibrated equipment. Height and body weight were measured using a portable stadiometer (Holtain, Crymych, UK) and a Seca-calibrated electronic weighing scale (Hamburg, Germany), respectively. A calibrated plastic measuring tape was used to measure waist circumference at the level of the umbilicus. All anthropometric measurements were taken twice, and the average of the two values was adopted. Body mass index (BMI) was calculated as the ratio of weight (kilograms) to the square of height (meters). A tetrapolar single-frequency (330 μA at 100 kHz) electrical bioimpedance analyzer (Inbody Body Composition Analyzer, Inbody 230, InBody Co., Ltd., Seoul, Korea) was used to measure body composition. Sitting blood pressure was obtained twice at 10 min intervals using a digital sphygmanometer.

Blood and urine sampling and storage

Blood was drawn into two chemistry tubes and an EDTA tube. First morning spot urine samples were collected in glass jars, aliquoted in glass containers. Samples were frozen at −20 °C until analysis.

Blood analysis

Biochemical assessment was performed to assess fasting glucose, HbA1C, insulin, creatinine, vitamin D, lipid profile, and CRP. Laboratory tests were performed with the following methodologies: fasting glucose by enzymatic method (Cobas 6000, Roche), HbA1C by HPLC (Bio-Rad), insulin by radioimmunoassay (Cisbio), creatinine by the Jaffe rate method (Cobas 6000, Roche), and 25(OH) vitamin D by electrochemiluminescence immunoassay (Cobas e 411, Roche). Levels of triglycerides, HDL, LDL, total cholesterol, and CRP were measured using Vitros 350 analyzer (Ortho Clinical Diagnostics, Johnson and Johnson).

Urine BPA measurement

Organic phase extraction followed by high performance liquid chromatography-mass spectroscopy (HPLC-MS) was used to analyze BPA according to Coughlin et al. (2011) and Ning et al. (2011).

All chemicals used were of analytical grade. BPA ≥ 99%, sulfatase enzyme (150 U/mL), B-d glucuronidase from *Helix pomatia* (2000 U/mL), citrate buffer PH 6.0, and 10× phosphoric acid were purchased from Sigma Aldrich (St. Louis, MO). 2,2-*bis*-(4-hydroxyphenyl) butane (BPB) and BPA beta-D-glucuronide were obtained from Santa Cruz Biotechnology (Santa Cruz, CA). All glassware and glass pipettes were from Boeco (Germany). HS C18 HPLC Column (5 μm particle size, L 25 mm, I.D. 4.6 mm), and its corresponding guard column were procured from Supelco (Bellefonte, PA).

Sample pretreatment and extraction

In order to measure total BPA, 10 μL internal standard (4000 μg/L BPB) and 300 μL urine aliquot were added to 300 μL B-D-glucuronidase (2000 U/mL) and sulfatase (150 U/mL) enzymes in 1 M citrate buffer at pH 6 and hydrolyzed at 37 °C overnight (16 h). The optimization of the hydrolysis duration was performed on BPA glucuronide solutions in water (100 μg/L). The samples were then extracted after the addition of 100 μL of 1 M phosphoric acid. After that, the mixture was added to 3 mL of dichloromethane and centrifuged for 10 min at

2500 rpm at 4 °C. A volume of 2.5 mL of the organic phase extracts were dried in the vacuum centrifuge and reconstructed in 250 μL of 75% acetonitrile in water. The unconjugated BPA was tested with the same method as conjugated BPA but without the enzyme hydrolysis step. Standard BPA solutions in 75% acetonitrile in water were prepared with the same internal standard amount such that each 300 μL standard was spiked with 10 μL internal standard (4000 μg/L BPB).

HPLC-MS instrument conditions and analysis

Extract of 30 μL were run on a 1100 LC/MSD TrapXCT instrument with electrospray ionization (ESI) and autosampler from Agilent (Santa Clara, CA). Chromatography separation was performed with the C18 column using a buffered acetonitrile mobile phase (70/30 acetonitrile/2 mM ammonium acetate at pH 6.6). The column compartment was held at 30 °C. The LC/MSD trap software 5.2 (Agilent, Santa Clara, CA) was used to analyze the extracted ion chromatograph of BPA and the internal standard BPB at 227 and 241 *m*/*z*, respectively.

Detection was conducted in the electrospray negative mode under the following optimized conditions: nebulizer gas pressure of 30 psi, drying nitrogen gas temperature at 350 °C, drying nitrogen gas flow at 8 L/min, capillary voltage of + 3500 V, skimmer cone voltage of − 40 V, and capillary exit voltage of − 108 V in the single MS mode and performed using non-extracted standard in phase (70/30 acetonitrile/ water) and by relating the area of the analyte to the area of an internal standard for quantitation.

Method validation

Samples were analyzed in duplicates and in batches. To insure data accuracy and precision, every batch included standards, blanks, and an internal quality control-spiked sample with known concentrations of 250 μg/L BPA and 133 μg/L BPB. Ultrapure water was used as blank control. To control for potential external BPA contamination, all solvents, water, and glassware were tested for BPA contamination.

The limit of BPA detection was 0.1 μg/L based on three times the signal-to-noise ratio. The spike recovery was 98.75 ± 0.25% for samples spiked with 250 μg/L BPA. The internal quality control relative error was 4.68%. The unconjugated urinary BPA concentration was at the level of limit of detection.

Statistical analysis

To correct for urinary dilution, the BPA level was divided by urinary creatinine (μg/g). A "definite diabetes" variable was computed for subjects who were diagnosed with diabetes and/or had both fasting blood sugar (FBS) of ≥ 126 mg/dL and HbA1C of ≥ 6.5% (American Diabetes 2014). Similarly for hypertension, a "definite hypertension" variable was computed for those who were diagnosed with hypertension or had an abnormal blood pressure reading upon recruitment (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) (Armstrong and Joint National 2014). MetS variable was computed based on the joint harmonized definition of the International Diabetes Federation Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity (Alberti et al. 2009). The 10-year cardiovascular risk was also calculated based on the American College of Cardiology and American Heart Association guideline issued in 2013. Participants with cardiovascular or cerebrovascular disease were excluded from analysis (Goff et al. 2014).

Categorical variables were presented using number and percent, whereas continuous ones were presented by mean and standard deviation (± SD). Association between BPA level (tertiles) and other categorical variables was assessed using the Chi-square test, whereas ANOVA test was used for the association with continuous variables. Multivariate analysis was carried out to adjust for potentially confounding variables. More specifically, multinomial regression was used to examine the association between BPA levels and the different predictors and outcomes. Factors included in these analyses were those which showed statistical significance at the bivariate levels. Results are presented as odds ratio (OR) and 95% confidence interval (CI). p value < 0.05 was used to indicate statistical significance. The Statistical Package for Social Sciences (SPSS, version 22) was used for data cleaning, management, and analyses.

Results

The mean ± SD BPA urinary concentration was 3.67 ± 4.75 μg/L, with a median of 3.08 μg/L (range, < LOD–59.72). Because one of the study aims is to

assess factors associated with BPA, the urinary concentration adjusted for urinary creatinine was used for the remainder of the statistics. The mean ± SD BPA urinary concentration adjusted for urinary creatinine for the whole cohort (n = 501) was 2.86 ± 4.73 μg/g with a 95% CI for the mean of 2.45–3.28 μg/g, where the median was 1.83 μg/g (range, < LOD–69.85). After excluding 15 subjects with decreased renal function (glomerular filtration rate (GFR) < 60), a total of 432 subjects (89%) had detectable urinary BPA levels. The mean ± SD BPA urinary concentration adjusted for urinary creatinine for the 486 subjects included in the analyses was 2.90 ± 4.79 μg/g with 95% CI for the mean of 2.47–3.33 μg/g and median = 1.86 μg/g (range, < LOD–69.85).

As shown in Table 1, several of the demographic variables, socioeconomic characteristics, and lifestyle habits were statistically significantly associated with higher urinary BPA concentrations after adjustment for urinary creatinine. For instance, older age, female gender, and lower education levels were significantly associated with higher BPA levels (p value < 0.0001, < 0.0001, and 0.01, respectively). On the contrary, a significantly higher percentage of current smokers (p value = 0.03), specifically narghile smokers (p value = 0.02) and current alcohol drinkers (p value = 0.03) had lower BPA levels. As for the dietary intake, participants whose levels were in the third tertile had a significantly lower total energy intake (p value = 0.01) with lower carbohydrates and total and saturated fats (p value = 0.02, 0.03, and 0.01, respectively).

Table 2 reports on the association of BPA with diseases and morbidities. A significantly higher percentage of participants whose BPA levels were in the third tertile were diagnosed with diabetes (p value = 0.03), on diabetes treatment (p value = 0.02), on hypertension treatment (p value = 0.004), diagnosed with dyslipidemia (p value = 0.01), or on dyslipidemia treatment (p value = 0.03). A similar, though not statistically significant, trend was shown with participants who were diagnosed with hypertension (p value = 0.07). Interestingly, participants in the third tertile also had a significantly lower muscle mass (p < 0.0001) when compared with those whose BPA levels were in the first and second tertiles.

Table 3 summarizes the results of the stepwise multinomial logistic regression analyses identifying the predictors of BPA. It was found that age, gender, and education were significant predictors of BPA. For instance, women remained at a statistically significant risk of having higher BPA (third tertile) levels when compared with men (OR (95% CI), 2.82 (1.69–4.69)).

Similarly, older participants were found to have higher BPA (third tertile); for those 40–60 years (OR (95% CI), 1.75 (1.04–2.93)) and for those > 60 years (OR (95% CI), 2.86 (1.38–5.90)). On the other hand, participants with higher education were more likely to have BPA in the second tertile and less likely to be in the third BPA tertile.

After performing a stepwise multivariate logistic regression and adjusting for potential confounders (Table 4), none of the effects of urinary BPA on chronic diseases, body composition, and laboratory measurements retained significance. Nevertheless, there was a trend towards an increased risk between higher BPA tertiles and all three T2D assessments (for example, definite diabetes OR = 1.22; 95% CI = 0.62–2.42) and MetS (OR = 1.42; 95% CI = 0.88–2.31).

Discussion

This study is among the first from the EMR to investigate the population's exposure to BPA, its determinants, and association with cardiometabolic risk factors. It showed that the population's mean urinary BPA level was 3.67 ± 4.75 μg/L (range, < LOD–59.72) and when adjusted for creatinine, it was 2.86 ± 4.73 μg/g (range, < LOD–69.85). In addition, higher urinary BPA levels were associated with age and female gender.

Comparing the study findings with other countries

Our results of total BPA levels are largely consistent, albeit with more variance, with the range of the concentrations found in other countries. Because of difference in assays, we only compare our results with studies which have used HPLC, GC/MS, or LC/MS. The earliest reports of urinary BPA measurements stem out of Japan and have been mainly conducted on younger adults or university students with a small number of subjects (ranging from 48 to 69) and showed a mean BPA level of 0.82 μg/L (range, 0.14–5.47) (Tsukioka et al. 2004) and 1.92 μg/L (± 0.27) (Fukata et al. 2006). In addition, in the USA, a convenience random urine sample of 30 healthy volunteers showed a mean level of 3.2 μg/L (range, < LOD–19.8) (Ye et al. 2005). On a larger scale, 394 adult men and women, randomly

Table 1 The association of BPA with baseline characteristics and lifestyle

		BPA (μg/g, creatinine adjusted)			
		≤ 1.264 (n = 161)	1.265–2.431 (n = 161)	≥ 2.432 (n = 164)	p value
Age (years)	Mean (± SD)	42.19 ± 14.35	42.93 ± 14.95	49.38 ± 14.14	< 0.0001
	< 40	73 (45.3)	65 (40.4)	42 (25.6)	0.002
	40–60	70 (43.5)	75 (46.6)	87 (53.0)	
	> 60	18 (11.2)	21 (13.0)	35 (21.3)	
Gender	Female	89 (55.3)	96 (59.6)	130 (79.3)	< 0.0001
Marital status	Married	109 (67.7)	100 (62.1)	113 (68.9)	0.02
	Single	37 (23.0)	39 (24.2)	21 (12.8)	
	Others[a]	15 (9.3)	22 (13.7)	30 (18.3)	
Estimated GFR	Mean (± SD)	106.34 ± 14.36	103.33 ± 18.44	102.68 ± 17.10	0.39
Income	< $600	44 (27.7)	45 (28.3)	54 (32.9)	0.08
	$600–999.9	61 (38.4)	54 (34.0)	51 (31.1)	
	≥ $1000	45 (28.3)	48 (30.2)	36 (22.0)	
	I do not know or no answer	9 (5.7)	12 (7.5)	23 (14.0)	
Education	No schooling or primary	57 (35.4)	41 (25.5)	75 (46.3)	0.01
	Intermediate	43 (26.7)	49 (30.4)	41 (25.3)	
	Secondary or technical diploma	41 (25.5)	52 (32.3)	32 (19.8)	
	University degree	20 (12.4)	19 (11.8)	14 (8.6)	
Crowding index	Mean (± SD)	1.54 ± 0.83	1.48 ± 0.81	1.56 ± 0.99	0.74
Current smoker		112 (69.6)	109 (67.7)	93 (56.7)	0.03
Current cigarette smoker		76 (47.2)	69 (42.9)	65 (39.6)	0.38
Current narghile smoker		52 (32.3)	54 (33.5)	34 (20.7)	0.02
Current alcohol drinker		39 (24.2)	32 (19.9)	21 (12.8)	0.03
Coffee drinker		129 (80.1)	132 (82.0)	129 (78.7)	0.75
Total energy (kcal)	Mean (± SD)	3765.7 ± 2079.6	3684.4 ± 2105.4	3164.8 ± 1547.6	0.01
Protein (g/day)	Mean (± SD)	466.7 ± 262.8	460.8 ± 291.0	405.8 ± 297.3	0.10
Carbohydrate (g/day)	Mean (± SD)	427.8 ± 239.0	426.6 ± 251.1	366.2 ± 185.0	0.02
Total fat (g/day)	Mean (± SD)	172.1 ± 102.4	169.2 ± 100.5	146.9 ± 82.5	0.03
Saturated fat (g/day)	Mean (± SD)	43.6 ± 29.0	43.9 ± 30.1	35.9 ± 22.0	0.01
Protein % of kcal	Mean (± SD)	12.68 ± 2.83	12.42 ± 3.00	12.68 ± 3.77	0.71
Carbohydrate % of kcal	Mean (± SD)	46.42 ± 9.14	46.91 ± 8.29	47.04 ± 9.37	0.80
Fat % of kcal	Mean (± SD)	40.93 ± 8.63	41.38 ± 8.55	41.40 ± 9.33	0.87
Saturated fat % of kcal	Mean (± SD)	10.15 ± 2.75	10.38 ± 2.49	10.07 ± 3.12	0.58
Physical activity	None	26 (16.1)	21 (13.0)	29 (17.7)	0.50
	Any	135 (83.9)	140 (87.0)	135 (82.3)	

GFR glomerular filtration rate

[a] Widow, divorced, or engaged

selected from the Third NHANES study had a mean urinary BPA of 1.28 μg/L (10th–95th centiles, 0.22–5.18) (Calafat et al. 2005). More recently, a large population study from six European countries on 639 females found a geometric mean BPA of 1.78 μg/L (95% CI, 1.62–1.94) (Covaci et al. 2015). Closer to our population in geographic area, one study sampled seven countries from Asia (China, Korea, Vietnam, Malaysia, India, Japan, and Kuwait) and found the highest urine BPA levels to be in Kuwait with a median of 3.05 μg/L and a geometric mean of 2.45 μg/g creatinine (Zhang et al. 2011), numbers highly consistent with our results. Two other community-based screens from the Mediterranean region reported urine BPA levels. In the first

Table 2 The association of BPA with chronic diseases, body composition, and laboratory measurements

		BPA (μg/g, creatinine adjusted)			
		≤ 1.264 (n = 161)	1.265–2.431 (n = 161)	≥ 2.432 (n = 164)	p value
Diabetes					
Definite diabetes[a]		17 (10.6)	21 (13.0)	30 (18.3)	0.12
Diabetes diagnosis[b]		14 (8.7)	15 (9.3)	28 (17.1)	0.03
Diabetes treatment		12 (7.5)	15 (9.3)	28 (17.1)	0.02
Hyperglycemia (mg/dL)	≥ 100	69 (43.1)	76 (47.5)	90 (54.9)	0.10
Insulin (μIU/mL)	Mean (± SD)	28.33 ± 12.57	28.68 ± 12.87	27.74 ± 18.45	0.875
HbA1C	Mean (± SD)	5.83 ± 1.26	5.78 ± 1.15	6.03 ± 1.39	0.18
Hypertension (HTN)					
Definite HTN[c]		55 (34.2)	55 (34.4)	62 (37.8)	0.74
HTN diagnosis[d]		37 (23.0)	27 (16.8)	45 (27.4)	0.07
HTN treatment		27 (16.8)	26 (16.1)	48 (29.3)	0.004
Systolic blood pressure (mmHg)	Mean (± SD)	121.17 ± 18.86	120.53 ± 18.46	121.23 ± 19.03	0.93
Diastolic blood pressure (mmHg)	Mean (± SD)	74.94 ± 10.17	75.05 ± 10.14	73.78 ± 9.62	0.45
Dyslipidemia					
Dyslipidemia diagnosis		32 (19.9)	30 (18.6)	51 (31.1)	0.01
Dyslipidemia treatment		22 (13.7)	25 (15.5)	40 (24.4)	0.03
Cholesterol (mg/dL)	Mean (± SD)	182.55 ± 49.90	187.94 ± 39.75	186.46 ± 40.17	0.52
HDL (mg/dL)	Mean (± SD)	49.03 ± 14.43	48.90 ± 13.41	51.28 ± 16.47	0.27
HDL—categorical	Abnormal HDL	69 (43.1)	67 (41.6)	76 (46.3)	0.68
LDL (mg/dL)	Mean (± SD)	108.22 ± 42.13	110.74 ± 35.52	106.59 ± 35.14	0.61
Triglyceride (mg/dL)	Mean (± SD)	137.63 ± 82.01	145.78 ± 140.17	138.58 ± 72.39	0.74
Hypertriglyceridemia	> 150	54 (33.8)	56 (34.8)	67 (40.9)	0.36
Obesity					
Body mass index (BMI) (kg/m^2)	Mean (± SD)	28.50 ± 5.77	28.95 ± 5.91	29.68 ± 5.55	0.18
BMI ≥ 30 (kg/m^2)		56 (34.8)	68 (42.2)	78 (47.6)	0.06
Waist circumference (cm)	Mean (± SD)	94.87 ± 14.04	95.34 ± 14.76	96.51 ± 17.65	0.62
Body fat (kg)	Mean (± SD)	27.31 ± 11.60	28.49 ± 12.02	29.80 ± 10.79	0.15
Muscle mass (kg)	Mean (± SD)	26.92 ± 6.79	27.23 ± 6.48	24.67 ± 5.72	< 0.0001
Metabolic syndrome		73 (45.6)	78 (48.4)	94 (57.3)	0.09
10-year ASCVD risk (%)[e]	Mean (± SD)	7.40 ± 6.85	7.43 ± 7.30	8.16 ± 9.23	0.78
C-reactive protein (mg/L)	Mean (± SD)	11.80 ± 9.50	11.73 ± 8.52	12.87 ± 12.23	0.53

[a] Subjects who were diagnosed with diabetes and/or had both fasting blood sugar (FBS) of ≥ 126 mg/dL and HbA1C of ≥ 6.5% (American Diabetes 2014)

[b] Subjects who were diagnosed with diabetes

[c] Subjects who were diagnosed with hypertension or had an abnormal blood pressure reading upon recruitment (systolic blood pressure ≥ 140 mm/Hg or diastolic blood pressure ≥ 90 mm/Hg) (Armstrong and Joint National 2014)

[d] Subjects who were diagnosed with hypertension

[e] Ten-year risk for having a cardiovascular event (Goff et al. 2014)

study, 200 men, women, and children from the rural area of Mersin, Turkey had a mean BPA of 0.61 μg/g creatinine (Battal et al. 2014). The authors argue that these lower levels may be related to the relative lack of urbanization and thus exposure to BPA-containing products. In the second study, an evaluation of 59 Arabs and 183 Jews from Israel found a geometric mean BPA of 1.90 μg/g creatinine (Berman et al. 2014). There was

Table 3 Stepwise multinomial logistic regression of potentially significant predictors of BPA tertiles

		BPA (μg/g, creatinine adjusted)			
	≤ 1.264	1.265–2.431		≥ 2.432	
		OR (95% CI)	*p* value	OR (95% CI)	*p* value
Gender	Reference	1.27 (0.80–2.02)	0.31	2.82 (1.69–4.69)	< 0.0001
Age					
40–60	Reference	1.24 (0.77–2.02)	0.38	1.75 (1.04–2.93)	0.03
> 60	Reference	1.62 (0.77–3.41)	0.21	2.86 (1.38–5.90)	0.005
Education					
Intermediate school	Reference	1.71 (0.95–3.07)	0.07	0.85 (0.48–1.52)	0.59
Secondary school	Reference	2.07 (1.13–3.79)	0.02	0.91 (0.49–1.70)	0.77
University degree	Reference	1.51 (0.70–3.26)	0.29	0.72 (0.32–1.62)	0.43

Age (reference, < 40); gender (reference, male); marital status (reference, married); education (reference, no schooling/primary school); current smoker (reference, no); current alcohol drinker (reference, no); total energy (kcal; per 500 kcal increase); BMI (reference, < 30)

however a difference by ethnicity with Arab-Israelis having a level of 0.80 μg/g versus Jewish-Israelis of 2.49 μg/g creatinine. The authors speculate that the difference may be due to area of residence and urban versus rural living.

Our study was conducted in a fully urban setting, with Greater Beirut being a densely populated city with heavy traffic, little exposure to nature, and possibly more processed food intake. Furthermore, drinking water is purchased in polycarbonate containers made with BPA (Dhaini and Nassif 2014) . One study assessing BPA levels in the water inside these containers found detectable BPA levels in the products of 13 out of 22 companies sampled in Lebanon, with a mean of 0.169 μg/L (Dhaini and Nassif 2014). Although the levels detected fall within previous reports of water stored in such containers from different areas worldwide (Chapin et al. 2008), the mildly higher mean BPA observed in this study may be explained by the excessive use of these containers in our community. As a matter of fact, 93.8% of the participants reported drinking from bottled water on a daily basis, with an average cups per day from water cooler of 4.31 (± 3.6) (data not shown).

Predictors of BPA levels

Older age and female gender were strong positive predictors of higher BPA levels. The age association is unlike most previous reports, where mean urine BPA tends to decrease with age (Calafat et al. 2008; Silver et al. 2011). However, one recent study on women from six European countries did find a positive correlation with age, in support of our findings (Covaci et al. 2015). The association of women having almost three times the odds of being in the upper tertile of BPA, as compared with men, is more complex. Previous studies have either reported no gender association with BPA (Mahalingaiah et al. 2008) or higher levels in men than in women, such as in the 2003–2008 NHANES population (Silver et al. 2011). To probe further into these inconsistencies, a review of the 2003–2012 NHANES dataset by Lakind and Naiman found that men had consistently higher urine BPA levels per volume, but when adjusted for creatinine, women had the higher BPA level, in line with our findings. The authors caution about interpretation of such association where BPA and creatinine kinetics may affect essentially the direction of the relationship. However, the adjustment corrects for dilution effect, and as such is likely more accurate than the unadjusted result. One intervention to minimize BPA exposure conducted in women where BPA-free make-up, hygienic products, and plastic ware were provided over a 3-week period, showed that this change was able to reduce significantly geometric mean of urinary BPA level, as compared with controls (Hagobian et al. 2017). Therefore, it is possible that a behavioral component in women is accounting for a true difference in BPA levels. In the current analysis, we can only speculate that the higher BPA levels found in older women

Table 4 Stepwise multivariate logistic regression of BPA tertiles with chronic diseases, body composition, and laboratory values with and without adjustment for potentially significant predictors of BPA

	BPA (μg/g, creatinine adjusted)				
	≤ 1.264 (n = 161)	1.265–2.431 (n = 161)	p value	≥ 2.432 (n = 164)	p value
Diabetes					
Definite diabetes[a]					
Cases (n (%))	17 (10.6)	21 (13.0)		30 (18.3)	
Unadjusted	Reference	1.27 (0.64–2.51)	0.49	1.90 (1.00–3.60)	0.05
Adjusted[f]	Reference	1.17 (0.58–2.39)	0.65	1.37 (0.70–2.68)	0.35
Adjusted[g]	Reference	1.07 (0.52–2.20)	0.85	1.22 (0.62–2.42)	0.56
Diabetes diagnosis[b]					
Cases (n (%))	14 (8.7)	15 (9.3)		28 (17.1)	
Unadjusted	Reference	1.08 (0.50–2.31)	0.85	2.16 (1.09–4.28)	0.03
Adjusted[f]	Reference	0.99 (0.45–2.17)	0.97	1.57 (0.77–3.20)	0.21
Adjusted[g]	Reference	0.91 (0.41–2.02)	0.82	1.43 (0.70–2.94)	0.33
Diabetes treatment					
Cases (n (%))	12 (7.5)	15 (9.3)		28 (17.1)	
Unadjusted	Reference	1.28 (0.58–2.82)	0.55	2.56 (1.25–5.23)	0.01
Adjusted[f]	Reference	1.18 (0.53–2.67)	0.68	1.92 (0.92–4.01)	0.08
Adjusted[g]	Reference	1.09 (0.48–2.48)	0.84	1.74 (0.82–3.67)	0.15
Hypertension (HTN)					
Definite HTN[c]					
Cases (n (%))	55 (34.2)	55 (34.4)		62 (37.8)	
Unadjusted	Reference	1.01 (0.64–1.60)	0.97	1.17 (0.74–1.84)	0.49
Adjusted[f]	Reference	0.92 (0.56–1.51)	0.73	0.81 (0.49–1.33)	0.40
Adjusted[g]	Reference	0.85 (0.51–1.41)	0.52	0.73 (0.44–1.23)	0.24
HTN diagnosis[d]					
Cases (n (%))	37 (23.0)	27 (16.8)		45 (27.4)	
Unadjusted	Reference	0.67 (0.39–1.17)	0.16	1.27 (0.77–2.09)	0.35
Adjusted[f]	Reference	0.57 (0.32–1.04)	0.07	0.85 (0.49–1.47)	0.57
Adjusted[g]	Reference	0.53 (0.29–0.97)	0.04	0.78 (0.45–1.37)	0.39
HTN treatment					
Cases (n (%))	27 (16.8)	26 (16.1)		48 (29.3)	
Unadjusted	Reference	0.96 (0.53–1.72)	0.88	2.05 (1.20–3.50)	0.008
Adjusted[f]	Reference	0.83 (0.43–1.58)	0.57	1.39 (0.77–2.51)	0.27
Adjusted[g]	Reference	0.75 (0.39–1.46)	0.40	1.25 (0.69–2.29)	0.46
Body composition					
Body mass index (BMI) ≥ 30 (kg/m^2)[h]					
Cases (n (%))	56 (34.8)	68 (42.2)		78 (47.6)	
Unadjusted	Reference	1.37 (0.87–2.15)	0.17	1.70 (1.09–2.66)	0.02
Adjusted[f]	Reference	1.32 (0.82–2.10)	0.25	1.35 (0.85–2.16)	0.21
Adjusted[g]	Reference	1.31 (0.82–2.10)	0.26	1.29 (0.80–2.07)	0.29
Muscle mass					
Mean (SD)	26.92 ± 6.79	27.23 ± 6.48		24.67 ± 5.72	
Unadjusted	Reference	0.32 (− 1.07; 1.71)	0.66	− 2.24 (− 3.63; − 0.86)	0.002
Adjusted[f]	Reference	0.82 (− 0.03; 1.68)	0.06	0.48 (− 0.39; 1.36)	0.28
Adjusted[g]	Reference	0.63 (− 0.13; 1.40)	0.11	0.29 (− 0.50; 1.08)	0.47
Dyslipidemia					
Dyslipidemia diagnosis					
Cases (n (%))	32 (19.9)	30 (18.6)		51 (31.1)	
Unadjusted	Reference	0.92 (0.53–1.61)	0.78	1.82 (1.09–3.03)	0.02
Adjusted[f]	Reference	0.82 (0.45–1.48)	0.50	1.29 (0.74–2.24)	0.36
Adjusted[g]	Reference	0.75 (0.41–1.38)	0.36	1.18 (0.67–2.07)	0.56

Table 4 (continued)

	BPA (μg/g, creatinine adjusted)				
	≤ 1.264 (n = 161)	1.265–2.431 (n = 161)	p value	≥ 2.432 (n = 164)	p value
Dyslipidemia treatment					
Cases (n (%))	22 (13.7)	25 (15.5)		40 (24.4)	
Unadjusted	Reference	1.16 (0.62–2.16)	0.64	2.04 (1.15–3.62)	0.02
Adjusted[f]	Reference	1.03 (0.53–1.99)	0.93	1.40 (0.76–2.59)	0.28
Adjusted[g]	Reference	0.95 (0.49–1.87)	0.89	1.32 (0.70–2.49)	0.38
Cholesterol (mg/dL)					
Mean (SD)	182.55 ± 49.90	187.94 ± 39.75		186.46 ± 40.17	
Unadjusted	Reference	5.39 (− 4.15; 14.93)	0.27	3.91 (− 5.58; 13.41)	0.42
Adjusted[f]	Reference	4.20 (− 5.07; 13.48)	0.37	− 0.59 (− 9.97; 8.78)	0.90
Adjusted[g]	Reference	3.58 (− 5.65; 12.80)	0.45	− 1.33 (− 10.66; 8.00)	0.78
HDL (mg/dL)					
Mean (SD)	49.03 ± 14.43	48.90 ± 13.41		51.28 ± 16.47	
Unadjusted	Reference	− 0.13 (− 3.38; 3.12)	0.94	2.25 (− 0.99; 5.49)	0.17
Adjusted[f]	Reference	− 0.53 (− 3.62; 2.56)	0.74	− 0.11 (− 3.26; 3.03)	0.94
Adjusted[g]	Reference	− 0.39 (− 3.46; 2.67)	0.80	− 0.26 (− 3.40; 2.87)	0.87
LDL (mg/dL)					
Mean (SD)	108.22 ± 42.13	110.74 ± 35.52		106.59 ± 35.14	
Unadjusted	Reference	2.52 (− 5.77; 10.80)	0.55	− 1.63 (− 9.86; 6.61)	0.70
Adjusted[f]	Reference	1.63 (− 6.47; 9.73)	0.69	− 5.12 (− 13.30; 3.05)	0.22
Adjusted[g]	Reference	1.22 (− 6.83; 9.27)	0.77	− 5.04 (− 13.19; 3.11)	0.22
Triglycerides (mg/dL)					
Mean (SD)	137.63 ± 82.01	145.78 ± 140.17		138.58 ± 72.39	
Unadjusted	Reference	8.16 (− 14.33; 30.65)	0.48	0.95 (− 21.43; 23.34)	0.93
Adjusted[f]	Reference	7.24 (− 14.65; 29.13)	0.52	5.05 (− 17.43; 27.54)	0.66
Adjusted[g]	Reference	5.40 (− 16.12; 26.92)	0.62	5.61 (− 16.30; 27.53)	0.61
Metabolic syndrome[i]					
Cases (n (%))	73 (45.6)	78 (48.4)		94 (57.3)	
Unadjusted	Reference	1.12 (0.72–1.74)	0.61	1.60 (1.03–2.48)	0.04
Adjusted[f]	Reference	1.08 (0.67–1.74)	0.74	1.42 (0.88–2.31)	0.15
Adjusted[g]	Reference	1.08 (0.67–1.74)	0.74	1.42 (0.88–2.31)	0.15
10-year ASCVD risk (%)[e, j]					
Mean (SD)	7.40 ± 6.85	7.43 ± 7.30		8.16 ± 9.23	
Unadjusted	Reference	0.03 (− 2.64; 2.69)	0.98	0.76 (− 1.78; 3.30)	0.55
Adjusted[f]	Reference	0.03 (− 2.64; 2.69)	0.98	0.76 (− 1.78; 3.30)	0.55
Adjusted[g]	Reference	− 0.25 (− 2.91; 2.40)	0.85	0.42 (− 2.12; 2.97)	0.74

[a] Subjects who were diagnosed with diabetes and/or both fasting blood sugar (FBS) was ≥ 126 mg/dL and HbA1C was ≥ 6.5% (American Diabetes 2014)

[b] Subjects who were diagnosed with diabetes

[c] Subjects who were diagnosed with hypertension or had an abnormal blood pressure reading upon recruitment (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) (Armstrong and Joint National 2014)

[d] Subjects who were diagnosed with hypertension

[e] Ten-year risk for having a cardiovascular event (Goff et al. 2014)

[f] Adjusted for gender; education, and age

[g] Adjusted for age, gender, current smoker, education, BMI (categorical), and physical activity

[h] BMI not included as a covariate in adjusted for age, gender, current smoker, education, BMI (categorical), and physical activity

[i] BMI not included as a covariate in adjusted for age, gender, current smoker, education, BMI (categorical), and physical activity

[j] Age and gender not included as covariates in adjusted for gender, education, and age. Age, gender, and smoking not included as covariates in adjusted for age, gender, current smoker, education, BMI (categorical), and physical activity

may be a result of increased exposure, in addition to possibly a kinetic effect.

In this study, having secondary school-level education made subjects more likely to be in the intermediate BPA tertile. Studies on education have not shown a definite consistent association with BPA (Silver et al. 2011; Berman et al. 2014). Again, the large 2003–2012 NHANES analysis sheds more light into this relationship, whereby education was inversely associated with urine BPA levels; however, this significance was lost when reporting creatinine-adjusted BPA (LaKind and Naiman 2015). The lack of trend and isolated finding in our study, in addition to having only a fraction of subjects with university degrees, make it difficult to draw any solid conclusion.

Associations with BPA levels

As for BPA's link to chronic conditions, there was a positive and incremental association between BPA tertiles and T2D, hypertension, dyslipidemia, obesity, and the MetS. However, only a trend remained after adjustment in support of confounding effect.

Despite the lack of significance, the incremental increase in odds ratios between second and third BPA tertiles for T2D and MetS is in support of a true link. This finding is supported by biologic plausibility and falls in line with the majority of published studies. For instance, the Nurses' Health Study II in a retrospective nested case-control design found higher odds of having T2D for the upper BPA quartile. However, this link was significant only after adjustment for BMI, where a large proportion of cases were obese as compared with controls. Therefore, the authors could not exclude a chance finding (Sun et al. 2014). The association with T2D was further affirmed by Shankar and Teppala, who reviewed the 2003–2008 NHANES data in 3967 adults with available fasting glucose and HbA1C values and found incremental increase in odds of T2D per BPA quartile after adjusting for several factors (Teppala et al. 2012). For the same population, the authors found a significant association with MetS and hypertension (Shankar and Teppala 2012; Teppala et al. 2012). Interestingly, reanalysis of the same NHANES data for the years 2003 through 2010 yielded no association with either T2D or heart disease (LaKind et al. 2012). The authors attributed the seemingly contradictory findings to differences in the definitions of the condition, exclusion criteria, or BPA categorizations. Rather than drawing a conclusion about the lack of association, the authors highlighted the difficulty of using cross-sectional data in interpreting variable associations to complex diseases.

Where does that leave the findings of this study? In our sample, the definition of chronic conditions were preset and based on standardized measures or laboratory values. Furthermore, a sensitivity analysis on the whole sample (including the 15 subjects with lower GFR) yielded similar findings (data not shown). In view of the above, the trend in metabolic relations in our study are likely real. We were unable to demonstrate statistical significance, possibly because of the insufficient sample size or the high variability of the observed BPA levels.

Strengths and limitations

This study should be viewed in light of some limitations. This was a cross-sectional study that might have been limited by the inability to assess time-dependent associations, as well as the potential variability of urinary BPA levels over time, although it was previously reported that a single BPA value correlates with repeat BPA measurements (Mahalingaiah et al. 2008). We have collected spot morning urine for BPA levels; however, one should keep in mind its shortcomings and how these can be remedied (Barr et al. 2005; Weaver et al. 2016). Nevertheless, despite its limitations, the adjusted urine BPA level remains the most valid and practical tool for any potential association (Ye et al. 2005). Another limitation could be the insufficient sample size which might have underpowered our study to detect significant associations. Moreover, there may be a selection bias as the study was conducted during working hours and as such, may have included more housewives or non-working people. Finally, the findings are for the Greater Beirut area and might not be generalizable to the whole Lebanese population.

Conclusion

In conclusion, this is among the first community-based studies to report on urine BPA levels from the EMR. Levels measured are overall comparable with the rest of the world. These were found to be highest among older women, but did not link to any chronic metabolic disease. Our results are fairly reassuring about current

status of BPA in Lebanon but call for longitudinal sampling and possibly from more regions in Lebanon.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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