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RESEARCH ARTICLE

Urinary concentrations of parabens amongst Iranian adults and their associations with socio-demographic factors

Ghasem Kiani Feizabadi[1,2] · Yaghoub Hajizadeh[3] · Awat Feizi[4] · Karim Ebrahimpour[3]

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Abstract

Background Parabens are widely used to prevent organism growth and increase the shelf life of foods, medicines and personal care products (PCPs). Recent studies indicate their potentially harmful effects on human health. There is no information on the extent of exposure to parabens among Iranians.

Methods We measured the concentration of urinary methylparaben (MP), ethylparaben (EP), propylparaben (PP) and butylparaben (BP) among Iranian adults and calculated their estimated daily intake (EDI). Also, association between the level of urinary parabens with socio-demographic and lifestyle variables were investigated.

Results Detection frequencies of MP, EP, PP, and BP were 98.9, 91, 94.3, and 88.2%, and their median urinary concentrations were 69.06, 9.10, 12.4, and 9.87 μg/l, respectively. Urinary parabens were higher in females, and the difference in the concentration of MP and PP was significant. A significantly positive correlation between MP and PP ($r = 0.638$) and a moderate to a weak correlation between other parabens were observed. There was a significantly negative weak correlation between age and MP, BP and PP. There was also a significant association between different age groups and MP, BP and PP as well as different BMI values and MP. The highest EDI value belonged to MP in the female group. Despite being lower than the acceptable daily intake (ADI), its value was higher than that reported in other countries (except the US).

Conclusions Our findings indicated that Iranians are widely exposed to the parabens and the range of exposure was associated with socio-demographic factors. These results could serve as a basis for assessing the risk of exposure to parabens amongst Iranians.

Keywords Parabens · Urine · Biomonitoring · Adults · Estimated daily intake

Introduction

Parabens are a family of alkyl esters of para-hydroxybenzoic acid. These compounds are the most widely used preservatives and antimicrobials used to prevent the growth of organisms and increase the shelf life of foods, medicines, and PCPs [1–4]. Parabens are widely used by companies producing these products worldwide because of their optimal stability, high water solubility, and relatively low cost. Methylparaben (MP), ethylparaben (EP), propylparaben

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✉ Yaghoub Hajizadeh
y_hajizadeh@hlth.mui.ac.ir

Ghasem Kiani Feizabadi
ghasem_kia@yahoo.com

Awat Feizi
awat_feiz@hlth.mui.ac.ir

Karim Ebrahimpour
ebrahimpour@hlth.mui.ac.ir

1 Student Research Committee, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

2 Department of Environmental Health Engineering, School of Health, Semnan University of Medical Sciences, Semnan, Iran

3 Environment Research Center, Research Institute for Primordial Prevention of Non-communicable Diseases, Isfahan University of Medical Sciences, Isfahan, Iran

4 Department of Biostatistics and Epidemiology, School of Health, and Psychosomatic Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

(PP), and butylparaben (BP) are among the most commonly used paraben derivatives [1, 5]. Recent studies have reported that parabens exposure leads to endocrine disruption and potentially harmful effects on human health. However, there are public concerns in recent decades regarding human exposure to these compounds, and epidemiological studies have reported the association between parabens exposure and potentially harmful consequences on human health. There were also reports on their potential harmful impacts on efficacy of the endocrine system, estrogenic [6, 7] and anti-estrogenic activity [8, 9], lead to impairment of male reproductive system [5, 8], breast cancer [7, 10, 11], and the association between birth outcomes and maternal exposure to parabens during pregnancy [12–15]. Human exposure to paraben compounds often occurs through the consumption of products containing these compounds, including foodstuffs, cosmetics, and pharmaceuticals [2, 4, 16, 17]. The urinary excretion is the major route of eliminating parabens and their metabolites. These compounds are excreted from the body in a mixed manner shortly after exposure and are therefore known as biomarkers in biomonitoring studies [18–23]. Biomonitoring can be used to estimate the cumulative exposure of humans to such pollutants [24]. Results of previous studies indicated widespread exposure and different patterns of distribution of urinary parabens among the population of different countries. These differences may be due to demographic and lifestyle differences as well as different patterns of exposure to parabens [25–27]. Therefore, it is important to understand the profiles of environmental exposure to parabens in vulnerable populations, especially in developing countries where exposures remain largely uncharacterized and the relationship of these compounds with various factors are unclear [28–30]. By now, only limited study exist in Iran reporting the urinary parabens level in association with socio-demographic and lifestyle factors, as well as their estimated daily intake (EDI). Therefore, further studies are needed to provide epidemiological information and shed light on the rate of exposure to parabens in Iranian population. According to the mentioned notes, the main goal of this study was to investigate urinary concentrations of four common parabens (MP, EP, PP and BP) in adult volunteers from Iran. Besides, we aimed to identify some socio-demographic and lifestyle determinants of exposure to parabens in order to set the basis for a large-scale biomonitoring study in Iran.

Materials and methods

Study population

This cross-sectional study was performed on people referring to health centres covered by Isfahan University of Medical Sciences. Participants were selected from health centres located in different areas of Isfahan city by multistage cluster random sampling with age and sex stratification. This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (Code: IR.MUI.RESEARCH.REC.1397.339). All participants completed the consent form before recruitment in the study. A total of 200 questionnaire containing demographic data, anthropometric factors and lifestyle information, and also zone and date/hour of sampling and other required parameters were completed for the participants by a trained expert in a face-to-face manner. Inclusion criteria were a minimum age of 20 years, the residence of more than one year in the current place, no history of chronic diseases, and no long-term medication. Lack of these criteria, incomplete checklists, and failure to deliver urine samples were considered as exclusion criteria. Anthropometric data, including weight, height, and waist circumference of participants were measured using calibrated instruments and following the standard protocols. Body mass index (BMI) was calculated by division of weight (kg) to squared height (m^2). BMI categorized as underweight (BMI < 18.5), normal weight (18.5 ≤ BMI < 23.0), overweight (23.0 ≤ BMI < 25.0) and obese (BMI ≥ 25.0) (25). Sampling was carried out from five regions (centre, east, west, north, and south) in the city based on different seasons of a year. Participants were categorized into three levels of education namely; lower than high school diploma, high school diploma, and upper than a high school diploma. The economic condition was categorized into low income (< 300$), middle income (300–1000$), and high income (> 1000$) based on their monthly income level. Data on tobacco use (cigarettes and hookah) were also categorized as current smokers, former smokers, and non-smokers.

Sampling and analysis

In this study, single-point urine samples were collected in pre-cleaned polypropylene containers in the early morning. The samples were coded, and transferred to the laboratory of Isfahan University of Medical Sciences under standard conditions. To determine the strength of urine samples and compensate any error of spot sampling, 5 ml of each sample was isolated for creatinine analysis. Hitachi 704 auto-analyzer (Jaffe Methodology) was used to measure the urinary creatinine levels of the samples. After analysis, the parabens concentrations were adjusted per unit mass of creatinine (μg per g of creatinine) [31]. All samples were kept at -70 °C until analysis of urinary concentrations of parabens. The standard solutions of MP, EP, PP, and BP were prepared in methanol and stored in dark glass containers at temperatures below zero. To determine MP, EP, PP, and BP levels, the urine samples were extracted using dispersive liquid-liquid micro-extraction (DLLME) and analyzed using GC/MS [32–35]. Briefly, we added 50 μL of the beta-glucuronidase solution to 1 ml of the urine sample, and incubated at 37 °C for 24 hours. After incubation, 0.1 g NaCl was added to each sample and centrifuged for 5 minutes. Then, the supernatant was transferred into a new 10 ml falcon. To form a cloudy state, chlorobenzene (30 µl) and acetone (500 µl) were rapidly injected into the falcon containing the urine sample. The formed cloud solution was then centrifuged for 5 minutes at 5000 rpm. Afterwards, a syringe was used to remove the 50 µl droplet formed at the end of the falcon tube and pour it into a vial. Then, it was dried with a slow flow of nitrogen gas. Later, the parabens were derivatized using N-methyl-N-trimethylsilyl trifluoroacetamide (MSTFA) to render them to be sufficiently volatile decreasing their elution temperature and adsorption in the GC column. 20 µl of MSTFA was injected into the vial and a vortex was used to prepare the complete mixture. Finally, 2µL of the mixture was injected into the GC/MS for analysis. The GC/MS settings and other parameters optimization were carried out based on similar previous studies [33, 34, 36, 37].

In this study, the paraben concentration range of 0.01–1000 ng/ml was used to draw the calibration curve of the device. The linear regression gave a good fit (R^2: 0.994 for MP, 0.989 for EP, 0.992 for PP, and 0.999 for BP) with high precision (≤ 8.4% RSD). The recovery of spiked samples was > 89% for all the analyzed compounds. Limit of detection (LOD) and limit of quantification (LOQ) of parabens were determined based on the lowest acceptable point on the calibration curve with a signal-to-noise ratio of 3 and 10, respectively, from the replicate analysis (n = 05) of standard solution at a concentration of 10 ng/ml. The LOD and LOQ values for MP, EP, and PP were 0.014 and 0.046, respectively, and those for BP were 0.049 and 0.154 ng/ml, respectively.

Calculation and statistical analysis

To evaluate the extent of exposure to parabens, EDI for MP, EP, PP, and BP was calculated based on previous studies and Eq. 1 [38].

$$EDI = \frac{C \times R}{F \times BW} \tag{1}$$

where, EDI (µg /kg-bw/day) is estimated daily intake of parabens, C (µg/L) denotes the urinary concentration of parabens, R (L/day) is the total volume of urine of an adult per day, F (dimensionless) is the paraben excretion factor, and BW (kg) is the bodyweight which was considered as 72.4 kg for the whole population, and 68 kg and 78.4 kg for females and males, respectively (Table 1). F for MP, EP, PP, and BP was equal to 17.4, 13.7, 10.2 and 6.8, respectively, according to previous studies [38, 39]. In this study, the R for our target population was calculated at 1.7 L/day based on similar studies [39, 40].

Data analysis was performed using SPSS software (SPSS, Inc., Chicago IL, USA; version 16). Sample size in the current study was determined based on the formula for estimating the mean difference of parabens levels in different categories of demographic and lifestyle variables; by considering type one error rate 0.05, statistical power 80% for detecting a standardized mean difference 0.3 (based on previous studies) led to 220 samples [41, 42]. To adjust the dilution difference in urine samples, urinary concentrations of parabens was adjusted with urine creatinine level. Kolmogorov-Smirnov test and Q-Q plot were used to determine the normal distribution of continuous variables. The distribution of parabens in the present study was positively skewed; accordingly logarithmic transformation was used to normalize the data. Continuous and categorical data were reported as mean, standard deviation, (and median, geometric mean (GM), minimum, maximum and some specific percentiles for non-normally distributed continuous variables), and frequency (percentage), respectively. Comparison of numerical variables at the level of qualitative variables was performed using independent sample t-test, and Multivariate Analysis of Covariance (MANCOVA). Spearman correlation coefficient was also used to investigate the relationship between numerical variables. All tests were two-tailed tests and $p < 0.05$ was considered as the statistical significance level.

Results

Of the 200 volunteers in this study, 22 of them lacked complete data or optimum urine samples so that laboratory and statistical analysis were performed for 178 participants. Table 1 presents the anthropometric and socio-demographic characteristics of the study population. Out of 178 participants, 103 (57.9%) were female and 75 (42.1%) were male. The mean age of participants was 43.7 ± 11.8 years, and their mean BMI was 26.4 ± 2.3 kg / m^2.

Table 2 presents both unadjusted and creatinine-adjusted urinary concentrations of parabens in Iranian adults. All four parabens were identified in most of the samples collected in this study. The detection frequency (DF) of MP, EP, PP, and BP in urine samples was 98.9%, 91%, 94.3%, and 88.2%, respectively. The highest unadjusted concentration of urinary parabens in this study belonged to MP (median = 69.06 µg / L). The median unadjusted concentrations of PP, EP, and BP were 9.10, 12.40, and 9.87 µg/L, respectively.

The urinary concentrations of parabens in the two sex groups and their comparative results are reported in Table 3. As can be observed, the concentrations of all parabens in males are lower than those in females. For example, the median urinary MP concentration was 60.12 µg/L in males and 83.85 µg/L in females. The statistical analysis showed a significant difference between both sexes in terms of MP and PP concentrations (P = 0.029 and P = 0.004, respectively).

The results presented in Table 4 show that the urinary parabens measured in the study participants differ from

Table 1 Socio-demographic characteristics of a population of Iranian adults participating in this study

Characteristics	Subgroup	Number	Percent	Mean(S.D)
Sex	Female	103	57.9	-
	Male	75	42.1	-
weight (kg)		178	100	72.4 ± 13.7
height(m)		178	100	1.66 ± 0.09
waist(cm)		178	100	89.6 ± 12.1
Pregnancy		34	-	-
Age(year)	All	178	178	43.7 ± 11.8
	21–35	48	27	30.65 ± 3.3
	36–50	88	49.4	42.81 ± 4.5
	> 50	42	23.6	60.57 ± 7.3
BMI (kg/m^2)	All	178	100	26.2 ± 4.3
	≤ 18.5	7	3.9	18.4 ± 0.7
	18.5-22.99	34	19.1	21.54 ± 1.0
	23-24.99	31	17.4	23.9 ± 0.7
	≥ 25	106	59.6	28.9 ± 3.3
Education	< High school diploma	48	27	-
	High school diploma	61	34.3	-
	>High school diploma	69	38.7	-
Occupational class	housewives	54	30.3	-
	Outside workers	89	50	-
	Students	35	19.7	-
Household income (US$/month)	Low (< 299)	39	21.9	-
	Moderate (299–999)	123	69.1	-
	High (> 1000)	16	9	-
Time of sampling	Spring	44	24.7	-
	Summer	45	25.3	-
	Autumn	45	25.3	-
	Winter	44	24.7	-
Location	North	35	19.7	-
	South	36	20.2	-
	East	36	20.2	-
	West	36	20.2	-
	Center	35	19.7	-
Smoking status (Cigarette &Hookah)	Current	22	12.4	-
	Former	18	10.1	-
	Never	138	77.5	-
Physical Activity	Low	109	61.2	-
	Moderate	48	27	-
	High	21	11.8	-

that reported in other countries. The highest urinary concentration of MP and EP has been reported in a study performed in Korea [41] while the highest urinary concentration of PP and BP was observed in the present study (Table 4). Also in this study, the median urinary concentrations of MP, PP, EP, and BP were higher than those reported in the US, Belgium, China, and Denmark [21, 22, 43, 44]. Figure 1 presents the composition profile of parabens (median concentrations) amongst the population of different countries. The results presented in Fig. 1 show that the distribution pattern of urinary parabens was different in Iranian population compared to other countries. The proportion urinary of MP, PP, EP, and BP were 68.8, 9.1, 12.3 and 9.8% among the Iranian adults respectively. The proportion urinary of BP in Iranian adults was much higher than in other countries.

Table 2 Parabens concentrations in urine samples of Iranian adults

Paraben	Concentration type	LOD	DF(%)	Mean (SD)	GM	Min	25P	50P	75P	95P	Max
MP	Unadjusted (μg/L)	0.01	98.9	192.05(299.64)		<LOD	27.46	69.06	227.47	927.03	1588.2
	Creatinine adjusted (μg/g)			190.28(245.20)	80.61	<LOD	28.02	94.12	257.57	760.02	1430.60
EP	Unadjusted (μg/L)	0.02	91	27.51 (52.25)		<LOD	2.36	9.10	26.96	146.70	431.3
	Creatinine adjusted (μg/g)			29.24 (55.26)	4.22	<LOD	2.48	9.82	29.00	172.20	418.74
PP	Unadjusted (μg/L)	0.02	94.3	31.68 (41.45)		<LOD	3.21	12.40	46.85	129.07	190.7
	Creatinine adjusted (μg/g)			32.24 (39.71)	7.95	<LOD	3.93	17.00	48.19	121.90	244.07
BP	Unadjusted (μg/L)	0.05	88.2	16.73 (24.66)		<LOD	1.28	9.87	20.72	59.04	195.8
	Creatinine adjusted (μg/g)			19.86 (33.38)	4.57	<LOD	1.45	8.54	25.79	74.70	281.51

DF: Detection Frequency (%); GM: Geometric Mean; P: Percentile.

The results of the bivariate correlation analysis showed a significant positive correlation between the parabens (Table 5). The results of the present study revealed a strong positive significant correlation between MP and PP ($r = 0.638$). BP had a statistically moderate significant correlation with MP, PP and EP, and a slightly lower correlation between EP with MP and PP was observed. The urinary concentrations of parabens were not significantly correlated with BMI and waist circumference, however, there was a significant negative correlation between age and urinary concentrations of MP, PP, and BP ($r = -0.223, -0.288, -0.277$).

The urinary concentrations of parabens based on different sociodemographic and lifestyle categories of the study population and season and location of sampling are presented in Table 6. The results showed a significant difference between age groups in terms of urinary concentrations of parabens. The present study showed significantly higher urinary concentrations of MP, PP, and BP in the younger age group (21–35 years) than those in the older age groups ($p < 0.05$). The median concentrations of MP, PP and BP in the age group of 21–35 years were approximately 5 times higher than those in the age group above 50 years. Concerning BMI, there was a statistically significant difference between different BMI groups in terms of urinary MP concentrations ($p = 0.026$) so that the highest urinary MP concentration was observed in the lower BMI group. Comparing urinary concentration of parabens during different seasons indicated that urinary concentrations of MP, PP, and BP were significantly higher in spring than in other seasons. There was no significant difference between educational level, smoking, place of residence, and physical activity in terms of urinary concentrations of parabens. However, Urinary PP and BP concentrations were slightly higher (marginally significant: $p < 0.1$) in the student occupational category than in other occupational categories. Moreover, urinary concentrations of MP, EP, and PP were higher in individuals with higher household income than other income groups, which was marginally significant ($p < 0.1$).

In this study, we determined the extent of exposure to parabens using EDI equation [38]. The EDI values determined for this study and those for other countries are reported in Table 7. According to the results, the highest and the lowest EDI values calculated in this study belonged to MP and EP, respectively. Mean EDI values for MP in females, males and the whole population were 25.9, 30.9, and 20.1 μg/kg-bw/day,

Table 3 Comparison of urinary concentrations of parabens by sex

Parabens		Unadjusted (μg/L)			Creatinine adjusted (μg/g)				
		Mean ± SD	GM	Median(min-max)	Mean ± SD	GM	Median(min-max)	Mean Dif.	*P*
MP	Female	215.08 ± 317.83	86.72	83.85(< LOD-1588.17)	218.67 ± 270.24	101.54	124.19(0.01-1430.60)	0.54	**0.029***
	Male	160.42 ± 271.59	56.14	60.12((< LOD-1455.99)	151.28 ± 201.20	58.71	56.72(0.01-887.97)		
EP	Female	28.28 ± 57.68	3.83	9.31(< LOD-431.30)	30.87 ± 62.29	4.48	10.11(< LOD-196.39)	0.14	0.754
	Male	26.44 ± 44.07	3.71	8.89(< LOD-197.56)	27.00 ± 44.13	3.88	9.31(< LOD-196.39)		
PP	Female	37.34 ± 44.48	10.94	16.07(< LOD-183.43)	38.97 ± 44.99	12.81	19.25(0.01-244.07)	1.13	**0.004***
	Male	23.91 ± 35.73	3.95	8.35(< LOD-190.67)	23.01 ± 28.86	4.13	11.27(< LOD-149.57)		
BP	Female	17.10 ± 25.66	4.72	11.06(< LOD-195.78)	21.59 ± 39.17	5.53	12.72(0.02-281.51)	0.45	0.216
	Male	16.22 ± 23.37	3.37	8.03(< LOD-141.77)	17.50 ± 23.27	3.52	7.21(0.01-105.01)		

*Mean differences are significant at the 0.05 level (2-tailed). *P*-values resulted from independent samples t-test after normalizing the distribution of parabens

Table 4 Urinary concentration of parabens measured in Iran in comparison with those reported from other countries

Country	Year	N	Population	Median urinary paraben concentration µg/L (%>LOD)				Ref
				MP	EP	PP	BP	
Belgium	2013	261	General population	16.1 (100%)	1.7 (96.6%)	1.2 (83.1%)	<LOD (41.8%)	[43]
Spain	2011	251	Young Men	17 (92%)	1.8 (75%)	0.7 (60%)	<LOD (9%)	[47]
USA	2005–2006	702	Adolescents	53.5 (99.1%)	0.20 (92.7%)	8.40 (42.4%)	<LOD (47%)	[21]
Saudi Arabia	2014	130	General population	11.7 (100%)	0.23 (87.7)	1.66 (85.4%)	0.15 (11.5%)	[45]
Korea	2010	359	Adolescents	135 (97.7%)	21.7(97.2%)	6.54 (96.7%)	0.33 (93.5%)	[41]
China	2010	109	young adults	4.63 (100%)	1.4(100%)	3.17(100%)	0.05(60%)	[22]
Greece	212	100	General population	11.6 (100%)	2.0(87%)	5.3(72%)	0.9(46%)	[46]
Denmark	2012	129	Children &Adolescent	7.7 (95.3%)	0.58(59.7%)	1.02(64.3%)	-	[44]
Tunisia	2012	34	women	34.94 (94.1%)	1.77 (67.6%)	3.06 (70.6%)	< 0.2 (38.2%)	[30]
Iran	2018	178	Adults	69.06(98.9%)	9.10(91%)	12.40 (94.3%)	9.87 (88.2%)	This study

respectively, and for EP were 4.72, 5.16, and 4.19 µg/kg-bw/day, respectively. The median EDI calculated for the whole population in Iran was higher than that in Germany [38], India, China, and Saudi Arabia [39], and less than that in the US [21] and South Korea [39]. In this study, the median EDI in males was higher than that reported in Germany[38] and China [48]. Inconsistent with our results, the median EDI of parabens in females was higher in Yu study than in our study, and the highest median EDI (24.6 µg/kg-bw/day) was reported for MP [48] (Table 7). The Acceptable Daily Intake (ADI) value was determined 10,000 µg /kg-bw/day for MP and EP [49] and 100 µg/kg-bw/day for PP alone based on the Non-Observable Effect Level (NOEL) [39].

Discussion

Due to the lack of research and information on urinary concentrations of parabens in the Iranian adults as well as the extent of their exposure to parabens, the present cross-sectional study measured for the first time the urinary concentrations of parabens and calculated exposure levels in a population of Iranian adults. Furthermore, some factors affecting the parabens concentration including socio-demographic and lifestyle were investigated. In this study, significant concentrations of parabens were measured in most the urine samples and MP was higher than the other urinary paraben compounds. The high concentration and detection frequency of urinary parabens in the present study indicate a wide exposure to the parabens from various sources. In similar studies, high urinary concentrations and detection frequency of MP have been reported [21, 22, 50]. According to the comparative table (Table 4), the overall composition of urinary parabens measured in adults in this study was different from the results reported by some other studies. The urinary concentrations of MP and EP reported in South Korea [41] were approximately 2 folds of the amounts obtained in the present study. On the contrary, the PP and BP concentrations in our study

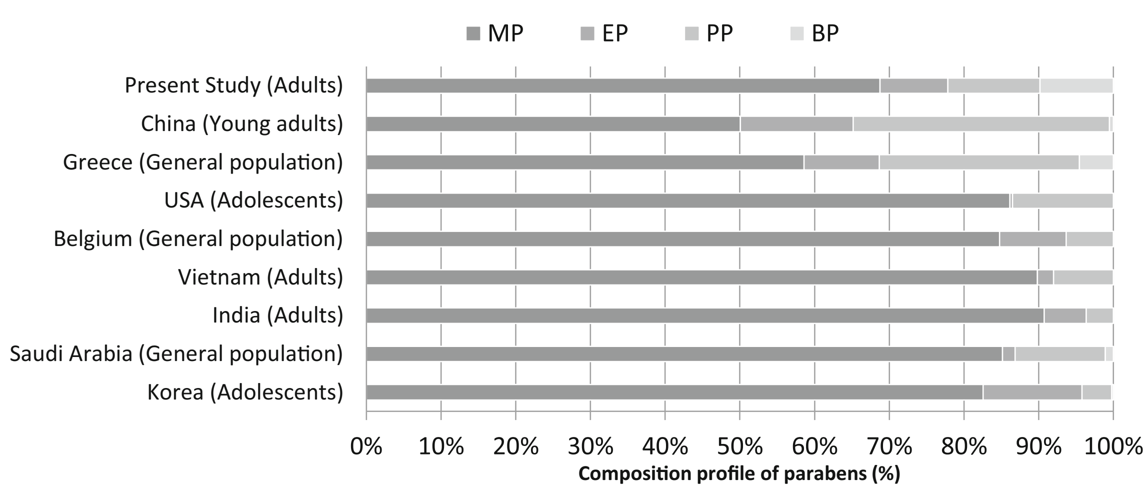

Fig. 1 Composition profile of parabens (median concentrations) amongst population of different countries derived from: [21, 22, 39, 43, 45, 46]

Table 5 Correlation coefficient between urinary parabens and demographic and anthropometric variables of Iranian adults

	MP	EP	PP	BP
Age	-0.223**	-0.095	-0.288**	-0.277**
BMI	-0.034	-0.089	-0.042	-0.004
Waist	-0.082	-0.071	-0.071	-0.115
MP	1	0.357**	0.638**	0.482**
EP		1	0.306**	0.403**
PP			1	0.524**
BP				1

**Correlation is significant at the 0.01 level (2-tailed),

*Correlation is significant at the 0.05 level (2-tailed)

The Spearman rank correlation coefficient was reported.

were approximately 2 and 20 times higher than those reported in the South Korean, respectively. Also, the urinary MP and PP concentrations measured in the present study were higher than those reported in Tunisia, Greece, China, Saudi Arabia, Belgium and Denmark [22, 30, 43–46]. The urinary BP concentrations (Median = 9.87 μg/L) in the present study was higher than those reported in other countries [30, 41, 45, 46]. This may be due to the highest frequency of detection of BP in this study. Besides, several factors, e.g. the methodologies used in collecting urine samples and the time of sample collection may influence the concentrations in different studies. The distribution pattern of urinary parabens was different in Iranian population compared to other countries, indicating different patterns of exposure in Iran. The variation of reported levels may be due to differences in analytical methods or study designs. Also, different socio-economic and geographical characteristics of societies may influence the change in patterns of exposure to the compounds [35]. Another reason for such differences might be due to the significant differences in lifestyle, including the frequency of makeup and PCPs use and exposure through food sources containing paraben preservatives. Furthermore, chemical legislation and temporal trends vary between countries.

The results showed a significant positive correlation between all the measured parabens (Table 5). Similar to previous studies, we observed strong correlations between the concentrations of MP and PP ($r = 0.638$), most likely due to the simultaneous use of MP and PP in many consumer products owing to they antimicrobial effects [5]. In the Ma study, no significant correlation between MP and EP, as well as between PP and EP has been reported [22]. Similar to the results reported in the study in the US [21], our study also showed a statistically moderate significant correlation between BP with MP, PP and EP. Moreover, a slightly lower correlation between EP with MP and PP was observed.. These findings suggest concomitant exposure of the Iranian population to several parabens, as these compounds are used in combination with various consumer products.

The results of this study showed a higher urinary concentration of parabens in females. Also, statistically significant differences were observed between the two sexes in terms of urinary levels of MP and PP. Similarly, several studies have reported different urinary concentrations of parabens for males and females [22, 44]. This was relatively consistent with the level of PP and MP in the previous study for the US population [21]. Another study showed no statistically significant difference between the two sexes in terms of urinary levels of parabens [51]. The differences in urinary parabens between the sexes were not the same in different societies. These differences may be related to varying exposure to paraben compounds because of lifestyle factors or behavioural differences [38]. Since PCPs are more commonly used by females than males, and these products are one of the most important sources of exposure to parabens, females are more likely exposed to parabens [5, 21, 22].

In this study, a negative significant association was found between age and the urinary concentrations of MP, PP, and BP ($p > 0.05$). The results also demonstrated a negative significantly weak correlation between age and concentrations of MP, PP, and BP (Table 5). Similarly, in Denmark, urinary levels of parabens were higher in younger individuals and a significantly negative relationship has been reported [44]. In the other study, Honda et al. (2018) showed no significant relationship between urinary concentrations of parabens and age [39]. Contrary to our results, in South Korea and the United States, urinary concentrations of parabens were higher in older individuals and the concentration differences were statistically significant at different age groups [21, 41, 52]. A change in the urinary concentration of parabens with age is predictable due to the different extent of exposure to parabens. The change in the extent of exposure to paraben compounds is probably due to a change in lifestyle, followed by a change in the amount and type of PCPs consumed throughout a person's life. Accordingly, the higher urinary concentration of parabens in younger individuals in the Iranian population is likely due to their greater exposure to paraben compounds in a variety of ways, including higher consumption of PCPs or foods containing parabens. Besides, individual differences and metabolic pathways of parabens in the human body can be other causes of differences in the urinary concentrations of parabens in different age groups [41].

The present study showed a statistically significant difference ($p < 0.05$) between people with different BMI values in terms of urinary concentrations of MP. Similar results also have been reported by the other studies conducted on adolescents in Iran [50] and in the US population [52, 53]. In other studies, some opposite results have also been reported. In this regard, Smith et al. (2012) and Kang et al. (2016) have reported a significant negative association between the urinary

Table 6 Urinary concentration of parabens (μg/g) based on demographic characteristics and lifestyle in the study population

characteristics	N	MP			EP			PP			BP		
		Mean ± SD	Median (Min-Max)	P	Mean ± SD	Median (Min-Max)	P	Mean ± SD	Median (Min-Max)	P	Mean ± SD	Median (Min-Max)	P
Age													
21–35	48	273.66 ± 321.10	151.35(2.18-1430.60)	**0.012***	29.44 ± 45.08	13.51(< LOD-232.63)	0.535	50.14 ± 51.06	38.76(0.02-244.07)	**0.001***	30.65 ± 52.63)	16.07(0.042–281.51)	**0.000***
36–50	88	178.75 ± 226.66	76.60(0.01-1040.80)		22.79 ± 36.33	8.48(< LOD-225.29)		27.42 ± 32.49	11.82(< LOD-127.94)		17.50 ± 21.47	12.81(< LOD-123.04)	
> 50	42	119.14 ± 136.90	51.19(0.01-614.28)		42.50 ± 88.23	10.43(< LOD-418.74)		21.90 ± 32.33	6.40(0.01-149.57)		12.49 ± 21.30	2.54(0.02-105.01)	
BMI													
≤ 18.5	7	642.04 ± 580.88	386.70(106.74-1430.60)	**0.026***	29.88 ± 25.20	28.24(5.09–64.76)	0.188	62.78 ± 58.27	31.66(4.64-144.43)	0.091	21.79 ± 13.26	17.65(6.83–41.78)	0.427
18.5–22.9	34	199.26 ± 199.52	123.59(11.66-189.22)		29.12 ± 36.17	20.53(0.01-189.22)		43.49 ± 44.46	31.55(0.02-150.84)		30.78 ± 61.19	6.13(0.03-281.51)	
23-24.9	31	215.32 ± 290.49	96.71(3.53-1040.80)		28.22 ± 51.76	9.19(< LOD-225.29)		33.45 ± 38.51	24.45(0.01-149.57)		16.95 ± 18.41	12.89(0.02–75.97)	
> 25	106	150.24 ± 173.24	71.76(0.02-801.81)		29.53 ± 62.72	7.81(< LOD-418.74)		26.27 ± 35.77	11.20(< LOD-244.07)		17.09 ± 23.37	7.75(< LOD-123.04)	
Education													
<High school diploma	48	156.02 ± 175.65	90.85(0.01-801.81)	0.350	39.06 ± 84.99	9.19(< LOD-418.74)	0.963	29.70 ± 45.41	11.39(0.01-244.07)	0.130	16.78 ± 25.01	6.79(0.02-123.04)	0.777
High school diploma	61	238.49 ± 290.95	145.09(2.18-1430.60)		28.85 ± 44.64	11.70(< LOD-225.29)		32.64 ± 37.92	21.51(< LOD-144.43)		23.33 ± 36.01	13.58(< LOD-227.65)	
> High school diploma	69	171.48 ± 239.19	66.25(0.01-1402.42)		22.75 ± 32.98	9.78(< LOD-189.22)		33.67 ± 37.47	17.98(0.01-149.91)		18.95 ± 36.14	8.20(0.02-281.51)	
Occupational class													
Homemakers	71	213.17 ± 260.56	131.04(0.01-1430.60)	0.380	35.07 ± 72.46	10.11(< LOD-418.74)	0.940	38.77 ± 46.40	19.83(0.01-244.07)	0.085	21.49 ± 33.89	12.72(0.03-227.65)	0.071
Outside workers	98	167.82 ± 234.60	58.57(0.01-1402.42)		24.89 ± 38.60	9.70(< LOD-196.39)		27.01 ± 34.32	12.68(< LOD-149.91)		18.29 ± 33.38	7.81(< LOD-281.51)	
Students	9	254.21 ± 231.17	255.51(2.18–712.00)		30.57 ± 55.02	8.00(0.01-171.79)		37.75 ± 32.07	33.97(0.10–95.70)		24.15 ± 31.98	19.46(0.45–103.50)	
Physical Activity													
Low	109	195.63 ± 239.63	96.71(0.01-1430.60)	0.912	29.52 ± 59.54	9.87(< LOD-418.74)	0.996	36.38 ± 44.03	19.83(< LOD-244.07)	0.510	18.50 ± 24.55	11.49(< LOD-123.04)	0.602
Moderate	48	185.23 ± 269.93	98.01(0.01-1402.42		30.81 ± 51.41	9.71(< LOD-225.29)		28.01 ± 34.82	9.32(0.01-123.01)		27.29 ± 51.58	11.45(0.03-281.51)	
High	21	174.01 ± 224.26	73.76(14.21-887.97)		24.19 ± 40.48	9.62(0.01-171.79)		20.43 ± 18.84	15.88(0.01–55.62)		9.97 ± 10.58	5.25(0.02–33.71)	
Period of sampling (Seasons)													
Spring	44	255.85 ± 199.91	221.27(17.88-887.97)	**0.001***	44.45 ± 84.02	17.05(< LOD-418.74)	0.162	53.58 ± 50.68	44.17(0.01-244.07)	**0.001***	28.06 ± 23.20	24.64(0.03-113.99)	**0.001***
Summer	45	217.69 ± 345.52	53.52(2.21-1430.60)		29.05 ± 49.89	8.16(< LOD-225.29)		24.47 ± 28.10	13.00(0.01-110.45)		10.11 ± 17.86	4.78(0.02-105.01)	
Autumn	45	147.80 ± 199.87	69.77(11.36-817.97)		21.61 ± 36.97	8.76(0.01-196.39)		24.46 ± 29.60	11.14(< LOD-114.09)		15.16 ± 21.61	8.20(< LOD-123.04)	
Winter	44	140.11 ± 186.63	53.98(0.01-739.47)		22.01 ± 34.87	9.92(< LOD-189.22)		26.81 ± 39.95	6.27(0.01-150.84)		26.45 ± 54.86	6.74(< LOD-281.51)	
Location													
North	36	172.30 ± 188.55	111.33(2.21-762.56)	0.964	23.09 ± 71.10	5.43(< LOD-418.74)	0.060	31.20 ± 37.03	19.83(< LOD-150.84)	0.952	18.59 ± 38.86	5.98(< LOD-227.65)	0.976
South	35	158.52 ± 151.77	69.21(11.74-550.39)		29.04 ± 49.47	10.62(< LOD-189.22)		29.80 ± 38.29	12.72(0.01-149.57)		12.93 ± 16.41	6.09(0.02–75.97)	
East	35	249.08 ± 289.09	146.67(0.011040.80)		34.64 ± 66.00	12.55(0.01–312.60)		39.48 ± 43.76	17.59(0.01-149.91)		23.31 ± 28.58	17.77(0.02-123.04)	
West	35	161.98 ± 214.07	86.26(2.18-801.81)		22.99 ± 43.70	6.99(< LOD-232.63)		31.41 ± 44.80	21.55(0.01-244.07)		26.21 ± 51.78	7.94(0.02-281.51)	
Center	36	209.53 ± 337.98	70.16(3.53-1430.60)		36.47 ± 41.34	23.25(0.01-196.39)		29.21 ± 34.92	8.91(0.01-124.66)		18.21 ± 17.41	15.57(0.01–73.43)	
Family Monthly income													
Low(< 299 US$/month)	39	130.41 ± 168.01	66.40(2.18-887.97)	0.096	10.65 ± 14.93	5.43(< LOD-69.89)	0.081	27.29 ± 29.32	15.91(0.01-109.23)	0.085	17.75 ± 23.28	8.86(0.02-123.04)	0.536
Moderate(299-999US/month)	123	188.71 ± 238.71	91.52(0.01-1402.42)		33.24 ± 60.64	10.32(< LOD-418.74)		29.84 ± 35.62	13.00(< LOD-149.91)		19.09 ± 35.55	7.42(< LOD-281.51)	
High (> 1000 US$/month)	16	348.21 ± 372.21	268.33(19.20-1430.60)		43.75 ± 67.01	25.06(0.01-232.63)		62.84 ± 70.74	26.58(2.64-244.07)		30.96 ± 36.79	14.23(0.03-113.99)	
Smoking status(Cigarette & Hookah)													
Current	22	325.28 ± 397.79	73.29(2.18-1402.42)	0.912	46.12 ± 60.37	22.02(< LOD-181.08)	0.473	27.68 ± 34.91	14.13(< LOD-110.45)	0.178	14.57 ± 14.50	12.53(< LOD-45.40)	0.603
Former	18	200.52 ± 336.44	90.85(17.03-1430.60)		18.51 ± 21.54	7.81(< LOD-66.74)		35.82 ± 43.26	25.18(0.02-127.94)		16.48 ± 16.60	12.81(0.03–40.45)	
Never	138	167.42 ± 189.50	100.01(0.01-1040.80)		27.94 ± 57.15	9.66(< LOD-418.74)		32.51 ± 40.17	17.00(0.01-244.07)		21.15 ± 36.96	8.20(0.02-281.51)	

*Mean differences are significant at the 0.05 level (2-tailed) ($p < 0.05$). The p-values resulted from MANCOVA, the adjustment was made for age and gender as a covariate

Table 7 Estimated daily intake (EDI) (μg/kg-bw/day) of parabens in Iranian people and comparison with other countries

Country	year	Gender	MP			EP			PP			BP			
			Mean	Median	P.95	Mean	Median	P.95	Mean	Median	P.95	Mean	Median	P.95	Ref
Iran	2018	Male &Female	25.9	9.32	125	4.72	1.56	25.1	7.30	2.85	29.7	5.78	3.42	20.4	This study
		Female	30.9	12.1	148	5.16	1.70	29.1	9.15	3.94	32.4	6.29	4.07	20.35	
		Male	20.1	7.49	99.7	4.19	1.41	23.6	5.08	1.77	22.9	5.17	2.56	19.4	
China	2013–2015	Female	11.4	24.6	66.6	18	38.4	134	9.03	28.2	145	-	-	-	[48]
		Male	6.67	1.64	30.1	7.55	1.07	77.8	12.2	0.26	56.4	-	-	-	
Germany	1995–2012	Male &Female	-	3.0	31.7	-	0.2	3.4	-	0.3 [a]	11.9 [a]	-	0.1 [b]	2.2 [b]	[38]
	2012	Female	-	9.7	43.5	-	1.3	19.8	-	2.7 [a]	21 [a]	-	0.2 [b]	10.1 [b]	
		Male	-	6.3	21	-	NA	1.5	-	NA [a]	6.5 [a]	-	0.1 [b]	0.9 [b]	
USA	2006	Male &Female	64.8	75.8	-	-	-	-	9.6	12.0	-	-	-	-	[21]
Korea	2010–2012	Male &Female	-	21.5	-	-	7.97	-	-	15.5	-	-	-	-	[39]
China	2010–2012	Male &Female	-	1.93	-	-	0.67	-	-	3.24	-	-	-	-	
Saudi	2010–2012	Male &Female	-	1.30	-	-	0.05	-	-	0.19	-	-	-	-	
USA	2010–2012	Male &Female	-	0.81	-	-	0.07	-	-	0.23	-	-	-	-	
India	2010–2012	Male &Female	-	1.20	-	-	0.06	-	-	0.13	-	-	-	-	

levels of parabens (MP and PP) and BMI among obese subjects compared to those had normal weight [41, 54]. Differences in the concentration of parabens between different BMI categories may be due to different exposure patterns to the sources of parabens such as PCPs, medications or foods containing parabens. This may also be due to different pharmacokinetics and metabolic pathways in the body of individuals with different BMI values.

We also examined the association between tobacco use and urinary concentrations of parabens. Despite the higher urinary concentrations of parabens in tobacco users, no significant association was found. These results were in agreement with the results of Yu' study in China [48]. The results of another study in China showed a significant negative association between urinary MP concentrations and smoking [55]. In contrast, the results of Geer's study showed that MP and PP concentrations were higher in smokers than in non-smokers [13]. It has been hypothesized that smoking may induce enzymes that accelerate the clearance rate of parabens [56]. Further epidemiological studies are needed to determine the precise effect of smoking on the urinary parabens concentrations. Our results showed that the urinary concentrations of MP, PP, and BP were significantly higher in spring than other seasons. Similarly, some previous studies, have shown the higher levels of urinary MP in spring than the other seasons [27, 35]. Results of another study showed a lower urinary level of MP in autumn and higher urinary level of BP in summer [57]. As usage patterns might differ by country, the association among variables may also vary. These differences can be due to the changes in the rate of use of cosmetics and foodstuffs as well as probably the changes in lifestyle habits. In Iran, it might be due to higher consumption of cosmetics and other PCPs during Iranian New Year celebrations (Nowrooz) held in early spring.

In this study, participants from the high-income group had higher urinary concentrations of parabens, but no significant association between family income and the urinary parabens concentrations was observed ($p > 0.05$). In agreement with our results, In South Korea [41] and China [55], no significant association was found between income level and urinary concentration of parabens. On contrast to our results, Calafat et al. (2010) found significantly higher urinary MP and PP concentrations among the high-income group [21]. The probable reason for the lack of this relationship in our study may be due to the larger number of people in the middle-income class (70%) and the uneven distribution of participants in different income groups.

There was no significant association between the urinary concentration of parabens and the level of participants' education. Similarly, In another study in Shanghai, the urinary concentration of parabens was not significantly associated with income and education levels of the study population [55]. The results of a study in China showed that people with tertiary education had a lower urinary concentration of PP than people with a lower level of education [48]. In contrast, in a study on the US population, people with a higher level of education had higher urinary concentrations of MP and PP. This is in agreement with the results of other studies conducted in South Korea [41]. However, there is no consensus regarding the effect of level of education on the urinary parabens concentration. Based on our results, most likely, the level of education are interlinked with other lifestyle factors and there is no significant association between educational level and urinary parabens concentration.

In this study, we observed no significant association between the intensity of physical activity and the urinary concentration of parabens ($p > 0.05$). Results of another study showed a significant negative association of physical activity with urinary concentrations of parabens [27]. However, positive associations have been reported between urinary MP and BP concentrations and the physical activity level [58]. The mechanism of the effect of intensity of physical activity on the increase or decrease of paraben excretion from the body is not well known. Physical activity increases sweat rates in the body, and likely a considerable portion of parabens are excreted in this way.

Our findings revealed no significant association between occupational class and the urinary concentration of parabens ($p > 0.05$). This is in line with the findings of other studies conducted in Iran. On contrast to our findings, Jimenez-Dıaz et al. (2016) have reported that housewives have significantly lower urinary concentrations of parabens compared to women who work outdoors. This probably might be because those women work outside use higher levels of personal care products and processed foods [30]. The possible reason for the lack of this association in our study may be due to the lower number of subjects in the students class (5%) and the non-uniform distribution of participants in different occupational classes. In summary, the findings of our study reveal a relationship between urinary parabens concentrations with some sociodemographic characteristics and lifestyle factors of adults in Iran.

Consistent with previous studies in other countries, the present study reported the highest EDI for MP, indicating higher exposure to MP in the Iranian population. Comparison of the median EDI reported in different countries (Table 7), the median EDI calculated in Iran is higher than in Germany [38], China [48], and lower than in the US [21] and South Korea [39]. EDI values calculated for a population in India, Saudi Arabia, Japan and Kuwait reported in HONDA's study were lower than values calculated in the present study [39]. In this study, the EDI value was higher in the female sex group than the male sex group so that the EDI calculated for MP and PP in the female sex group is more than 1.5 times the EDI calculated for the male sex group, which were consistent with previous studies in Germany and China [22, 38, 48]. Although the EDI of parabens was higher in the Iranian population than many other countries, the EDI value for MP and PP was lower than the ADI value. However, to further evaluate the daily exposure of the Iranian population to parabens and identify sources of exposure and metabolism of parabens, further studies on the larger target population using 24-h urine samples are needed. Overall, the urinary concentration and detection of parabens in the Iranian population is higher than in most countries. These results indicate widespread exposure to parabens in the Iranian population as well as a difference in distribution pattern of parabens compare with other countries. This differences may be due to racial and lifestyle differences, different concentrations of parabens in consumables as well as different patterns in the consumption of PCPs.

Study applications and limitations

The present study, as a population-based study, has several limitations. First, an adult population from Isfahan was investigated in the present study, so, caution must be exercised while generalizing the results to the whole population of Iran. Second, demographic characteristics and lifestyle checklists were completed in a self-reported manner in the presence of the study expert, and some information may be written in the checklist inaccurately due to forgetfulness or lack of accuracy. Third, in the present study, the paraben levels were measured in spot urine samples. The timing of sample collection may affected the.

urinary parabens concentrations. Forth, we did not investigate the relationship between the different sources of exposure and the concentrations of parabens due to the lack of access to information on the sources of paraben exposure, including the use of PCPs, foods, and medicines. Fifth, although the sample size was calculated according to the statistical criteria, we considered the minimum but reasonably acceptable size due to funding limitation. However, the present study evaluated for the first times the urinary concentrations and extent of exposure of parabens in a population of Iranian adults. The present study also showed an association between urinary concentrations of parabens and sociodemographic and lifestyle factors in Iranian adults. Accordingly, the results can serve as a basis for assessing the risk of exposure to parabens in future studies on the Iranian population. It is also suggested to carefully evaluate the sources of paraben exposure, including cosmetics, and investigate their relationship with concentrations of parabens in future studies.

Conclusion

In the present study, we measured the concentration of parabens in a population of Iranian adult, calculated EDI of parabens, and investigated the relationship between urinary concentrations of parabens with socio-demographic characteristics and lifestyle factors. As far as we know, this is the first study reporting the concentration and extent of exposure to urinary parabens in Iranian adults. The results indicate high urinary concentrations of parabens in Iranian adults, especially BP is several times higher than that in other countries with different patterns of exposure. Despite that, the EDI value calculated in this study was not exceeded from the recommended ADI value. Urinary concentrations of parabens are higher in females than males and there is a statistically significant difference between the two sexes in terms of urinary concentrations of MP and PP. Besides, there is a negative correlation between age with MP, PP and BP concentrations as well as between BMI with the urinary concentration of MP. The results can serve as a basis for assessing the risk of exposure to parabens in future studies on the Iranian population.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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