Associations of Urinary Metabolites of Parabens and Bisphenol a with Premature Thelarche among a Sample of Iranian Girls

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What is already known on this topic?

Endocrine-disrupting chemicals might influence the process of puberty including the development of premature thelarche.

What this study adds?

Exposure to bisphenol A and methyl paraben and ethyl paraben is related to increased odds of early breast development in girls.

ABSTRACT

Objective: Endocrine-disrupting chemicals may influence the process of puberty including the development of premature thelarche (PT). Our aim was to investigate the relationship between exposure to bisphenol A (BPA) and parabens with PT among a sample of Iranian girls.

Methods: This case-control study was conducted in 2022-2023 on girls with a mean (standard deviation) age of 7.5 (0.6) years in Isfahan, Iran. Participants were 90 newly diagnosed PT cases and 114 healthy controls. Spot urine samples were collected from both groups to measure the

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levels of BPA and paraben metabolites. Analyses of BPA and paraben metabolites included methyl paraben (MeP), ethyl paraben (EtP), propyl paraben, and butyl paraben and benzyl paraben and were performed by gas chromatography-mass spectrometry. The association between concentrations of creatinine-standardized urinary BPA and parabens and PT was analyzed with multiple logistic regression models, after adjusting for potential confounders.

Results: The results showed that individuals in the highest quartile of MeP [odds ratio (OR)=4.3, 95% confidence interval (CI): 1.2-14.9, p=0.023], EtP (OR=4.7, 95% CI: 1.3-17.2, p=0.018) and BPA (OR=5.03, 95% CI: 1.4-17.9, p=0.013) had a significantly higher odds for PT compared to those in the lowest quartile.

Conclusion: The findings of this study suggest that exposure to BPA, MeP and EtP is related to increased odds of early breast development in girls. Limiting the exposure to these chemicals may help to reduce the risk of PT.

Keywords: Bisphenol A, parabens, early puberty, thelarche, girls

Introduction

Puberty is a stage of development marked by significant physical and physiological changes. The early onset of secondary sexual characteristics in girls, particularly breast development, before the age of 8 is termed precocious puberty (1). Recent global data showed a downward trend in the age of thelarche in girls over recent decades (2).

As genetic factors remain relatively constant in this short period of time, this declining trend may be related to other factors including improved health and nutrition status, as well as various biological and lifestyle-related factors such as birth weight, sleep duration, physical activity levels, vitamin D status, socioeconomic status (SES), and maternal age at menarche and environmental exposures (3,4,5,6,7,8,9).

A particular concern is that exposure to endocrine disruptor chemicals (EDCs) might change hormonal balance (10), and may thus be related to this widely observed decrease in the age of onset of puberty (11). However, the consequences of exposure to EDCs on child reproductive development have not been comprehensively described.

Several materials with endocrine disrupting activity have been recognized, like bisphenol A (BPA) and parabens. According to the available literature, BPA and parabens have estrogenic and anti-androgenic properties (12,13,14,15). Exposure to these chemicals is widespread in the world. Humans are exposed to BPA and parabens through oral intake, as the major route, as well as inhalation and dermal absorption (16,17,18,19). Children may be exposed to BPA and parabens through various common sources encountered in daily life.

BPA, an organic monomer, is widely used in the production of epoxy resin and polycarbonate plastics. Epoxy resin is used in the inner lining of cans and jar caps. Polycarbonate plastics are used in a wide range of consumer goods, such as food packaging and plastic bottles, medical equipment, thermal paper and toys (20). Parabens are widely used as antibacterial preservatives in a diverse range of cosmetic and personal care products (21).

Parabens are found in more than half of personal care products and nearly 90% of processed foods and beverages (22,23).

Several biomonitoring studies conducted in Iran have reported detectable levels of BPA and parabens in urine samples from both children and adults, indicating widespread exposure across the population. For example, a cross-sectional study by Malakootian et al. (24), involving 96 women in Kermanshah, detected methyl paraben (MeP), ethyl paraben (EtP), propyl paraben (PrP), and butyl paraben (BuP) in 100% of urine samples. Among these, PrP had the highest mean concentration, while BuP had the lowest (24). Similarly, a 2020 cross-sectional study among 117 pregnant women in Isfahan found detection rates of MeP, EtP, PrP, and BuP in 92%, 36%, 65%, and 89% of urine samples, respectively (25). Furthermore, Kiani Feizabadi et al. (26) reported widespread exposure of Iranian adolescents to paraben compounds.

Exposure to EDCs such as BPA and parabens is concerning because these compounds can mimic or interfere with endogenous hormone activity, potentially disrupting the finely tuned hypothalamic-pituitary-gonadal axis signaling. Furthermore, evidence suggests that EDCs may influence gene expression through epigenetic mechanisms, such as DNA methylation and histone acetylation, without altering the underlying DNA sequence (27,28,29). These disruptions may ultimately lead to alterations in the timing of pubertal onset.

Due to well-established evidence regarding the harmful health effects of BPA, several countries have implemented restrictions on its use in consumer products. For instance, the European Union has banned BPA in baby bottles and children's toys (30,31). Similarly, the U.S. Food and Drug Administration has prohibited the use of BPA in the manufacture of baby bottles, training cups, and packaging for infant foods, citing concerns about its potential biological effects (32,33). In addition, the European Union regulates the use of parabens in cosmetic and personal care products, setting a maximum allowable concentration of 0.8% for mixtures of parabens and 0.4% for any individual paraben (34). Furthermore, in Denmark, the use of PrP and

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BuP in products intended for children has been completely prohibited (35).

During the last few decades, several human and animal studies have investigated the potential impact of chemicals on the odds of precocious puberty in girls. Some studies have indicated a significant relationship between BPA (10,36,37,38) and concentrations of parabens (39) in urine and precocious puberty in girls. However, the results of other studies showed that BPA exposure may be weakly related to pubertal timing in girls (40,41,42). In addition, very few studies have examined the association between exposure to parabens and timing of pubertal development in girls (39,43). As far as we know, the association between BPA and parabens with PT have not been previously evaluated among Iranian girls. Therefore, our goal was to evaluate the associations between exposure to BPA and parabens with PT among a sample of Iranian girls.

Methods

This case-control study was performed from 2022 to 2023 on girls with a mean [standard deviation (SD)] age of 7.5 (0.6) years in Isfahan. This research received ethical approval from Isfahan University of Medical Sciences (code: IR.MUI.MED.REC.1399.176, project number: 398986). Informed consent was obtained from the parents and their daughters involved in the study, after they were fully informed about the research objectives. The parents were assured that their personal information will be kept confidential. The present study was carried out with the cooperation of the Department of Education and the Health Center of Isfahan province.

Girls with newly diagnosed PT as cases were selected by consecutive sampling method from pediatric endocrinology clinics.

Control subjects, girls without premature thelarche, were selected from seven elementary schools in five educational districts of Isfahan city. The sampling method has been described previously (44). Briefly, the schools were selected randomly. Then, girls aged 6-8 years were invited to participate in the study as control group, Students who were willing to give a urine sample were included in the study.

Participants with a history of chronic diseases and genetic syndromes or any long-term medication use (such as use of gonadotropin releasing hormone agonist) were excluded. Those participants who refused the clinical examination were also excluded. All participants were of Iranian nationality.

Data were collected through clinical examinations, laboratory measurements and questionnaires. The questionnaires were completed during an interview with the mothers of selected students.

Anthropometric Measurements

Anthropometric variables including height and weight of participants were measured according to the standard protocols using validated instruments. Body mass index (BMI) was calculated as weight divided by height squared (kg/m²). According to the World Health Organization guidelines, we classified the adolescents' weight status using the BMI-for-age and gender. The following cut off points were used: underweight: BMI <5th percentile; normal weight: 5-84.9th percentile, overweight: 85-94.9th percentile, and obesity: ≥95th percentile (45).

Clinical Examination

Clinical breast tanner staging was assessed by pediatric endocrinologists for both case and control groups using Tanner's rating scale. Breast development was examined through both visual inspection and palpation (46). The first appearance of breast buds (B2) was considered as the onset of puberty (47). Achieving B2 before age 8 years was considered as precocious puberty (1).

Measurement of Urinary BPA and Parabens

Spot urine samples were collected from case and control groups to measure the levels of BPA, MeP, EtP, PrP and BuP and also benzyl paraben (BzP), as well as urinary creatinine concentrations. Samples were collected in polypropylene containers and were stored at -20 °C until analysis of the metabolites.

To extract parabens and BPA from urine samples, dispersive liquid-liquid microextraction (DLLME) approach was used (48).

The gas chromatography-mass spectrometry (GC-MS) device used was manufactured by Agilent (USA), model 7890, equipped with an Agilent mass spectrometer model 5975 and a Split/Splitless inlet (49). The mass spectrometer is of the quadrupole type. Separation was carried out using a capillary column made of silica, coated with poly (dimethylsiloxane) [HP-5 MS (5% phenyl)-95%] with dimensions of 30 m × 0.25 mm I.D. and a film thickness of 0.25 μm. For tuning of the mass spectrometer, perfluorotributylamine (PFTBA) was used. Selected Ion Monitoring (SIM) mode was applied for each target compound. In this mode, instead of scanning a wide range of m/z values, only a limited number of user-defined m/z values with the highest abundance are detected, thus enhancing sensitivity and making it more suitable for quantitative measurement. The device software was MSD ChemStation, version E.02.01.1177. The figure below shows an image of the GC-MS system.

The injection was performed in splitless mode with an injection volume of 1 μL, and the inlet temperature was set at 290 °C. Helium was used as the carrier gas at a constant flow rate of 1.0 mL/min. The oven temperature program started at 60 °C (held for 2 minutes), followed by an increase at a rate of 6 °C

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per minute up to 280 °C, where it was held for an additional 2 minutes. The interface temperature was set at 290 °C, while the ion source and quadrupole temperatures were maintained at 230 °C and 150 °C, respectively.

Isotopically labeled internal standards were used in the analysis. Specifically, we used ¹³C12-BPA for BPA and D4-MeP, D4-EtP, D4-PrP, and D4-BuP for the respective parabens.

Quality Assurance and Quality Control (QA/QC)

The GC/MS method was validated following the ICH guidelines (50). To assess precision, samples were analyzed in triplicate, and the standard deviations were calculated and reported as relative SD. Accuracy was evaluated by performing triplicate analyses using high-performance liquid chromatography-grade water as a blank substitute for human urine. The limits of detection (LOD) and quantification (LOQ) were determined by injecting diluted standard solutions with known concentrations, where LOD and LOQ corresponded to signal-to-noise ratios of 3 and 10, respectively.

The detection rates of BPA, MeP, EtP and PrP ranged between 93.2 and 98%. Urine concentrations of the metabolites lower than LOD were replaced by LOD/2 (51).

The detection rates of BuP and BzP were only 70.2 and 60%. Consequently, concentrations below the LOD were replaced with random values from a uniform distribution between zero and the respective LOD (52).

To minimize bias from variations in urine dilution, creatinine concentrations were measured using a calorimetric method (Jaffe) on a Mindray BS-800 Chemistry Analyzer. The concentrations of BPA and parabens were expressed as micrograms per gram of creatinine (µg/g Cr).

Then, the urine concentrations of BPA and parabens were categorized into quartiles to estimate the relationship between the biomarkers and odds of PT in girls. The first quartile (the lowest concentration) was considered as a reference group in the analysis.

Assessment of Physical Activity and Screen Time

We assessed physical activity levels in participants using the Physical Activity (PA) Questionnaire.

The questionnaire's validity and reliability were previously confirmed in an Iranian population (53). PA scores were obtained from various items about the activities of the students during the preceding week, including various sports (16 items), and as well as subjects' activities during physical education classes, school breaks, lunch hours, after school, in the evenings, on weekends and in general. Then, we classified the score to a dichotomous variables: PA score: 1-1.9 as low PA level; and PA score: 2-5 as high PA level, as previously described (54).

To measure screen time (ST), the hours of watching TV and using a personal computer (PC) or playing electronic games were asked separately for weekdays and weekends. Then, the weighted average of these hours was calculated as ST activity. Then ST was again categorized into two groups: <2 and ≥2 hours/day (55).

Moreover, the parents reported that their daughters usually spend outdoors per day between 10 AM and 4 PM on weekdays and on weekends. The weighted average hours of sun exposure were calculated for each participant.

In addition, mothers were asked how many hours their daughter usually sleeps at night. Sleep duration was categorized as a dichotomous variable. Long sleep was defined as sleep duration >8 hours/day (56).

SES

Family SES was estimated using a validated questionnaire; the method and variables were previously reported (57). Mothers were asked about parents' education, parents' occupation, owning a private car, type of school (public/private), type of home (private/rented) and having a PC at home. The variables were combined as one main component of SES by principle component analysis (PCA). Then, this main component was classified into quartiles, with the first quartile being considered as the "lowest SES" and the fourth quartile as the "highest SES" group (58).

Statistical Analysis

Data analysis was done using STATA 10 software (Stata Corp, College Station, Texas, USA). A p<0.05 was considered significant. Continuous variables were reported as mean and median (25th-75th percentile) and geometric mean. Categorical variables are presented as frequency (%). Independent t-test and chi-square and/or Fisher's exact test were used to compare continuous and categorical variables between two the groups. Urinary BPA and paraben levels were compared between cases and controls groups using the Mann-Whitney U test.

We performed multiple logistic regressions to examine associations between urinary paraben metabolites or BPA concentrations and PT in girls. Based on this regression, parabens and BPA were considered as independent.

Potential confounders were selected after literature review (3,4,5,6,7). These included birth order, birth weight, season of birth, sun exposure, type of delivery, maternal weight before pregnancy, height of mother, maternal age at delivery, breast feeding duration, feeding with soymilk, feeding method in the first year of life, is the child a single or one of multiple twins?,

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variables of SES and health behaviors of girls (watching TV, computer time, physical activity, sun exposure time and sleep duration).

All the variables with differences between the case and control groups at the level of p<0.2 were included in the multiple logistic regression analyses as confounding variables.

Since the normal range of urinary creatinine is 0.3-3 g/L (59,60), in a further analysis we excluded 11 participants (case=4 and control=7) with urinary creatinine less than 0.3 g/L.

Results

In this case-control study, 90 newly diagnosed PT cases and 114 healthy controls were included. The mean (SD) ages of participants were 7.7 (0.6) and 7.3 (0.6) years for the case and control group, respectively. Table 1 presents the characteristics of the participants in both groups.

The parameters of Quality Assurance/Quality Control (QA/QC) for BPA and parabens determination is presented in Table 2.

Table 1. Characteristics of the children with and without premature thelarche					
Characteristics	Category	Total n=195	Control n=110	Case n=85	p*
Child characteristics					
Age (year)[a]		7.5 (0.6)	7.3 (0.6)	7.7 (0.6)	<0.001
Child BMI (kg/m²)	Underweight	11 (5.4)	8 (7)	3 (3.3)	0.003**
	Normal weight	123 (60.3)	79 (69.3)	44 (48.9)	
	Overweight	28 (13.7)	12 (10.5)	16 (17.8)	
	Obese	42 (20.6)	15 (13.2)	27 (30)	
Child BMI (kg/m²)	Underweight and normal	134 (65.7)	87 (76.3)	47 (52.2)	<0.001
	Overweight and obese	70 (34.3)	27 (23.7)	43 (47.8)	
Breastfeeding duration	Not breastfed	7 (3.6)	2 (1.8)	5 (5.8)	0.357**
	<6 months	13 (6.6)	7 (6.3)	6 (7)	
	≥6 months	177 (89.8)	102 (91.9)	75 (87.2)	
Feeding with soymilk	No	189 (95.9)	106 (95.5)	83 (96.5)	1.000**
	Yes	8 (4.1)	5 (4.5)	3 (3.5)	
Feeding method in the first year of life	Breastfeeding	147 (74.6)	87 (78.4)	60 (69.8)	0.350**
	Formula	8 (4.1)	4 (3.6)	4 (4.7)	
	Mixed feeding	42 (21.3)	20 (18)	22 (25.6)	
Is the child under investigation a twin?	Singleton	191 (96)	110 (99.1)	81 (92)	0.023**
	Twins and more	8 (4)	1 (0.9)	7 (8)	
Birth weight, g	<2500	21 (10.6)	5 (4.5)	16 (18.2)	0.002
	≥2500	178 (89.4)	106 (95.5)	72 (81.8)	
Season of birth	Spring	57 (27.9)	34 (29.8)	23 (25.6)	0.152
	Summer	64 (31.4)	41 (36)	23 (25.6)	
	Fall	44 (21.6)	19 (16.7)	25 (37.8)	
	Winter	39 (19.1)	20 (17.5)	19 (21.1)	
Birth order	First born	110 (55.8)	49 (44.1)	61 (70.9)	<0.001
	Second born or later	87 (44.2)	62 (55.9)	25 (29.1)	
ST duration (hour)[a]		3.3 (1.5)	3.02 (1.4)	3.8 (1.6)	0.001

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Table 1. Continued					
Characteristics	**Category**	**Total n=195**	**Control n=110**	**Case n=85**	**p***
Sleep duration (hour)	≤8	50 (25.4)	33 (29.7)	17 (19.8)	0.111
	>8	147 (74.6)	78 (70.3)	69 (80.2)	
Physical activity[a]		1.9 (0.6)	2.0 (0.7)	1.8 (0.5)	0.021
Physical activity	Low PA	122 (61.9)	64 (57.7)	58 (67.4)	0.161
	High PA	75 (38.1)	47 (42.3)	28 (32.6)	
Sun exposure time (hour)	<1	22 (11.2)	16 (14.4)	6 (7)	0.157
	1-2	134 (68)	69 (62.2)	65 (75.6)	
	2-3	20 (10.2)	14 (12.6)	6 (7)	
	>3	21 (10.7)	12 (10.8)	9 (10.5)	
Sociodemographic characteristics of parent					
SES	Q1 (lowest SES)	49 (24.9)	35 (31.5)	14 (16.3)	0.057
	Q2	49 (24.9)	22 (19.8)	27 (31.4)	
	Q3	51 (25.9)	29 (26.1)	22 (25.6)	
	Q4 (highest SES)	48 (24.4)	25 (22.5)	23 (26.7)	
Maternal age at menarche (years)	<12	19 (9.6)	9 (8.1)	10 (11.5)	0.016
	12-13	95 (48)	45 (40.5)	50 (57.5)	
	>13	84 (42.4)	57 (51.4)	27 (31)	
Type of delivery	Natural birth	57 (28.9)	30 (27)	27 (31.4)	0.502
	Cesarean section	140 (71.1)	81 (73)	59 (68.6)	
Mother's height		161.7 (7.17)	162.4 (8.1)	160.9 (5.8)	0.142
Maternal weight before pregnancy (kg)[a]		61.6 (10.5)	61.2 (11.0)	62.2 (9.9)	0.524
Maternal prepregnancy BMI (kg/m^2)	Underweight	11 (5.6)	9 (8.2)	2 (2.4)	0.311**
	Normal weight	127 (65.1)	72 (65.5)	55 (64.7)	
	Overweight	44 (22.6)	22 (20)	22 (25.9)	
	Obese	13 (6.7)	7 (6.4)	6 (7.1)	
Maternal age at delivery (years)	<25	42 (21.4)	18 (16.2)	24 (28.2)	0.085
	25-29	84 (42.9)	48 (43.2)	36 (42.4)	
	>30	70 (35.7)	45 (40.5)	25 (29.4)	
[a]Data are presented as mean (SD) other data are presented as number (%) *p values using the chi-square (χ2) and t-test between the case and control group (where appropriate). **p values using Fisher's exact test. BMI: body mass index, ST: screen time, PC: personal computer, TV: television, PA: physical activity, SES: socioeconomic status					

Distribution of urinary concentrations of BPA and parabens among case and control groups is presented in Table 3.

Table 4 presents results of the multiple logistic regression models to estimate the association between urinary BPA and parabens levels with PT.

After adjusting for age, BMI, birth order, birth weight, season of birth, maternal age at menarche, maternal age at delivery, mother's height, SES, ST, sleep duration, physical activity and time of sun exposure, significant positive association was found between the highest quartile for BPA and PT (OR=3.1; 95% CI: 1.0-9.5, p=0.046).

In addition, after adjustment for confounding variables, the highest concentrations of EtP were associated with 3.2-fold increased odds of PT (OR=3.2, 95% CI: 1.02-9.97, p=0.045) compared to those in the lowest quartile for this analyte.

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Table 2. The parameters of Quality Assurance/Quality Control (QA/QC) for bisphenol A and parabens determination						
Compound name	RT (min)	Units	LOD*	LOQ**	R2***	RSD****
Methyl paraben	13.82	ppb	0.10	0.33	0.992	8.6
Ethyl paraben	15.49	ppb	0.10	0.34	0.997	5.9
Propyl paraben	17.69	ppb	0.09	0.28	0.996	10.1
Butyl paraben	19.89	ppb	0.10	0.33	0.991	6.7
Benzyl paraben	23.01	ppb	0.06	0.19	0.998	7.7
Bishphenol A	28.82	ppb	0.10	0.33	0.996	6.7

*Limit of detection, **Limit of quantitation, ***R-squared correlation, ****RSDs% (relative standard deviation)
RT: retention time, LOD: limit of detection, LOQ: limit of quantitation, RSD: R-squared correlation

Table 3. Concentrations of parabens and bisphenol A in urine of case and control groups									
Compound (µg/g creatinine)	%> LOD	Mean (SD)	GM (95% CI)	Min.	Max.	Total* (n=204)	Control* (n=114)	Case* (n=90)	p
MeP	94.6	5.4 (10.96)	3.06 (2.60-3.60)	0.035	107.85	3.26 (2.34-5.14)	3.17 (2.19-4.57)	3.28 (2.42-6.25)	0.462
EtP	94.1	5.4 (10.0)	3.17 (2.71-3.73)	0.035	88.75	3.37 (2.38-5.43)	3.31 (2.30-4.90)	3.47 (2.59-6.39)	0.382
PrP	93.2	4.41 (9.77)	2.32 (1.95-2.76)	0.032	101.10	2.60 (1.86-4.08)	2.84 (1.95-3.83)	2.33 (1.51-4.45)	0.177
BuP	70.2	2.62 (5.49)	0.76 (0.58-0.99)	0.005	55.10	1.79 (0.14-2.92)	1.91 (0.48-2.96)	1.67 (0.07-2.69)	0.149
BzP	60	2.57 (7.17)	0.46 (0.33-0.63)	0.002	92.30	1.47 (0.04-2.95)	2.13 (0.99-3.30)	0.05 (0.02-1.95)	<0.001
BPA	98	6.32 (24.4)	3.09 (2.72-2.80)	0.045	323.57	2.86 (2.08-4.61)	2.93 (2.01-4.22)	2.86 (2.17-5.39)	0.337

p values using Mann-Whitney U test, *Data are represented as median (IQR, interquartile range)
Min: minimum, Max: maximum, GM: geometric mean, LOD: limit of detection, MeP: methyl paraben, EtP: ethyl paraben, PrP: propyl paraben, BuP: butyl paraben, BzP: benzyl paraben, BPA: bisphenol A

The results showed a lower odds ratio of PT in participants who were in the third and fourth quartile for BzP, compared to those in the lowest quartile (p<0.05).

The results indicated a higher odds ratio of PT in participants who were in the fourth quartile for MeP (OR=4.3, 95% CI: 1.2-14.9, p=0.023) and EtP (OR=4.7, 95% CI: 1.3-17.2, p=0.018) and BPA (OR=5.03, 95% CI: 1.4-17.9, p=0.013), compare to those in the first quartile.

Discussion

The purpose of the present study was to compare the urinary concentrations of five parabens and BPA in girls with or without PT. We found that exposure to these EDCs was common among Iranian girls from Isfahan.

In the present study, the geometric mean (GM) of BPA was 3.09 (2.72-3.52) µg/g creatinine, and BPA was detectable in 98% of the samples. Various studies have also been conducted in other countries (Table 5). For example, a 2021 study in Spain found a GM BPA level of 0.90 ng/mL, detectable in 63% of samples (59). In China (2020), the GM BPA levels in 3- and 7-year-old girls were 2.88 and 4.66 µg/g creatinine, respectively (61). In the U.S. (2019), BPA was detected in 97.5% of samples, with a GM (SD) of 1.23 (0.06) µg/g creatinine (62).

Furthermore, the GM urinary concentrations of MeP, EtP, and PrP were relatively high and detectable in most samples, while BuP and BzP were found in about 60% of the samples (Table 6). Although the concentrations of MeP and EtP were higher in the case group than in the control group, the difference was not significant. Previous studies conducted in countries including Spain (59), California (39), and Iran (26) have also shown that MeP and PrP are detected in a high percentage of children and adolescents. However, exposure levels in Iran, particularly for MeP, were reported to be significantly higher than in European and Asian countries (26).

Our findings suggest that exposure to BPA and MeP and EtP might be linked to early breast development (p<0.05). A small number of human studies have assessed the link between prenatal exposure to BPA and the stages of puberty (63,64,65). For instance, a cohort study in Mexico City in 120 girls aged 8-13 years in 2017 reported that BPA levels in the second trimester were related to an increased risk of early breast development (63).

In line with the present study, studies also evaluated urinary levels of BPA in children. Some studies found significant associations between urinary BPA levels and precocious puberty.

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Table 4. Association of bisphenol A and paraben concentrations (µg/g creatinine) with premature thelarche

Compound		Range	Crude models (n=204) case=90, control=114		Adjusted model1 (n=195) case=85, control=110		Adjusted model2* (n=184) case=81, control=103	
			OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
MeP	Q1	<2.34	1		1		1	
	Q2	2.35-3.26	1.4 (0.6-3.0)	0.424	1.6 (0.5-4.9)	0.421	1.6 (0.5-5.1)	0.431
	Q3	3.27-5.14	0.8 (0.4-1.9)	0.682	1.1 (0.3-3.5)	0.881	1.2 (0.4-4.1)	0.754
	Q4	>5.14	1.9 (0.9-4.1)	0.114	2.7 (0.9-8.1)	0.077	4.3 (1.2-14.9)	0.023
EtP	Q1	<2.38	1		1		1	
	Q2	2.39-3.37	1.2 (0.5-2.6)	0.687	1.6 (0.5-4.8)	0.433	1.5 (0.5-4.8)	0.486
	Q3	3.38-5.43	1.2 (0.5-2.6)	0.687	1.7 (0.5-5.3)	0.390	1.7 (0.5-5.8)	0.371
	Q4	>5.43	1.6 (0.7-3.5)	0.324	3.2 (1.02-9.97)	0.045	4.7 (1.3-17.2)	0.018
PrP	Q1	<1.86	1		1		1	
	Q2	1.87-2.60	0.7 (0.3-1.5)	0.323	0.7 (0.2-2.1)	0.524	0.7 (0.2-2.2)	0.565
	Q3	2.61-4.08	0.3 (0.1-0.6)	0.003	0.4 (0.1-1.2)	0.099	0.4 (0.1-1.5)	0.187
	Q4	>4.08	0.9 (0.4-1.9)	0.692	1.1 (0.4-3.3)	0.807	1.7 (0.5-5.5)	0.398
BuP	Q1	<0.14	1		1		1	
	Q2	0.14-1.79	0.4 (0.2-0.8)	0.011	0.2 (0.05-0.6)	0.006	0.2 (0.05-0.6)	0.009
	Q3	1.80-2.92	0.6 (0.3-1.3)	0.167	0.3 (0.09-1.1)	0.072	0.3 (0.08-1.1)	0.076
	Q4	>2.92	0.5 (0.2-0.997)	0.049	0.31 (0.09-1.0)	0.053	0.4 (0.1-1.4)	0.137
BzP	Q1	<0.04	1		1		1	
	Q2	0.05-1.47	0.4 (0.2-0.9)	0.033	0.3 (0.09-1.1)	0.080	0.2 (0.06-0.9)	0.029
	Q3	1.48-2.95	0.08 (0.03-0.21)	<0.001	0.08 (0.02-0.3)	<0.001	0.05 (0.01-0.2)	<0.001
	Q4	>2.95	0.14 (0.06-0.3)	<0.001	0.14 (0.04-0.5)	0.003	0.15 (0.04-0.6)	0.007
BPA	Q1	<2.08	1		1		1	
	Q2	2.09-2.86	1.3 (0.6-2.8)	0.550	1.6 (0.5-5.1)	0.397	1.7 (0.5-5.4)	0.407
	Q3	2.87-4.61	0.7 (0.3-1.6)	0.413	1.1 (0.4-3.6)	0.821	1.3 (0.4-4.2)	0.687
	Q4	>4.61	1.7 (0.8-3.8)	0.167	3.1 (1.0-9.5)	0.046	5.03 (1.4-17.9)	0.013

Model 1 and 2 are adjusted for age, child BMI, birth order, birth weight, season of birth, maternal age at menarche, maternal age at delivery, mother's height, socioeconomic status, screen time, sleep duration, physical activity and time of sun exposure.
*The subjects with urinary creatinine less than 0.3 g/L were excluded from the model[2].
MeP: methyl paraben, EtP: ethyl paraben, PrP: propyl paraben, BuP: butyl paraben, BzP: benzyl paraben, BPA: bisphenol A, Q: quartile, OR: odds ratio, CI: confidence interval

For example, a study that was conducted in 2022 in China on 76 girls showed that urinary BPA levels in the case group were significantly higher than those in the control group (66). In addition, a case-control study in 2018 in China on 272 girls reported that BPA exposure was also related to a higher odds of precocious puberty (38). However, other studies reported no significant association between BPA and precocious puberty (40,41). For example, a Chinese case control study in 2023 that was conducted among 120 girls with precocious puberty (cases) and 145 healthy girls (controls) did not find significant association between exposure to BPA and odds of early puberty (41). Similarly, a cohort study in 2017 among 1051 American girls aged 6-8 years did not document a significant association between exposure to BPA and age of menarche (67). However,

some other studies reported significant relationship between BPA exposure with delayed menarche. A cross-sectional study on 655 girls aged 9-18 years from Shanghai in 2017 showed BPA exposure was related to delayed menarche (68). Similarly, a cross-sectional study conducted in the USA involving 987 adolescent girls aged 12-19 years demonstrated an association between urinary BPA levels and delayed menarche (36).

To date, few studies have been conducted to assess the link between paraben exposure and timing of puberty, and have reported inconsistent results. A longitudinal cohort study in 2019 in USA showed that peripubertal exposure to MeP was related to earlier thelarche, pubarche and menarche. The results also suggested an association of peripubertal PrP with earlier

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Table 5. Bisphenol A concentration in a range of studies for comparison with results of the present study

First author	Publication year	Location	Study design	Sample size	Age	Median	GM (g/g crµ)
Dualde et al. (59)	2021	Spain	Cross-sectional	562	5-12		0.90*
Guo et al. (61)	2020	China	Longitudinal	229	3	2.59	2.88
				412	7	2.41	4.66
Jacobson et al. (62)	2019	U.S.	Cross-sectional	894	6-19		1.23
Çok et al. (72)	2020	Türkiye	Cross-sectional	125	3-6	0.60	1.05
Zhou et al. (66)	2022	China	Case-control	Case=30	7.1 (0.7)	5.87	
				Control=46	7.3 (0.7)	0.24	
Supornsilchai et al. (73)	2016	Thailand	Case-control	Case=41	7.44 (1.03)	1.44	
				Control=47	7.44 (1.03)	0.59	
Buttke et al. (40)	2012	U.S.	Cross-sectional	440	12-16		2.25
Current study	2024	Isfahan	Case-control	Case=90	6-8	2.86	3.04
				Control=114	6-8	2.93	3.17

*ng/mL
GM: geometric mean

Table 6. Paraben concentrations in some studies

First author	Publication year	Location	Study design	Sample size	Age (year)	Statistic	Unit	MeP	EtP	PrP	BuP	BzP
Present study	2024	Isfahan	Case-control	204	6-8	Median	µg/g cr	3.26	3.37	2.60	1.79	1.47
						GM	µg/g cr	3.06	3.17	2.32	0.76	0.46
Dualde et al. (59)	2021	Spain	Cross-sectional	562	5-12	GM	ng/mL	1.4	<0.2	0.39	<0.2	-
Lu et al. (74)	2019	China	Cross-sectional	255	3-11	Median	µg/L	2.3	0.33	0.50	0.02	0.03
Kiani Feizabadi et al. (26)	2020	Isfahan	Cross-sectional	100	12-20	Median	µg/g cr	92.2	8.46	12.26	8.42	-
						GM	µg/g cr	93.6	4.37	6.13	5.59	-
Harley et al. (39)	2019	California	Cohort	179	9-13	GM	ng/g cr	44.9	-	4.9	-	-
Guth et al. (75)	2021	Canada	Cross-sectional	382	6-17	GM	µg/g cr	10.7	0.84	1.8	0.23	-

MeP: methylparaben, EtP: ethylparaben, PrP: propylparaben, BuP: butylparaben, BzP: benzylparaben, BPA: bisphenol A, GM: geometric mean

pubarche in girls (39). A recent systematic review of seven studies reported higher peripubertal paraben exposure was related to precocious puberty but the effect sizes were very small (43). However, a cross-sectional study in 2012, on American girls aged 12-16 years reported total parabens were not related to age of menarche (40). Similarly, another cohort study of 200 Chilean girls in 2018 found no link between concentrations of MeP and PrP and earlier menarche (69). In 2015, a prospective study was conducted among 1239 girls aged 6-8 years in the USA. They were followed annually for 7 years. After adjustment for confounding factors, including race/ethnicity and caregiver education, paraben levels were not linked with earlier thelarche and pubarche (70). A cohort study of 1151 American girls aged 6-8 years at enrollment reported that after adjusting for some confounding variables, urinary paraben concentrations were not linked with breast and pubic hair development (71).

Several factors may be behind these differences in the results of various studies. First, methods to assess sexual maturity were different across studies. Some studies used maternal and self-assessment and some used clinical examinations for assessing pubertal status. Second, the controlled confounding factors varied between studies. Moreover, the differences in study methodology, study design, sample size, statistical analysis methods and adjustment for urine creatinine may also contribute to the inconsistent results of different studies.

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To the best of our knowledge, no previous study has examined the association between urinary paraben and BPA levels with premature thelarche among Iranian girls. However, the present study had some potential limitations. The cross-sectional study design limits assessment of causal relationships between the chemicals and onset of puberty. One spot urine was collected for the measurement of concentration of BPA and parabens so exposure misclassification may have affected our findings.

Conclusion

Our findings provide evidence of an association between higher exposure to BPA, MeP and EtP and precocious puberty among a cohort of Iranian girls. Considering that the evidence related to this topic is scarce and controversial, further cohort studies with large sample sizes and more repeated measures of the chemicals during the prepubertal years are suggested. This will enable a more reliable assessment of the clinical importance of the current findings. In addition, future research should explore potential mechanisms of action and interactions with nutritional, and lifestyle factors.

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