DOI: 10.4274/jcrpe.galenos.2025.2025-3-22

Research Article

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

Mozafarian et al. Associations of Urinary Metabolites of Parabens and Bisphenol A with Premature Thelarche

Nafiseh Mozafarian[1], Mahin Hashemipour[2*], Mohammad Reza Maracy[3,4*], Hamid Galehdari[5], Roya Kelishadi[1]
[1]Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Metabolic Liver Disease Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Department of Biostatistics and Epidemiology, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran
[4]Environment Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran
[5]Department of Dermatology, Skin Diseases and Leishmaniasis Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

*Co-corresponding authors.

What is already known on this topic?
Endocrine-disrupting chemicals (EDC) might influence the process of puberty including the development of premature thelarche (PT).

What this study adds?
Exposure to BPA and MeP and EtP is related to increased odds of early breast development in girls.

*Mahin Hashemipour, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Noncommunicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran; and Metabolic Liver Disease Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, **E-mail:** mahin.hashemipour@gmail.com; and Mohammad Reza Maracy, Department of Biostatistics and Epidemiology, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran; and Environment Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran, **E-mail:** maracy@med.mui.ac.ir

30.03.2025
06.07.2025

Epub: 12.08.2025

Abstract
Objective: Endocrine-disrupting chemicals (EDC) may influence the process of puberty including the development of premature thelarche (PT). This study aimed to investigate the relation 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 (SD) 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 levels of BPA and paraben metabolites. We performed analyses of BPA and paraben metabolites including methylparaben (MeP), ethylparaben (EtP), propylparaben (PrP), and butylparaben (BuP) and benzylparaben (BzP) using gas chromatography-mass spectrometry. The association between concentrations of creatinine-standardized urinary bisphenol A 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 methyl paraben (OR=4.3, 95% CI:1.2-14.9, P=0.023), ethyl paraben (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 precocious puberty.
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, 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, and maternal age at menarche and environmental exposures (3-9).
Of special concern is that exposure to endocrine disruptor chemicals (EDCs) might change the hormonal balance (10), and can be related to the change in the age of onset of puberty (11). However, the consequences of exposure to these substances on child reproductive development have not been comprehensively described.
Several materials with endocrine disrupting activity have been recognized, like bisphenol (BPA) and parabens. According to the available literature, BPA and parabens have estrogenic and anti-androgenic properties (12-15). Exposure to the 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 (16-19). 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 is used in a wide range of consumer goods such as food packaging and plastic bottles, medical

equipment, thermal receipts 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. (2022), involving 96 women in Kermanshah, detected methylparaben (MeP), ethylparaben (EtP), propylparaben (PrP), and butylparaben (BuP) in the majority 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 et al. emphasized the extensive exposure of Iranian adolescents to paraben compounds (26).

Exposure to endocrine-disrupting chemicals (EDCs) such as BPA and parabens is concerning because these compounds can mimic or interfere with endogenous hormone activity, potentially disrupting the finely tuned HPGA 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 (27-29). These disruptions may ultimately lead to alterations in the timing of pubertal onset.

Due to well-established evidence regarding the harmful health effects of bisphenol A (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 (FDA) 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). Additionally, in Denmark, the use of propylparaben and butylparaben in products intended for children has been prohibited (35).

During the recent 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, 36-38) and parabens concentration (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 (40-42). In addition, very few studies have examined association between parabens exposure and timing of pubertal development in girls (43, 44). 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 (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 department of education and the health center of Isfahan province.

Newly diagnosed girls with premature thelarche as cases were selected by consecutive sampling method from pediatric endocrinology clinics. Control subjects, the students without premature thelarche, were selected from seven elementary schools in five educational districts of Isfahan city. The sampling method has been described previously (45). 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 GnRH 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 filled 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/m^2). 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: ≥95thpercentile (46).

Clinical examination

Clinical breast tanner staging was assessed by pediatric endocrinologists' women for both case and control groups using Tanner's rating scale. Breast development was examined through both visual inspection and palpation (47). The first appearance of breast buds (B2) was considered as the onset of puberty (48). The 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, methylparaben (MeP) and ethylparaben (EtP), propylparaben (PrP) and butylparaben (BuP) and benzylparaben (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.

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 measurements .The device software was MSD ChemStation, version E.02.01.1177. The figure below shows an image of the gas chromatography–mass spectrometry 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 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 bisphenol A and D4-methylparaben, D4-ethylparaben, D4-propylparaben, and D4-butylparaben 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 standard deviation (RSD). Accuracy was evaluated by performing triplicate analyses using HPLC-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. Details of the method validation and QA/QC parameters are summarized in Table 2.
The detection rates of BPA, MeP, EtP and PrP were ranged between 93.2 to 98%. Urine concentrations of the metabolites lower than limits of detection (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 to quartile to estimate the relationship between the biomarkers and odds of PT in girls. The first quartile (the lowest concentration) was considered as reference group in the analysis.

Assessment of physical activity and screen time

We assessed physical activity levels in participants using Physical Activity Questionnaire (PAQ).
The questionnaire's validity and reliability were previously confirmed in Iranian population (53). PA scores were obtained from various items about the activities of the students during last 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 during past week. 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 (54).
To measure screen time (ST), the hours of watching TV and using a personal computer (PC) or playing electronic games (EG) were asked separately for weekdays and weekends. Then, the weighted average of these hours was calculated as screen time activity. Then ST was categorized into two groups: <2 and ≥2hours/day (55).
Moreover, the parents reported that their daughters usually spend outdoors per day between 10 AM and 5 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 >8hours /day(56).

Socioeconomic status (SES)

Family socioeconomic status was estimated using a validated questionnaire; the method and variables were previously approved(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 personal computer 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. Accordingly, the first quartile was considered as "lowest SES" and the fourth quartile as a "highest SES" group(58).

Statistical analysis

Data analysis was done using STATA 10 software (Stata Corp, College Station, Texas, USA). P<0.05 was considered as 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/ Fisher's exact test were used to compare continuous and categorical variables between two the groups. Urinary BPA and parabens levels were compared between cases and control groups using the Mann–Whitney test.
We performed multiple logistic regressions to examine associations between urinary parabens metabolite or BPA concentrations and precocious puberty in girls. Based on this regression, parabens and BPA were considered as independent.
Potential confounders were selected using previous knowledge(3-7). 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 under investigation single or multiple twins?, variables of socioeconomic status 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) (9, 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.
Distribution of urinary concentrations of BPA and parabens among case and control groups is presented in Table 3.
Table 4 presents 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, socioeconomic status, screen time, sleep duration, physical activity and time of sun exposure, significant positive association was found between the highest level of 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 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 concentrations of ethyl paraben.
The results showed a lower odds ratio of PT in participants who were in the quartile 3 and 4 of 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 quartile 4 of methyl paraben (OR=4.3, 95% CI:1.2-14.9, P=0.023) and ethyl paraben (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 quartile1.

Discussion

In this study aiming to compare the urinary concentrations of the five parabens and BPA in girls with or without PT, we found that exposure to these EDCs is common among Iranian girls.
In this study, the geometric mean of Bisphenol A (BPA) was reported as 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 geometric mean BPA level of 0.90 ng/mL, detectable in 63% of samples (59). In China (2020), the geometric mean 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 geometric mean (standard deviation) of 1.23 (0.06) µg/g creatinine (62).
In this study, the geometric mean urinary concentrations of methyl, ethyl, and propyl parabens were relatively high and detectable in most samples, while butyl and benzyl parabens were found in about 60% of the samples (Table 6). Although the concentrations of methyl and ethyl parabens were higher in the case group than in the control group, the difference was not statistically significant. Previous studies conducted in

countries such as Spain (59), California (44) , and Iran (26) have also shown that methyl and propyl parabens are detected in a high percentage of children and adolescents. However, exposure levels in Iran—particularly for methyl paraben—were reported to be significantly higher than in European and Asian countries (26)

Our findings suggest that exposure to BPA and methyl and ethyl paraben 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 (63-65). For instance, a cohort study in Mexico City on 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 bisphenol A in children. Some studies found significant associations between urinary BPA levels and precocious puberty. 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 12 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). In this regard, a cohort study in 2017 among 1051 American girls aged 6–8 years did not document 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 demonstrated an association between urinary BPA levels and delayed menarche(36).

To date, few studies have conducted to assess the link of parabens and timing of puberty, and reported inconsistent results. A longitudinal cohort study in 2019 in USA showed that peripubertal exposure to methyl paraben was related to earlier thelarche, pubarche and menarche. The results also suggested an association of peripubertal propyl paraben with earlier pubarche in girls(44). A recent systematic review on 7 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 on 200 Chilean girls in 2018 found no link between concentrations of Methyl and Propyl Paraben and earlier menarche(69). In 2015, a prospective study conducted among 1239 girls aged 6–8 years in USA. They were followed for 9 years annually. After adjustment for confounding factors including race/ethnicity and caregiver education, paraben levels were not link with earlier thelarche and pubarche (70). A cohort study on 1151 American girls aged 6-8 years at enrollment reported that after adjusting for some confounding variables, urinary parabens concentrations were not linked with breast and pubic hair development (71).

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

To our knowledge, no previous study has examined the association between parabens and BPA with premature thelarche among Iranian girls. The present study had some potential limitations. The cross-sectional study design limits to assess the causal relationship of 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 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 prepubertal years are suggested to assess the clinical importance of the current findings. In addition, future research should explore potential mechanisms of action and interactions with nutritional, and lifestyle factors.

Acknowledgments

We would like to thank of the staff of Isfahan Provincial Health Office and also the provincial Education and Training Office for their cooperation. We are also grateful to Dr. Pourmirzaei, Dr. Madineh, Mr. Sakhai, Dr. Nazarian, Mr. Faal (from department of education in Isfahan province) and Mrs. Ghane for their assistance as well as the participants and their families.

Author contribution All authors (NM, MH, MRM, HG, and RK) participated in the conception of the study as well as in the elaboration, or critical reviews of the report. NM and MRM contributed to the analysis and interpretation of data. All the authors have read and agreed to the published version of the manuscript.

Funding: Support for this work was provided by Isfahan University of Medical Sciences and the Health Center of Isfahan province with code of IR.MUI.MED.REC.1399.176 and project number 398986.

Data availability: The datasets used during the current study are available from the corresponding authors on reasonable request.

Declarations

Ethical approval: The study protocol was approved by the ethics committee of Isfahan University of Medical Sciences with code of IR.MUI.MED.REC.1399.176 and project number 398986. All methods were performed in accordance with the relevant guidelines and regulations. The purposes of the research were explained to the parents, then an informed consent was obtained from the parents and their daughters. The participants were assured that their personal information will be kept confidential.

Consent to participate: Informed consent was obtained from the parents and their daughters.

Consent for publication: Not applicable.

Competing interests: The authors declare no competing interests.

References

1. Lebrethon M-C, Bourguignon J-P. Management of central isosexual precocity: diagnosis, treatment, outcome. Current opinion in pediatrics. 2000;12(4):394-9.

2. Eckert-Lind C, Busch AS, Petersen JH, Biro FM, Butler G, Bräuner EV, et al. Worldwide secular trends in age at pubertal onset assessed by breast development among girls: a systematic review and meta-analysis. JAMA pediatrics. 2020;174(4):e195881-e.

3. Day FR, Forouhi NG, Ong KK, Perry JR. Season of birth is associated with birth weight, pubertal timing, adult body size and educational attainment: a UK Biobank study. Heliyon. 2015;1(2).

4. Marks KJ, Howards PP, Smarr MM, Flanders WD, Northstone K, Daniel JH, et al. Prenatal exposure to mixtures of persistent endocrine disrupting chemicals and early menarche in a population-based cohort of British girls. Environmental pollution (Barking, Essex : 1987). 2021;276:116705.
5. Mozafarian N, Yazdi M, Hashemipour M, Hovsepian S, Maracy MR. Association between sleep duration and early pubertal timing in children and adolescents: A systematic review and meta-analysis. Current Pediatric Reviews. 2023;19(3):318-28.
6. Kehm RD, Knight JA, Houghton LC, McDonald JA, Schwartz LA, Goldberg M, et al. Childhood physical activity and pubertal timing: findings from the LEGACY girls study. International Journal of Epidemiology. 2024;53(1):dyad193.
7. Calcaterra V, Magenes VC, Tagi VM, Grazi R, Bianchi A, Cena H, et al. Association between vitamin D levels, puberty timing, and age at menarche. Children. 2023;10(7):1243.
8. Bigambo FM, Wang D, Niu Q, Zhang M, Mzava SM, Wang Y, et al. The effect of environmental factors on precocious puberty in children: a case–control study. BMC pediatrics. 2023;23(1):207.
9. Darendeliler F. IUGR: Genetic influences, metabolic problems, environmental associations/triggers, current and future management. Best practice & research Clinical endocrinology & metabolism. 2019;33(3):101260.
10. Durmaz E, Asci A, Erkekoglu P, Balcı A, Bircan I, Koçer-Gumusel B. Urinary bisphenol A levels in Turkish girls with premature thelarche. Human & experimental toxicology. 2018;37(10):1007-16.
11. Euling SY, Selevan SG, Pescovitz OH, Skakkebaek NE. Role of environmental factors in the timing of puberty. Pediatrics. 2008;121 Suppl 3:S167-71.
12. Chapin RE, Adams J, Boekelheide K, Gray Jr LE, Hayward SW, Lees PS, et al. NTP-CERHR expert panel report on the reproductive and developmental toxicity of bisphenol A. Birth defects research Part B, Developmental and reproductive toxicology. 2008;83(3):157-395.
13. Lee HJ, Chattopadhyay S, Gong E-Y, Ahn RS, Lee K. Antiandrogenic effects of bisphenol A and nonylphenol on the function of androgen receptor. Toxicological sciences. 2003;75(1):40-6.
14. Oishi S. Effects of butylparaben on the male reproductive system in rats. Toxicology and industrial health. 2001;17(1):31-9.
15. Kjærstad MB, Taxvig C, Andersen HR, Nellemann C. Mixture effects of endocrine disrupting compounds in vitro. International Journal of Andrology. 2010;33(2):425-33.
16. Papadimitriou A, Fytanidis G, Douros K, Bacoula C, Nicolaidou P, Fretzayas A. Age at menarche in contemporary Greek girls: evidence for levelling- off of the secular trend. Acta Paediatr. 2008;97.
17. Wang L, Wu Y, Zhang W, Kannan K. Characteristic profiles of urinary p-hydroxybenzoic acid and its esters (parabens) in children and adults from the United States and China. Environmental science & technology. 2012;47(4):1969-76.
18. Morgan MK, Jones PA, Calafat AM, Ye X, Croghan CW, Chuang JC, et al. Assessing the quantitative relationships between preschool children's exposures to bisphenol A by route and urinary biomonitoring. Environmental science & technology. 2011;45(12):5309-16.
19. LaKind JS, Naiman DQ. Daily intake of bisphenol A and potential sources of exposure: 2005–2006 National Health and Nutrition Examination Survey. Journal of Exposure Science and Environmental Epidemiology. 2011;21(3):272.
20. Kang J-H, Kondo F, Katayama Y. Human exposure to bisphenol A. Toxicology. 2006;226(2-3):79-89.
21. Karthikraj R, Kannan K. Human biomonitoring of select ingredients in cosmetics. Analysis of cosmetic products: Elsevier; 2018. p. 387-434.
22. Guo Y, Kannan K. A survey of phthalates and parabens in personal care products from the United States and its implications for human exposure. Environmental science & technology. 2013;47(24):14442-9.
23. Liao C, Liu F, Kannan K. Occurrence of and dietary exposure to parabens in foodstuffs from the United States. Environmental science & technology. 2013;47(8):3918-25.
24. Malakootian M, Chavoshani A, Hashemi M, Amin MM, Ghoshtari-Yeganeh B, Fadaei S, et al. Concentrations of urinary parabens and reproductive hormones in Iranian women: Exposure and risk assessment. Toxicology Reports. 2022;9:1894-900.
25. Fadaei S, Pourzamani H, Ebrahimpour K, Feizi A, Emiali SS, Kelishadi R. Association of maternal urinary concentration of parabens and neonatal anthropometric indices. Journal of Environmental Health Science and Engineering. 2020;18:617-28.
26. Kiani Feizabadi G, Hajizadeh Y, Fadaei A, Ebrahimpour K. Urinary concentrations of parabens in a population of Iranian adolescent and their association with sociodemographic indices. Archives of environmental contamination and toxicology. 2020;79:195-207.
27. Lizcano F, Garcia J. Epigenetic control and cancer: the potential of histone demethylases as therapeutic targets. Pharmaceuticals. 2012;5(9):963-90.
28. McCarthy N. Showing a more sensitive side. Nature Reviews Cancer. 2013;13(10):680-.
29. Diamanti-Kandarakis E, Bourguignon J-P, Giudice LC, Hauser R, Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocrine reviews. 2009;30(4):293-342.
30. EC. Commission Directive 2011/8/EU of 28 January 2011 amending Directive 2002/72. OJ. 2011;26:11.
31. Authority EFS. Report on the two-phase public consultation on the draft EFSA scientific opinion on bisphenol A (BPA). Wiley Online Library; 2015. Report No.: 2314-8325.
32. Food, Administration D. Indirect Food Additives: Polymers. Fed Reg 77: 41899–41902. 2012.
33. Food, Administration D. Indirect food additives: adhesives and components of coatings. Fed Regist. 2013;78:41840-3.
34. UNION P. Regulation (EC) No 1223/2009 of the european parliament and of the council. Official Journal of the European Union L. 2009;342:59.
35. Kirchhof MG, de Gannes GC. The health controversies of parabens. Skin Therapy Lett. 2013;18(2):5-7.
36. McGuinn LA, Ghazarian AA, Su LJ, Ellison GL. Urinary bisphenol A and age at menarche among adolescent girls: evidence from NHANES 2003–2010. Environmental research. 2015;136:381-6.
37. Miao M, Wang Z, Liu X, Liang H, Zhou Z, Tan H, et al. Urinary bisphenol A and pubertal development in Chinese school-aged girls: a cross-sectional study. Environmental Health. 2017;16:1-7.
38. Chen Y, Wang YC, Ding GD, Tian Y, Zhou ZJ, Wang XM, et al. Association between bisphenol a exposure and idiopathic central precocious puberty (ICPP) among school-aged girls in Shanghai, China. Environment International. 2018;115:410-6.
39. Harley KG, Berger KP, Kogut K, Parra K, Lustig RH, Greenspan LC, et al. Association of phthalates, parabens and phenols found in personal care products with pubertal timing in girls and boys. Human Reproduction. 2019;34(1):109-17.
40. Buttke DE, Sircar K, Martin C. Exposures to endocrine-disrupting chemicals and age of menarche in adolescent girls in NHANES (2003-2008). Environ Health Perspect. 2012;120(11):1613-8.
41. Bigambo FM, Wang D, Sun J, Ding X, Li X, Gao B, et al. Association between Urinary BPA Substitutes and Precocious Puberty among Girls: A Single-Exposure and Mixed Exposure Approach from a Chinese Case—Control Study. Toxics. 2023;11(11):905.

42. Meng H, Zhou Y, Jiang Y. Association of bisphenol A with puberty timing: a meta-analysis. Reviews on environmental health. 2020;aheadofprint(aheadofprint):459-66.
43. Rivera-Núñez Z, Kinkade CW, Zhang YT, Rockson A, Bandera EV, Llanos AAM, et al. Phenols, Parabens, Phthalates and Puberty: a Systematic Review of Synthetic Chemicals Commonly Found in Personal Care Products and Girls' Pubertal Development. Current Environmental Health Reports. 2022;9(4):517-34.
44. Harley KG, Berger KP, Kogut K, Parra K, Lustig RH, Greenspan LC, et al. Association of phthalates, parabens and phenols found in personal care products with pubertal timing in girls and boys. Hum Reprod. 2019;34(1):109-17.
45. Mozafarian N, Hashemipour M, Maracy MR, Pourrajab M, Omidi R, Kelishadi R. The study of pubertal stage and age of menarche in girls in Isfahan province, Iran. BMC pediatrics. 2025;25(1):87.
46. Onis Md, Garza C, Onyango A, Martorell R. WHO Child Growth Standards based on length/height, weight and age. 2006.
47. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Archives of disease in childhood. 1969;44(235):29
48. Abreu AP, Kaiser UB. Pubertal development and regulation. The lancet Diabetes & endocrinology. 2016;4(3):254-64.
49. Amin MM, Tabatabaeian M, Chavoshani A, Amjadi E, Hashemi M, Ebrahimpour K, et al. Paraben content in adjacent normal malignant breast tissues from women with breast cancer. Biomedical and Environmental Sciences. 2019;32(12):893-904.
50. Song Z-H,Wang Y-H,Qian Z-Z, Smillie TJ, Khan IA. Quantitative determination of 10 phenylpropanoid and lignan compounds in Lancea tibetica by high-performance liquid chromatography with UV detection. Planta Med. 2011;77(13):1562–6.
51. Hornung RW, Reed LD. Estimation of average concentration in the presence of nondetectable values. Applied occupational and environmental hygiene. 1990;5(1):46-51.
52. Rocque DA, Winker K. Biomonitoring of contaminants in birds from two trophic levels in the North Pacific. Environmental Toxicology and Chemistry: An International Journal. 2004;23(3):759-66.
53. Faghihimani Z, Nourian M, Nikkar AH, Farajzadegan Z, Khavariyan N, Ghatrehsamani S, Poursafa P, Kelishadi R. Validation of the Child and Adolescent International physical activity questionnaires in Iranian children and adolescents. ARYA Atherosclerosis Journal. 2010 Nov 30;5(4).
54. Adeniyi AF, Okafor NC, Adeniyi CY. Depression and physical activity in a sample of nigerian adolescents: levels, relationships and predictors. Child and adolescent psychiatry and mental health. 2011;5:1-10.
55. American Academy of Pediatrics: Children, adolescents, and television. Pediatrics. 2001;107(2):423-6.
56. Hemati Z, Mozafarian N, Heshmat R, Ahadi Z, Motlagh ME, Ziaodini H, et al. Association of sleep duration with metabolic syndrome and its components in children and adolescents; a propensity score-matched analysis: the CASPIAN-V study. Diabetology & metabolic syndrome. 2018;10:1-9.
57. Caro DH, Cortés D. Measuring family socioeconomic status: An illustration using data from PIRLS 2006. IERI Monograph Series Issues and Methodologies in Large-Scale Assessments. 2012;5:9-33.
58. Abdi H, Williams LJ. Principal component analysis. Wiley Interdisciplinary Reviews: Computational Statistics. 2010;2(4):433-59.
59. Dualde P, León N, Sanchis Y, Corpas-Burgos F, Fernández M, Hernández S, et al. Biomonitoring of phthalates, bisphenols and parabens in children: exposure, predictors and risk assessment. International Journal of Environmental Research and Public Health. 2021;18(17):8909.
60. Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. Urinary creatinine concentrations in the US population: implications for urinary biologic monitoring measurements. Environmental health perspectives. 2005;113(2):192-200.
61. Guo J, Zhang J, Wu C, Xiao H, Lv S, Lu D, et al. Urinary bisphenol A concentrations and adiposity measures at age 7 years in a prospective birth cohort. Chemosphere. 2020;251:12[illegible]340.
62. Jacobson MH, Woodward M, Bao W, Liu B, Trasande L. Urinary bisphenols and obesity prevalence among US children and adolescents. Journal of the Endocrine Society. 2019;3(9):1715-26.
63. Watkins DJ, Sánchez BN, Téllez-Rojo MM, Lee JM, Mercado-García A, Blank-Goldenberg C, et al. Phthalate and bisphenol A exposure during in utero windows of susceptibility in relation to reproductive hormones and pubertal development in girls. Environmental research. 2017;159:143-51.
64. Watkins DJ, Téllez-Rojo MM, Ferguson KK, Lee JM, Solano-Gonzalez M, Blank-Goldenberg C, et al. In utero and peripubertal exposure to phthalates and BPA in relation to female sexual maturation. Environmental research. 2014;134:233-41.
65. Berger K, Eskenazi B, Kogut K, Parra K, Lustig RH, Greenspan LC, et al. Association of prenatal urinary concentrations of phthalates and bisphenol A and pubertal timing in boys and girls. Environmental health perspectives. 2018;126(9):097004.
66. Zhou F, Jin ZZ, Li J, Huang J, Ye AZ, Hou CG. A preliminary study on the relationship between environmental endocrine disruptors and precocious puberty in girls. Journal of Pediatric Endocrinology & Metabolism. 2022;35(8):989-97.
67. Wolff MS, Pajak A, Pinney SM, Windham GC, Galvez M, Rybak M, et al. Associations of urinary phthalate and phenol biomarkers with menarche in a multiethnic cohort of young girls. Reproductive toxicology (Elmsford, NY). 2017;67:56-64.
68. Miao M, Wang Z, Liu X, Liang H, Zhou Z, Tan H, et al. Urinary bisphenol A and pubertal development in Chinese school-aged girls: a cross-sectional study. Environmental health : a global access science source. 2017;16(1):80.
69. Binder AM, Corvalan C, Calafat AM, Ye X, Mericq V, Pereira A, et al. Childhood and adolescent phenol and phthalate exposure and the age of menarche in Latina girls. Environmental health : a global access science source. 2018;17(1):32.
70. Wolff MS, Teitelbaum SL, McGovern K, Pinney SM, Windham GC, Galvez M, et al. Environmental phenols and pubertal development in girls. Environment International. 2015;84:174-80.
71. Wolff MS, Teitelbaum SL, Pinney SM, Windham G, Liao L, Biro F, et al. Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates, and phenols and pubertal stages in girls. Environmental health perspectives. 2010;118(7):1039-46.
72. Çok İ, İkidağ ÖT, Battal D, Aktaş A. Assessment of bisphenol a levels in preschool children: results of a human biomonitoring study in Ankara, Turkey. Journal of Clinical Research in Pediatric Endocrinology. 2020;12(1):86.
73. Supornsilchai V, Jantarat C, Nosoognoen W, Pornkunwilai S, Wacharasindhu S, Soder O. Increased levels of bisphenol A (BPA) in Thai girls with precocious puberty. Journal of Pediatric Endocrinology & Metabolism. 2016;29(11):1233-9.
74. Lu SY, Ren L, Liu YL, Ma HM, Liu S, Zhu Z, et al. Urinary parabens in children from South China: Implications for human exposure and health risks. Environmental Pollution. 2019;254.
75. Guth M, Pollock T, Fisher M, Arbuckle TE, Bouchard MF. Concentrations of urinary parabens and reproductive hormones in girls 6–17 years living in Canada. International Journal of Hygiene and Environmental Health. 2021;231:113633.

Table 1. Characteristics of the children with and without premature thelarche

Characteristics	Category	Total n=195	Control n=110	Case n=85	P value*
Child characteristics					
Age(year) [a]		7.5(0.6)	7.3 (0.6)	7.7(0.6)	<0.[illegible]01
Child BMI (kg/m2)	Underweight	11(5.4)	8(7)	3(3.3)	0.0[illegible]**
	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)	<[illegible]01
	Overweight and obese	70(34.3)	27(23.7)	43(4[illegible]8)	
Breastfeeding duration	Not breastfed	7(3.6)	2(1.8)	5([illegible])	0.357**
	<6 months	13(6.6)	7(6.3)	6(7)	
	>=6 months	177(89.8)	102(91.9)	[illegible](87.2)	
Feeding with soymilk	No	189(95.9)	106(95.5)	83([illegible]6.5)	1.000**
	yes	8(4.1)	5(4.5)	[illegible](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)	[illegible](4.7)	
	Mixed feeding	42(21.3)	[illegible](18)	22(25.6)	
Is the child under investigation 1 or multiple twins?	Singleton	191(96)	110(99.1)	81(92)	0.023**
	Twins and more	8(4)	[illegible](0.9)	7(8)	
Birth weight, g	<2500	21(10.6)	5([illegible])	16(18.2)	0.002
	≥2500	178(8[illegible]4)	106(9[illegible])	72(81.8)	
Season of birth	Spring	57(27.[illegible])	34(2[illegible]9.8)	23(25.6)	0.152
	Summer	[illegible](31.4)	4[illegible](36)	23(25.6)	
	Fall	[illegible](21.6)	19(16.7)	25(37.8)	
	winter	39([illegible].1)	20(17.5)	19(21.1)	
Birth order	First born	110([illegible]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]		[illegible]3(1.5)	3.02(1.4)	3.8(1.6)	0.001
Sleep duration (hour)	≤8	[illegible]0(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
	H[illegible]	75(38.1)	47(42.3)	28(32.6)	
Sun exposure time (hour)	[illegible]1	22(11.2)	16(14.4)	6(7)	0.157
	[illegible]-2	134(68)	69(62.2)	65(75.6)	
	2[illegible]	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)	
	Q3 (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/m2)	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 were according the chi-square (χ^2) and t test between the case and control group (where appropriate). **P values were according Fisher's exact test.
Abbreviations: BMI body mass index, ST screen time, PC personal computer, TV television, PA physical activity, SES socioeconomic status

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	
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
*Limit of detection. **Limit of quantitation. ***R-squared correlation. ****RSDs% (relative standard deviation)						

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=20	Control* n=114	Case* n=90	Pvalue
MeP	94.6	5.4(10.96)	3.06(2.60-3.60)	0.035	107.[illegible]	.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	3.3[illegible].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	101.0	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(0.3[illegible].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.[illegible]-2.[illegible])	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 referred to Mann-Whitney Test. Data are presented as median (IQR, interquartile range) Abbreviations: Minimum (Min), Maximum (Max), geometric mean (GM), Limit of detection (LOD), methylparaben (MeP), ethylparaben (EtP), propylparaben (PrP), butylparaben (BuP), benzylparaben (BzP) and bisphenol A(BPA)									

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

Compound		Range	Crude models (n=204) Case=90, control=114		Adjusted model[1] (n=195) case=85, control=110		Adjusted model[2*] (n=184) case =81, control=103	
			OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
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)	<0.00
	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)	0.0
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)	0.4
	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)	.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	0.0

Model 1 and 2 are adjusted for age, child BMI, birth order, birth weight, season of birth, maternal age at menarche, maternal age at deli ry, mother's height, socioeconomic status, screen time, sleep duration, physical activity and time of sun exposure
*The subjects with urinary creatinine less than 0.3g/l were excluded from the model[2].
Abbreviations: methylparaben(MeP), ethylparaben(EtP), propylparaben(PrP), butylparaben(BuP), benzylparaben (BzP) and isphenol A (BPA), Q: Quartile , OR=Odds ratio, CI=Confidence interval

Table 5. Bisphenol A concentration in some studies

First author	Publication year	Location	Study design	Sample size	ge	Median	GM (µg/g cr)
Dualde (59)	2021	Spain	Cross-sectional	562	5-12		0.90*
Jianqiu (61)	2020	China	Longitudinal	229	3	2.59	2.88
				412	7	2.41	4.66
Jacobson (62)	2019	U.S.	Cross-sectional	394	6-19		1.23
Çok (72)	2020	Turkey	Cross-sectional	125	3-6	0.60	1.05
Zhou (66)	2022	China	Case–control	Case=30	7.1(0.7)	5.87	
				Control=46	7.3(0.7)	0.24	
Supornsilchai (73)	2016	Thailand	Case–control	Case=41	7.44(1.03)	1.44	
				Control=47	7.44(1.03)	0.59	
Buttke (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
geometric mean (GM)

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 (59)	2021	Spain	Cross-sectional	562	5-12	GM	ng/ml	1.4	<0.2	0.39	<0.2	-
Lu (74)	2019	China	Cross-sectional	255	3-11	median	µg/l	2.3	0.33	0.50	0.02	0.03
Kiani (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 (44)	2019	California	cohort	179	9-13	GM	ng /g cr	44.9	-	4.9	-	-
Guth (75)	2021	Canada	Cross-sectional	382	6-17	GM	µg/g cr	10.7	0.84	1.8	0.23	-

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