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Urinary concentrations of bisphenols and parabens and their association with attention, hyperactivity and impulsivity at adolescence

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ABSTRACT

Background: Neurobehavioural disorder diagnoses have been increasing over the last decades, leading to heightened interest in the aetiological factors involved. Endocrine disrupting chemicals, such as parabens and bisphenols, have been suggested as one of those factors. It is unknown whether exposure during adolescence may affect neurobehavioural development.
Objective: To determine whether urinary concentrations of parabens and bisphenols are associated with attention and concentration in adolescents, in general and sex-specific.
Methods: We invited 188 adolescents (13–15 years old) for the follow-up birth cohort-study. Concentrations of five parabens and three bisphenols (BPA; BPF; BPS) were measured in morning urine after overnight fasting, using a validated LC-MS/MS method. Attention and concentration were assessed at the clinic with subtests of the Test of Everyday Attention in Children and the Dutch Attention Deficit Hyperactivity Disorder questionnaire (AVL), the latter being filled in by parents. Linear regression analyses were performed, adjusting for urine creatinine concentrations and potential confounding factors.
Results: 101 (54%) adolescents participated (46 girls; 55 boys). Urinary paraben concentrations were higher in girls than in boys. Methylparaben was positively associated with attention in girls ($p \leq .05$; B= −2.836; 95%CI= −5.175;−.497), ethylparaben negatively with hyperactivity ($p \leq .05$; B= −1.864; 95%CI= −3.587;−.141). Butylparaben was associated with more optimal scores on parent reported attention. Propylparaben was negatively associated with scores on sustained auditory attention in girls ($p \leq .10$; B=.444; 95%CI= −.009;.896). Bisphenol concentrations were not associated with scores on attention and concentration after adjusting for confounders.
Conclusion: In 13–15-year-old Dutch adolescents, urinary concentrations of methylparaben and ethylparaben were associated with better attention and less hyperactivity, whereas a trend toward significance was found between higher urinary propylparaben concentrations and poorer attention. Bisphenol concentrations were not associated with attention and concentration after adjusting for confounders.

1. Introduction

An increase in the prevalence of diagnosed neurobehavioural disorders, including attention deficit hyperactivity disorder (ADHD), has underscored the need to investigate the factors that may be involved in the aetiology of these disorders. ADHD, with a prevalence of 5% on

Abbreviations: AVL, Dutch Attention Deficit Hyperactivity Disorder Questionnaire; BenP, Benzylparaben; BMI, Body Mass Index; BPA, Bisphenol A; BPF, Bisphenol F; BPS, Bisphenol S; ButP, Butylparaben; EtP, Ethylparaben; LC-MS/MS, Liquid Chromatography-tandem Mass Spectrometry; LOD, Limit of Detection; MetP, Methylparaben; OH-PCB, Hydroxylated PCB; PCB, Polychlorinated Biphenyl; ProP, Propylparaben; TEA-Ch, Test of Everyday Attention in Children.

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average, has an early onset and often persists into adulthood. ADHD predisposes to other mental health disorders and generally leads to difficulties at school and at work (Sayal et al., 2018).

In the current study group, we previously found that prenatal exposure to certain persistent environmental chemicals was associated with attention at adolescence (Berghuis et al., 2018). Besides these persistent organic chemicals, there is increasing evidence for negative effects on human health by other endocrine disrupting chemicals (EDC) which are considered less persistent.

Two groups of these EDCs are bisphenols and parabens. Bisphenol A (BPA) and other phenols are mainly found in plastic food packaging and personal care products. The use of BPA has been limited or even prohibited in certain countries (Kolatorova et al., 2017). BPA is, however, often replaced by an analogue, such as bisphenol S (BPS) or bisphenol F (BPF). Parabens are primarily found in cosmetics and personal care products (Kolatorova et al., 2017). Exposure can occur through either inhalation, ingestion or dermal absorption (Harley et al., 2013; Kolatorova et al., 2017; Myridakis et al., 2016; Philippat et al., 2014; Rochester, 2013; Schug et al., 2015). Considering the mechanisms of exposure, children and adolescents would be at an increased risk for the effects of compound exposure due to the various ongoing endocrine processes that can be influenced by the endocrine disrupting compounds (Mundy et al., 2013).

Prenatal and childhood BPA exposure were found to be associated with adverse behavioural outcomes at school age, albeit with gross heterogeneity in the type of behavioural outcome between studies. Differences between sexes have been reported but again with great heterogeneity (Berghuis et al., 2015; Ejaredar et al., 2017; Mustieles et al., 2015; Li et al., 2020; Shoaff et al., 2020). The effects of BPF and BPS on human health are relatively unknown (Andra et al., 2015; Kolatorova et al., 2017). Regarding the effects of paraben exposure, Shiue reported that increased concentrations of butylparaben (ButP), methylparaben (MetP) and ethylparaben (EtP) were associated with increased need for emotional support in adults (Shiue, 2015). Baker et al. found that MetP measured in meconium was associated with ADHD at the age of 6–7 years old (Baker et al., 2020).

The aim of this study, therefore, was to examine whether urinary concentrations of bisphenols and parabens are associated with attention, hyperactivity and impulsivity in adolescents. Our secondary aim was to investigate whether there are sex-specific associations.

2. Materials and methods

2.1. Study design and cohort selection

This study is part of the Development at Adolescence and Chemical Exposure (DACE)-study, a longitudinal follow-up study of 13–15 year old adolescents, who were earlier included in two Dutch birth cohorts, studied during their prenatal period (Meijer et al., 2008; Soechitram et al., 2004), infancy (Berghuis et al., 2013, 2014; Meijer et al., 2012; Soechitram, 2013; Soechitram et al., 2017), toddlerhood (Ruel et al., 2019) and/or at school age (Roze et al., 2009). The DACE-study aims to investigate the associations between prenatal and adolescent exposure to persistent and non-persistent chemicals and neurobehavioral, endocrine, metabolic and anthropometric measures at adolescence.

The first cohort is the Risk of Endocrine Contaminants on human health (RENCO)-cohort (Soechitram et al., 2004), included in a prospective study on the effects of exposure to polychlorinated biphenyls (PCBs) and hydroxylated PCB metabolites (OH-PCBs) on human health. It consists of 104 mother-child-pairs enrolled between 1998 and 2000. The second cohort is the Groningen-Infant-COMPARE (Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens)-cohort, also known as GIC-cohort (Meijer et al., 2008), included in a prospective study on the effects of exposure to neutral and phenolic organohalogens on human health. The GIC-cohort consists of 90 mother-child-pairs enrolled between 2001 and 2002. Both studies originally met the following inclusion criteria: singleton pregnancy, term-born, healthy infants, living in the northern provinces of The Netherlands, and their mothers had to be of Western-European descent and without perinatal problems.

Inclusion in the follow up study was between April 2014 and December 2014, and between October 2015 and August 2016. At the time of follow-up, all adolescents were between 13 and 15 years old. Of the 194 eligible participants, six were excluded before invitation due to various reasons: four had no available data on prenatal persistent organic pollutant concentrations, one suffered severe cognitive impairment of unknown origin after inclusion in the cohort, and one had moved abroad. The remaining 188 were invited to participate in this study. One reminder was sent in case of no response. All adolescents and their parents provided their written informed consent before participation in the follow-up program. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen (UMCG), the Netherlands (2014/029).

2.2. Quantification of urinary paraben and bisphenol concentrations

To assess associations between adolescent urinary levels and developmental outcomes at adolescence, one morning urine sample after overnight fasting was collected on the same day that the attention was tested at the clinic. For almost all participants the morning urine sample was collected in a glass jar, except for five participants of which the urine was collected in a plastic jar. Until analysis, urine samples were stored at − 20 °C in glass tubes with a Teflon cap which had been prewashed twice with N-heptane. The concentrations of five parabens, three bisphenols and creatinine were measured at the department of Laboratory Medicine of the UMCG. The methodology of the analyses has been thoroughly described previously (Van der Meer et al., 2019).

In short, the urinary concentrations of MetP, EtP, propylparaben (ProP), ButP and benzylparaben (BenP) were simultaneously analysed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The urinary content of BPA, BPS, and BPF was analysed by the modified method for simultaneous quantitative determination using isotope dilution LC-MS/MS (Van der Meer et al., 2019). Three urine quality control samples (at low, medium and high concentrations), that were used for the validation procedure, were also analyzed when this study was analyzed. These were found within mean + /- 2 SD of the target values established during the validation procedure. A calibration curve is run every time samples are analyzed.

The limits of detection (LOD) were 0.14 ng/ml for MetP, 0.09 ng/ml for EtP, 0.07 ng/ml for ProP, 0.06 ng/ml for ButP, 0.07 ng/ml for BenP, 0.22 ng/ml for BPA, 0.23 ng/ml for BPF and 0.06 ng/ml for BPS.

2.3. Assessment of attention, hyperactivity and impulsivity

Attention, hyperactivity and impulsivity were assessed using the 'Test of Everyday Attention for Children' (TEA-Ch) and the parent-rated Dutch Attention Deficit Hyperactivity Disorder Questionnaire (AVL) (Scholte and van der Ploeg, 2004). The TEA-Ch is set up for children aged 6–16 years old and aims to identify attention problems. We applied the subtests 'Score!' and 'Sky Search'. The subtest 'Score!' assesses sustained auditory attention and the subtest 'Sky Search' assesses focused/selective visual attention (Schittekatte et al., 2007). The tests were performed in a one-on-one setting at the outpatient clinic with as little distraction as possible. The same room was used for all participants. The tests were administered by author SAB, trained by a child neuropsychologist, or administered by a trained research assistant under supervision of author SAB. Prior to the TEA-Ch tasks, the adolescents performed tasks on verbal and performance intelligence for 30 min. One hour before the neuropsychological part of the follow-up program they underwent a physical examination and a blood draw by venepuncture. Higher raw scores on 'Score!' and lower raw scores on 'Sky Search'

indicate a better outcome (Schittekatte et al., 2007).

The AVL questionnaire was completed by one of the parents in a separate room. It includes questions on three domains: attention deficit, hyperactivity and impulsivity. After filling in the questions, the parents got the opportunity to ask for clarification by the examiner, and to complete a question in case the examiner observed lacking answers. Higher raw scores on the AVL indicate a poorer outcome (Scholte and van der Ploeg, 2004).

2.4. Statistical analyses

Compounds with over 40% of the samples ≥LOD were analysed as continuous variables. For these compounds, values <LOD were taken into account as LOD/$\sqrt{2}$. Compounds with less than 40% of samples ≥LOD were analysed as dichotomous variables (<LOD versus ≥LOD) and compounds with less than 20% of samples ≥LOD were excluded from further statistical analyses. For uniformity, the raw 'Score' scores were inverted. For all analyses, positive correlation coefficients therefore indicate that higher compound concentrations were associated with poorer attention. Normal distribution of data was checked using Q/Q-plots and log10 transformations were performed when the data was not normally distributed.

We performed linear regression analyses with two main models. Our first model, the 'crude' model, only included urinary creatinine level in addition to the urinary compound level and the test score. Creatinine was used as a covariate in the multivariable analyses instead of using creatinine-adjusted urinary compound concentrations, as that would lead to overcorrection in the samples with compound concentrations <LOD.

For our second model, we considered to adjust for several confounders, in addition to the urinary creatinine level. We considered age at examination in years, sex (male=0; female=1), type of feeding (breast feeding =0/ formula feeding=1), body mass index (BMI), maternal age at delivery in years, maternal education, maternal alcohol use during pregnancy (yes/no) and maternal cigarette use during pregnancy (yes/no) as possible confounders (Arbuckle et al., 2016; Braun et al., 2011; Lim et al., 2017; Park et al., 2015; Perez-Lobato et al., 2016; Roen et al., 2015; Tseng et al., 2019). Maternal education was based on a < 14/≥ 14 years categorization. An education ≥ 14 years includes higher general senior secondary education, pre-university secondary education, higher vocational education and university. The BMI was calculated based on height and weight measurements at the clinic (for details on procedure see: Berghuis et al., 2022). Confounders with $p \leq 0.10$ in univariable linear regression analyses were included in our second model. The outcomes on the univariable analyses of the final confounders included in the models can be found in Supplementary Table A. In addition, we added the sex-compound concentration interaction term into the model to assess possible effects of sex on the correlation between compound exposure and behavioural outcome. Finally, parents were asked to report on their child's psychiatric history and use of ADHD medication which was used as an additional confounder in a supplementary third model.

A p-value < 0.05 was considered statistically significant. Considering the explorative nature of our study, we decided to also report associations with a p-value between 0.05 and 0.10 and consider them marginally significant, as is common in toxicological research. All data were statistically analysed using the Statistical Package for the Social Sciences version 23 (SPSS; IBM Corporation, Armonk, USA).

3. Results

3.1. Participants and clinical characteristics

Of the 188 adolescents invited, 101 (53.7%; 55 boys and 46 girls) consented and participated in this study. Forty-three (22.9%) mother-child pairs did not respond to the invitation and 44 (23.4%) declined to participate. Clinical characteristics of the 101 mother-child pairs are presented in Table 1. Within the GIC cohort, there was no significant difference between participating and non-participating adolescents in attention scores ('Score!' and 'Sky Search') at the age of 5–6 years. There was also no difference in total motor performance scores at school age or in maternal education level (Roze et al., 2009). The GIC cohort and the RENCO cohort differed significantly, with higher age at participation in the RENCO cohort ($p < .001$), higher BMI in the RENCO cohort ($p = .02$), higher MetP exposure in the GIC cohort ($p = .03$) and poorer Score and SkySearch attention scores in the GIC cohort ($p < .01$). Within our cohort, parent reported diagnosis of ADHD or ADD, or components of ADHD/ADD combined with a prescription of a psychostimulant was mentioned for 12 out of 101 adolescents (4 out of 46 girls; 8 out of 55 boys).

3.2. Compound concentrations

The concentrations of the parabens and bisphenols are presented in Table 2.

ButP, BPF and BPS were in less than 40% of samples ≥LOD and included as dichotomous variables (≥LOD versus <LOD), and BenP was in 5% of the samples ≥LOD and therefore excluded for further statistical analyses. Urinary Prop and BPS concentrations were significantly higher in girls compared with boys (Table 2). There was no significant difference in mean urinary concentrations of BPA, MetP, EtP, ProP between adolescents who collected their urine in plastic jar compared to adolescents who collected in a glass jar. Pearson correlation analyses for compound concentrations are shown in Supplementary Table B.

3.3. Outcomes of assessment of attention, hyperactivity and impulsivity

In Table 3 we present the raw scores and the number of adolescents with a (sub)clinical outcome based on scores in a norm population. No AVL was filled out for three adolescents, five adolescents had missing data on the subtest 'Score!' and one had missing data on the subtest 'Sky Search'. The missing data was the result of an error in testing procedure, or due to suboptimal testing circumstances. Poorer total scores on the parent-rated AVL questionnaire were associated with poorer scores on the researcher-rated 'Score' ($p = .012$; B= 2.955) and related with poorer scores on the researcher-rated 'SkySearch' ($p = .222$; B= 1.995). Poorer attention scores on the parent-rated AVL questionnaire were associated with poorer scores on the researcher-rated 'Score' ($p = .022$; B= 1.049), and related with poorer scores on the researcher-rated 'SkySearch'($p = .148$; B= 0.939).

Table 1
Characteristics of the study group (N = 101).

Characteristic	Total	Boys	Girls
Sex (n)	101	55	46
Age (years; mean ± SD)	14.40 ± 0.81	14.25 ± 0.75	14.58 ± 0.85
Child's BMI (kg/m^2; mean ± SD)	20.03 ± 3.58	19.46 ± 3.81	20.71 ± 3.20
ADHD medication at follow up (yes/no)[b]	7/94	4/51	3/43
Maternal age at delivery (years; mean ± SD)	32.07 ± 3.84	31.69 ± 3.57	32.52 ± 4.13
Smoking during pregnancy (yes/no)	13/88	6/49	7/39
Alcohol during pregnancy (yes/no)	21/80	9/46	12/34
Breastfeeding (yes/no)	63/38	35/20	28/18
Maternal education (<14 years / ≥14 years)[a]	50/51	25/30	25/21

BMI = Body Mass Index. SD= Standard Deviation. [a]≥ 14 years= higher general senior secondary education, pre-university secondary education, higher vocational education and university. [b] Based on medication use mentioned during hetero anamnesis.

Table 2
Urinary concentrations of parabens and phenols in 13- to 15-year-old adolescents (N = 101; 55♂; 46♀).

Compound	LOD (ng/ml)	n (%) above LOD	Median (IQR; ng/ml)	Geometric mean (95% CI; ng/ml)	*p* value t-test
Methylparaben	0.14	101 (100)	3.83 (1.73–13.22)	5.05 (3.76 – 6.93)	
Boys		55 (100)	3.23 (1.62–11.90)	4.24 (2.79 – 6.43)	.451
Girls		46 (100)	3.98 (1.88–15.00)	6.23 (4.07 – 10.22)	
Ethylparaben	0.09	85 (84)	0.25 (0.15–0.73)	0.35 (0.27 – 0.45)	
Boys		44 (80)	0.23 (0.12–0.42)	0.27 (0.19 – 0.38)	.342
Girls		41 (89)	0.39 (0.18–1.31)	0.47 (0.32 – 0.72)	
Propylparaben	0.07	74 (73)	0.30 (<LOD - 1.60)	0.43 (0.29 – 0.65)	
Boys		33 (60)	0.17 (<LOD - 0.78)	0.25 (0.16 – 0.39)	.030
Girls		41 (89)	0.64 (0.18–3.27)	0.85 (0.49 – 1.48)	
Butylparaben	0.06	22 (22)	<LOD (<LOD - <LOD)	0.06 (<LOD – 0.07)	
Boys		5 (9)	<LOD (<LOD - <LOD)	<LOD (<LOD - <LOD)	< .001
Girls		17 (37)	<LOD (<LOD - 0.22)	0.08 (0.06 – 0.11)	
Benzylparaben	0.07	5 (5)			
Boys		3 (6)			
Girls		2 (4)			
Bisphenol A	0.22	101 (100)	1.64 (0.96–2.99)	1.75 (1.46 – 2.10)	
Boys		55 (100)	1.71 (0.87–3.22)	1.81 (1.42 – 2.32)	.804
Girls		46 (100)	1.58 (1.03–2.72)	1.69 (1.33 – 2.22)	
Bisphenol F	0.23	35 (35)	<LOD (<LOD - 0.58)	0.30 (0.25 – 0.37)	
Boys		19 (35)	<LOD (<LOD - 0.65)	0.31 (0.24 – 0.41)	.859
Girls		16 (35)	<LOD (<LOD - 0.43)	0.30 (0.23 – 0.40)	
Bisphenol S	0.06	26 (26)	<LOD (<LOD - 0.07)	0.06 (<LOD – 0.08)	
Boys		12 (22)	<LOD (<LOD - <LOD)	<LOD (<LOD – 0.07)	.012
Girls		14 (30)	<LOD (<LOD - 0.09)	0.07 (<LOD – 0.10)	

Values <LOD were taken into account as LOD/$\sqrt{2}$ when calculating the mean and median in these analyses.

3.4. Associations between urinary parabens and phenols and test scores

In Tables 4 and 5 we present the associations between the urinary paraben concentrations and the outcomes on the TEA-Ch and AVL for the two main models. Details on the confounders included in each model can be found in Supplementary Table A. The results of all statistical analyses on associations between compound concentrations and outcome measurements can be found in the Supplementary Tables C and D. The outcomes of the supplementary model with ADHD medication use as confounder can be found in Supplementary Table E. Lastly, two scatterplots of the main outcomes can be found as Supplementary data F and G.

In girls, we found that higher urinary concentrations of MetP were associated with more optimal outcomes on parent-rated attention. These associations remained significant after adjusting for confounders. This association was also found to be marginally significant in the total cohort after adjusting for being formula-fed.

Table 3
Outcomes on attention and concentration in 13–15- year-old adolescents.

Outcome	*n*	Raw score (mean ± SD)	(Sub)clinical[a,b]
AVL total score	98	12.6 ± 14.3	7%
Boys			6%
Girls			9%
AVL attention	98	5.1 ± 5.7	12%
Boys			13%
Girls			11%
AVL hyperactivity	98	4.1 ± 5.0	6%
Boys			8%
Girls			4%
AVL impulsivity	98	3.4 ± 4.8	5%
Boys			4%
Girls			7%
TEA-Ch 'Score!' sustained attention	96	9.0 ± 1.3	10%
Boys			15%
Girls			5%
TEA-Ch 'SkySearch' selective attention	100	2.5 ± 0.9	9%
Boys			9%
Girls			9%

[a]For AVL ≥ 90th percentile, based on sex-based parent-rated standard,
[b]For TEA-Ch ≤ 15th percentile.
AVL = Dutch ADHD Questionnaire, TEA-Ch = Test of Everyday Attention in Children.

A trend towards significance was found between higher urinary concentrations of EtP and more optimal outcomes on parent-rated attention. After adjusting for confounders, higher urinary concentrations of EtP were associated with better hyperactivity subscores in the total cohort and a trend was found with better total AVL scores in the total cohort.

A trend was found between higher urinary concentrations of ProP and poorer scores in the female sub cohort on the sustained auditory attention task at the clinic. This trend remained after adjusting for confounders.

With regard to ButP, trends towards significance as well as significant associations were found between ButP concentrations ≥LOD, compared to concentrations <LOD, and more optimal scores on the AVL and TEA-Ch. The associations with the AVL sub scores remained significant for the total cohort after adjusting for confounders whereas almost none of the associations with TEA-Ch scores did. In the female participants of the cohort, ButP was not associated with the AVL sub scores on attention and hyperactivity in the crude model. However, after adjusting for confounders, there were marginally significant associations between higher ButP concentrations and better scores on attention and hyperactivity in girls, as scored by their parents.

Finally, with regard to bisphenols, a trend was found between urinary BPS concentrations ≥LOD and poorer scores on the sustained auditory attention task ('Score') at the clinic in the crude model (B= 0.533; 95% CI= −0.070; 1.137; and for girls: B= 0.841; 95%CI= −0.052; 1.733). These associations were no longer significant after adjusting for confounders. No significant associations were found between BPA concentrations or BPF concentrations (≥ LOD compared to <LOD) and scores on attention or parent-reported ADHD-like behaviour. The sex-compound concentration interaction term was not significant in any of the analyses.

3.5. Sub analyses including scores at school age

For the significant or marginal significant associations displayed in Tables 4 and 5 we performed subanalyses for the adolescents who also performed exactly the same tasks at school age ('Score' n = 40; 'Sky Search' n = 44; AVL n = 34) (Roze et al., 2009). With regard to the 44 participants also included at school age, the participants with (sub) clinical scores on 'Score' (n = 7) and 'SkySearch'(n = 6) at school age had poorer scores at adolescence compared with participants with

Table 4
Multivariate linear regression analyses between urinary Methyl-, Ethyl- and Propylparaben concentrations and the scores on attention and concentration at adolescence.

			Model 1[a]			Model 2[b]		
Compound	Outcome	n	B	95% CI	R^2	B	95% CI	R^2
Log Methylparaben[c]	AVL Attention	98	-1.388	-3.111;0.336	.027	-1.671[d] *	-3.419; 0.077	.052
		♀45	-2.299 * *	-4.547;− 0.052	.121	-2.836[d] * *	-5.175;− 0.497	.165
Log Ethylparaben[c]	AVL Total	98	-3.244	-8.332;1.843	.018	-4.368[d] *	-9.422;0.686	.074
		♀45	-4.130	-10.645;2.385	.055	-5.568[d] *	-12.198;1.062	.113
	AVL Attention	♀45	-2.335 *	-4.828;0.158	.108	-2.766[d] *	-5.336;− 0.197	.142
	AVL Hyperactivity	98	-1.367	-3.135;0.401	.025	-1.864[d] * *	-3.587;− 0.141	.116
Log Propylparaben[c]	TEA-Ch 'Score'	♀44	0.469 *	-0.023;0.962	.090	0.444[e] *	-0.009;0.896	.253

AVL: Dutch Attention Deficit Hyperactivity Disorder questionnaire;
TEA-Ch: Test of Everyday Attention in Children;
'Score' tests sustained auditory attention; the 'Score' score was inverted in order to create a uniform meaning of a negative coefficient;
Only associations with $p \leq .10$ in at least one model are displayed in this Table; no significant associations were found for SkySearch;
* = p ≤ .10 and * * = p ≤ .05. Negative correlation coefficients indicate that higher compound concentrations were associated with better attention and vice versa;
[a] Model 1: Crude model: urinary compound concentrations + creatinine;
[b] Model 2: Urinary compound concentrations + creatinine + confounders p ≤ .10 according to univariate analyses [d,e];
[c] Values <LOD were replaced by LOD/$\sqrt{2}$;
[d] Adjusted for: Creatinine and being formula-fed;
[e] Adjusted for: Creatinine and age at examination.

Table 5
Multivariate linear regression analyses between urinary Butylparaben concentrations (≥LOD vs <LOD) and the scores on attention and concentration at adolescence.

		Model 1[a]			Model 2[b]		
Outcome	n ≥ LOD; (%)	B	95% CI	R^2	B	95% CI	R^2
AVL							
Total	22 (22%)	-8.721 * *	-15.479; − 1.962	.066	-8.950[c] * *	-15.575; − 2.324	.113
	♀ 17 (38%)	-7.208 *	-14.947; 0.531	.094	-7.346[c] *	-15.030; 0.338	.130
Attention	22 (22%)	-3.170 * *	-5.869; − 0.471	.055	-3.224[d] * *	-5.914; − 0.533	.071
	♀17 (38%)	-2.815	-5.842;0.212	.107	-2.847[d] *	-5.893; 0.199	.119
Hyperactivity	22 (22%)	-2.957 * *	-5.320; − 0.595	.062	-3.058[d] * *	-5.337; − 0.779	.137
	♀ 17 (38%)	-2.081	-4.646;0.483	.060	-2.139[d] *	-4.653;0.375	.120
Impulsivity	22 (22%)	-2.594 * *	-4.846; − 0.341	.063	-2.668[d] * *	-4.879; − 0.457	.107
	♀ 17 (38%)	-2.312 *	-5.032;0.409	.090	-2.360[d] *	-5.062; 0.342	.126
TEA-Ch							
'Score'	22 (23%)	-0.631 * *	-1.254;− 0.009	.042	-0.393[c]	-0.986;0.200	.177
	♀17(39%)	-0.769 *	-1.604;0.066	.085	-0.493[c]	-1.311;0.324	.209
'SkySearch'	22 (22%)	-0.605 * *	-1.048; − 0.162	.080	-0.405[e] *	-0.861; 0.051	.189
	♀ 17 (38%)	-0.538 *	-1.093; 0.017	.121	-0.437[e]	-0.997;0.123	.225

AVL: Dutch Attention Deficit Hyperactivity Disorder questionnaire;
TEA-Ch: Test of Everyday Attention in Children;
LOD: Limit of Detection;
'Score' tests sustained auditory attention; the 'Score' score was inverted in order to create a uniform meaning of a negative coefficient;
'Sky Search' tests selective visual attention; Only associations with $p \leq .10$ in at least one model are displayed in this Table;
* = $p \leq .10$ and * * = $p \leq .05$; Negative correlation coefficients indicate that higher compound concentrations were associated with better attention and vice versa.
[a] Model 1: Crude model: Butylparaben level (≥LOD vs <LOD) + creatinine;
[b] Model 2: Butylparaben level (≥LOD vs <LOD) + creatinine + confounders $p \leq .10$ according to univariate analyses[c,d,e];
[c] Adjusted for: Creatinine and age at examination;
[d] Adjusted for: Creatinine and being formula-fed;
[e] Adjusted for: Creatinine, age and sex of the child, education level of the mother.

normal scores at school age (Score: mean= 7.57 ± 1.90 versus 8.82 ± 1.16; $p = .02$; Sky Search (mean = 3.52 ± 1.48 versus 2.56 ± 0.77; $p = .017$). After adding the scores at school age as a confounder to Model 1 (which includes attention score, urinary compound level and urinary creatinine level), a marginally significant correlation remained between ProP concentrations and poorer 'Score' scores in girls at adolescence (n = 16; B= 0.912; $p = .071$). For MetP, the association with lower attention deficit scores on the AVL became marginally significant after including the score on the same domain at school age into Model 1 (total group n = 34; B= −1.76; 95%CI= −3.61 to 0.09; $p = .062$). After adjusting for the AVL score at school age, EtP was significantly associated with higher hyperactivity scores on the AVL(n = 15; B= 2.43; 95% CI= 0.88–3.97; $p = .005$).

4. Discussion

This study determined the associations between urinary bisphenol and paraben concentrations and attention, hyperactivity and impulsivity in Dutch adolescents, aged 13–15 years old. The results indicated that higher urinary concentrations of MetP and EtP were associated with better parent reported attention, and that there was a trend between higher concentrations of ProP in girls and poorer scores on sustained auditory attention. Urinary ButP concentrations ≥LOD, compared to concentrations <LOD, were found to be related with more optimal scores on both parent reported attention and the attention tasks at the clinic. After adjusting for confounders, none of the bisphenol compounds was associated with attention or parent-reported ADHD-like behaviour in our study group.Regarding MetP, EtP, ProP and ButP concentrations and their association with attention, hyperactivity and

impulsivity, only a few studies have been performed. Baker et al. found that higher concentrations of MetP, measured in meconium, were associated with a higher risk of ADHD at the age of 6–7 years old, which is in contrast to our findings (Baker et al., 2020). A recent study by Shoaff et al. found no significant associations between paraben concentrations and ADHD-like behaviour (Shoaff et al., 2020). To our knowledge no other previous studies have been performed to compare our findings with.

When comparing the measured urinary paraben concentrations in our study-group with those measured in children by other studies, our concentrations measured appear to be relatively low (Calafat et al., 2010; Larsson et al., 2014; Shoaff et al., 2020). The paraben concentrations measured in our study are more in line with the concentrations reported by Larsson et al. than with the higher concentrations reported by Shoaff and Calafat et al. This might be explained by the population differences. Our cohort and the cohort of Larsson et al. are both European cohorts, whereas the cohorts by Calafat et al. and Shoaff et al. are American. It is, however, difficult to compare compound exposure concentrations as the different studies use different methods and units for compound levels.

Regarding bisphenols, we found no associations between higher BPA or BPF concentrations and the test results on attention, hyperactivity and impulsivity. A trend was found between BPS and poorer sustained attention in the crude model but it was not significant in the adjusted model. Various studies found prenatal and postnatal BPA to be associated with adverse behavioural outcomes in children at school age, although the exact effects were heterogeneous between study cohorts (Berghuis et al., 2015; Ejaredar et al., 2017; Mustieles et al., 2015). More in accordance with our results, the previously mentioned study by Shoaff et al. found no significant associations between BPA, BPF or BPS and ADHD-like behaviour, even though their participants had higher concentrations (Shoaff et al., 2020). Studies on the analogues BPF and BPS are scarce and to our knowledge no previous other studies have been performed to compare our findings with.

When comparing our median BPA exposure to those in other studies displayed in the review by Mustieles et al., our relatively low BPA exposure compared with the other childhood BPA measurements might be explained by the older age at examination in our study, as Mustieles et al. clearly shows BPA exposure to decrease with age (Mustieles et al., 2015). This might be related to the fact that young children mouth on plastic more frequently and that metabolism improves with age. Our cohort consisted of adolescents aged 13–15 years and the concentrations measured in our cohort may therefore be more comparable, age-wise, to the maternal BPA concentrations than to the childhood BPA concentrations measured in children aged 1–5 years mentioned in the review by Mustieles et al. (Mustieles et al., 2015). Taking this into regard, the urinary BPA concentrations measured in the adolescents in our cohort are similar to the maternal urinary BPA concentrations in several studies mentioned by the review by Mustieles et al., and to the BPA concentrations in 8–11 year-old children in the study by Hong et al., 2013 (Braun et al., 2009, 2011; Evans et al., 2014; Harley et al., 2013; Hong et al., 2013; Miodovnik et al., 2011; Mustieles et al., 2015; Perera et al., 2012; Roen et al., 2015; Yolton et al., 2011).

Few studies have reported on the mechanisms behind the effects of parabens and bisphenols on behavioural outcome. Recurring theories report on possible effects on oestrogen concentrations and thyroid function (Li et al., 2020; Rochester, 2013; Roen et al., 2015; Schug et al., 2015; Kolatorova et al., 2017; Baker et al., 2020), with oestrogen concentrations affecting dopamine concentrations and thereby causing inattention and impulsivity (Schug et al., 2015; Sharma and Couture, 2014) and thyroid hormones being important for neurodevelopment and development of the hippocampus with abnormal development being associated with deficits in learning and memory (Chopra et al., 2014). In our study we did not find associations between BPA and outcome measures, but we did find a trend between BPS and poorer attention. To the best of our knowledge, no research has been published about underlying mechanisms for associations between higher BPS concentrations and behavioural outcomes. Considering that BPS is an analogue of BPA, BPS might act in a similar way as BPA.

Studies on possible explanations for the associations between chemical exposure and more optimal outcome are scarce. Previous studies on the effects of BPA at school age have shown that there are differences in the direction of effects and sex-specific effects, depending on whether the associations were reported for concentrations measured during the prenatal or postnatal period. Prenatal exposure seems to be associated with more internalizing and externalizing behaviour in boys and less in girls, whereas postnatal exposure was associated with more internalizing and externalizing behaviour in girls but less symptoms in boys (Roen et al., 2015). Studies reporting these effects have not addressed possible working mechanisms for higher exposure resulting in fewer symptoms (Roen et al., 2015). Even positive associations are a cause of concern, as we do not know whether the mechanisms behind these associations may have adverse effects in the long run or on other processes in the body. Future research should focus on whether exposure concentrations measured at different moments (prenatally; early or late postnatally) can differentially influence the outcomes, and on whether associations can change over time during development, by including assessments at several ages.

Regarding the sex-specific associations found in this study, previous studies suggest that parabens and bisphenols can affect the male and female endocrine system in different ways (Ejaredar et al., 2017; Mustieles et al., 2015). However, our analyses with sex-compound exposure interaction term suggest that there are other factors at play than sex for the sex-specific associations. The higher levels of exposure to endocrine disrupting compounds in girls found in our study, possibly explained by the more frequent cosmetic use, might be one of these factors, as a broader range of exposure will more likely accommodate the discovery of exposure-outcome associations. Future studies should consider individual-specific use of products to find the main sources of paraben and bisphenol exposure and the differences in exposure for sex.

The main strength of our study is the fact that we assessed urinary levels of BPS and BPF, BPA analogues of which effects on behaviour are still relatively unknown. To our knowledge, we are one of the first to report on the urinary concentrations of BPS and BPF in children. Another strength of this study is that our participants were seen at the clinic for assessment of their performance on attention tasks, in addition to the questionnaires filled in by the parents. This increases the reliability of the assessment as parents may interpret their child's functioning in a different way than clinicians. The attention tasks were administered by the same examiner for 74% of our cohort and the remaining 26% were seen by either one of two research assistants working with supervision of this examiner, thereby limiting the risk for bias due to inter-observer variation. In addition, we were able, albeit in a smaller sample size, to adjust for attention scores on the same sub tasks and parental questionnaire at school age. Finally, the urinary samples were collected on the same day as the attention tasks, therefore limiting the time between assessment of exposure and outcome measure.

We also recognize some limitations of our study. First, for some compounds the number of samples with detectable urinary compound concentrations were too low to be included as continuous variable in the analyses. To address this limitation without losing information, we decided to use dichotomized variables ($<$LOD and $\geq$LOD) for all compounds with 20–40% of samples $\geq$LOD. Second, our cohort was relatively small and the explorative aspect might lead to type I errors. Nevertheless, we believe that the results of our explorative study on a relatively large number of EDCs, may add to the currently scarce knowledge on the effects of these EDCs on the development of children. A third limitation is that our data on urinary compound concentrations was limited to one sample of urine for each participant, making it impossible to adjust for the fluctuation of the compound concentrations over 24 h, or to estimate exposures earlier in life. To address this limitation, we did adjust for urinary creatinine concentrations. Data on long-

term exposure estimates of bisphenols and parabens are limited. Being non-persistent compounds, results based on spot urine samples of bisphenols and parabens should be interpreted with caution, as mentioned by LaKind et al. (LaKind et al., 2019). However, in a Dutch cohort including adults with impaired fasting glucose, van der Meer et al. observed that within-person temporal correlations over a median follow-up time of 47 months were significant for all parabens but not for BPA and BPF measured in 24 h urine samples (Van der Meer et al., 2021). This implies that paraben exposure remains relatively consistent over longer time periods. Concerning spot urine samples versus 24 h urine samples, Christensen et al. tried to compare results of several studies using either spot urine samples versus 24–48-h samples, and found that overall spot urine concentrations of BPA have variability roughly comparable with corresponding 24-h average concentrations obtained from a comparable population, which might suggest that spot samples can be used to characterize population distribution of intakes (Christensen et al., 2012). Christensen et al. wrote that surveys using one sample during a day may miss some of the high concentrations that would be seen if they sampled all urine events over the course of a day (Christensen et al., 2012). The time of sampling was similar across the samples in our study, and we corrected for urinary creatinine levels. Caution is warranted with interpretation of the results. The half-life of BPA is considered to be around 21 h (Sasso et al., 2020), the half-life of parabens less than 24 h (Fransway et al., 2019). The samples were taken after an overnight sleep. Compound levels might peak shortly after individual exposure events. We suggest that less exposure events take place during night time compared to day time and that therefore sampling after an overnight sleep might reduce heterogeneity between the samples due to individual exposure events. Because other studies also used morning urine samples as estimation of daily exposure, we were able to compare the levels. Interpretation of the results should be done with caution, because peaks of high exposure after exposure events may be missed as suggested by Christensen et al. (Christensen et al., 2012). A fourth limitation is that the urine was collected in a clean glass jar provided by the participants. We cannot rule out the possibility of contamination during the cleansing or collection procedure. The urine sample was stored a limited time (approximately one to two hours) in the sampling jar after the sample was transferred with a glass pipet to a prewashed glass tube. For future studies, it is important to use prewashed glass collection jars/tubes to lower the risk of the collection jar as potential source of analyte contamination. A fifth limitation is that we did not quantify the use of products containing parabens and bisphenols in the weeks prior to the urine sample collection. We were therefore not able to assess whether the factor of avoiding paraben-containing cosmetic products is associated with attention and concentration in adolescents. A final limitation is the possibility of selection bias. Our cohort consisted of families with relatively well-educated mothers. We therefore adjusted our analyses for maternal education as confounder. Also, participants who volunteered to participate in a study on the effects of environmental chemicals might be more conscious on the use of chemicals in their household products or personal care products and might avoid the use of these chemicals more than the overall population.

Our study may have implications. The associations between concentrations of several compounds and altered attention may have consequences for public health. Exposure is ubiquitous, as it occurs via daily used consumer products. Our study suggests that parabens are associated with outcomes at adolescence and therefore caution is warranted for their use and particularly for the introduction of new chemicals like analogues. Some countries have already installed rules for the use of bisphenols and parabens (European Parliament, 2014, 2018; FDA, 2018). The findings of our study underline the importance of adequate legislation regarding the use and production of these chemicals. Our data raises important questions, which warrants further study. Future studies are needed to explore whether the associations found in our study might be caused by a short-term effect of the compounds or by disturbances of developmental trajectories, whether the effects of the compounds we found in our study are lasting, and whether similar associations are observed in adulthood. Future studies should aim for a larger cohort, adjust for ADHD family history and prenatal compound concentrations. Another very important future objective would be to investigate the underlying mechanisms for the effects of bisphenols and parabens on ADHD-like behaviour.

5. Conclusion

In this explorative study, we found that higher urinary concentrations of MetP and EtP were associated with less parent-reported ADHD-like behaviour. ButP concentrations ≥LOD, compared to concentrations <LOD, were associated with more optimal scores on parent reported attention. Higher urinary concentrations of ProP were associated with less optimal sustained auditory attention in 13–15-year-old girls. After adjusting for confounders, none of the bisphenols were associated with attention, hyperactivity or impulsivity. Taken together, the findings of this explorative study suggest that exposure to bisphenols during adolescence is not associated with an increase in ADHD-like symptoms. However, our findings do suggest that ProP exposure may increase ADHD-like symptoms and that parabens can influence attention scores, and therefore warrant cautious use and awareness when introducing new compounds.

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Approval by medical ethical committee

This study is part of the Development at Adolescence and Chemical Exposure (DACE)-study, which has been approved by the Medical Ethical Committee of the University Medical Center Groningen (2014/029: 'Effects of exposure to environmental chemicals on development during adolescence').

CRediT authorship contribution statement

A.B. Foreman: Conceptualization, Methodology, Validation, Formal analysis, Writing – original draft, Project administration. **J.V. van Vliet:** Resources, Investigation, Writing – review & editing, Supervision, Funding acquisition. **M. van Faassen:** Resources, Investigation, Formal analyses, Writing – review & editing. **I.P. Kema:** Resources, Investigation, Writing – review & editing. **B.H.R. Wolffenbuttel:** Resources, Writing – review & editing. **P.J.J. Sauer:** Conceptualization, Resources, Writing – review & editing. **A.F. Bos:** Conceptualization, Methodology, Resources, Data curation, Writing – REview & Editing, Supervision, Project administration. **S.A. Berghuis:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuro.2023.01.006.

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