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Prenatal bisphenol A exposure is associated with language development but not with ADHD-related behavior in toddlers from the Odense Child Cohort

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ABSTRACT

Bisphenol A (BPA) is a non-persistent chemical with endocrine disrupting abilities widely used in a variety of consumer products. The fetal brain is particularly sensitive to chemical exposures due to its rapid growth and complexity. Some studies have reported associationbetween maternal BPA exposure and behavior but few have assessed impact on cognitive development, and to our knowledge no studies have specifically assessed the impact on language development. We therefore assessed whether maternal urinary BPA concentration during pregnancy was associated with language development and attention-deficit and hyperactivity disorder (ADHD) symptoms in offspring aged 18–36 months in the prospective Odense Child Cohort. BPA was analyzed in 3rd trimester maternal fasting urine spot samples. Language development was addressed among 535 children using the Danish adaptation of the MacArthur-Bates Communicative Development Inventories at median age 21 months; ADHD traits were assessed by parents of 658 children using the Child Behavior Checklist for ages 1½-5 years at mean age 2.7 years. Associations were assessed using logistic regression models comparing children below the 15th percentile score for language and above the 85 percentiles score for ADHD with the other children while stratifying by sex and adjusting for maternal education, duration of breastfeeding and maternal urine phthalates. BPA was detected in 85.3% of the urine samples (median 1.2 ng/ml). Boys of mothers with BPA exposure in the highest tertile had an odds ratio of 3.70 (95% CI 1.34–10.21) of being in the lowest 15th percentile of vocabulary score compared to boys of mothers within the lowest tertile of BPA exposure after adjustment, whereas no association was found in girls. No clear dose-response relationship between maternal BPA and ADHD scores above the 85th percentile was found for either sex. Since early language development is a predictor of future reading skills and educational success, more epidemiological studies assessing BPA exposure and language skills are needed to confirm our findings.

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1. Introduction

Bisphenol A (BPA) is a non-persistent chemical produced in very large quantities worldwide to make polycarbonate plastics and epoxy resins. It is widely used in a variety of consumer products including some food and beverage storage plastic containers, food can linings, thermal paper receipts, medical equipment, dental sealants, and children's toys, clothes among other applications (Vandenberg et al., 2007; Xue et al., 2017). The primary source of exposure to BPA is through the diet and BPA has been detected in urine samples of 95% of the general population in the US and Europe (LaKind and Naiman, 2015; Vandenberg et al., 2007). BPA has weak estrogenic properties and has been recently recognized as a suspected agent causing developmental neurotoxicity (Grandjean and Landrigan, 2014).

The fetal brain may be particularly sensitive to endocrine disrupting effects of BPA due to its rapid growth and complexity, and exposure occurring during this vulnerable time window can have a lifelong health impact (Schug et al., 2011, 2015). A number of epidemiologic studies have reported associations between maternal urinary BPA concentrations at different time points during gestation and child behavior, including more symptoms of hyperactivity, aggression and anxiety, especially in boys (Braun et al., 2009, 2011; Casas et al., 2015; Evans et al., 2014; Harley et al., 2013; Hong et al., 2013; Maserejian, 2014; Perera et al., 2016; Perez-Lobato et al., 2016; Philippat et al., 2017; Roen et al., 2015). Only one study did not find association in boys but found increased externalizing behavior in girls (Braun et al., 2011). Few studies have assessed neuropsychological outcomes and most have reported no associations (Braun et al., 2017b; Casas et al., 2015; Nakiwala et al., 2018; Stacy et al., 2017). However, these studies are characterized by differences in the exposure assessment (urine or dental composite), the time window of exposure (pre- or postnatal), the sex-specific directions of the associations, the specific behavioral domain tested and/or the sociodemographic characteristics of the populations (Mustieles et al., 2015). Importantly, the relationship between BPA exposure and language development as an independent outcome and not a part of IQ assessment has not been previously addressed. In a previous study among 518 mother-child pairs from the Odense Child Cohort, we found associations between higher maternal phthalate exposure and poorer language development in 20–36 months old boys, whereas no association was found in girls (Olesen et al., 2018). We therefore wanted to explore if this association was also found for prenatal BPA exposure.

Given the importance of language development for the prediction of future educational success and neuropsychological health (Bleses et al., 2016; Elbro et al., 2011), and that the relationship between BPA exposure and children's neurobehavior is in the spotlight (Mustieles et al., 2018), we aimed to assess whether maternal urinary BPA concentration during pregnancy was associated with language development and attention-deficit and hyperactivity disorder (ADHD) symptoms in toddlers aged 18–36 months among mother-child pairs from the Odense Child Cohort.

2. Materials and methods

2.1. Study population

All pregnant women living in the Municipality of Odense from 2010 to 2012 were invited to participate in the prospective Odense Child Cohort (OCC) at a voluntary information meeting introducing the ultrasound examinations at Odense University Hospital or at their first antenatal visit at gestational week 8–16 (Kyhl et al., 2015). A total of 2874 pregnant women were recruited and 2490 families are still participating in 2018. The non-participants were on average younger, more often smokers and multiparous, whereas educational level and birth weight did not differ between participants and non-participants (Kyhl et al., 2015).

At gestational weeks 28, women were asked to deliver a spot urine sample at the visit site stored in freezers at the Odense Patient data Explorative Network (OPEN) at −80 °C. Information regarding maternal health was obtained through questionnaires filled in during pregnancy. Self-reported education was obtained from questionnaires; this information was missing for 131 women and was therefore instead coded from the occupational status listed in the birth records. Maternal ethnicity was obtained from data from the municipality which have information about all women within the municipality.

Data on birth characteristics was extracted from obstetric and pediatric hospital records. Information regarding the child's health, including duration of breastfeeding, was obtained from questionnaires answered by the parents when the child was 3 and 18 months. These data were supplemented with data from a clinical examination at approximately 18 months of age (median 19.2, range = 17.5–23.5 months) performed by trained technicians. The clinical examination included anthropometric measurements [length (cm), weight (g), head circumference (cm)].

2.2. BPA exposure assessment

Maternal concentration of BPA in overnight fasting morning spot urine samples was measured in a subset of 849 women (including mothers with twins and non-ethnic Danish mothers). The urine samples were collected in gestational week 28 (median 28.7, range 26.4–34.0) and before 09:30 a.m. All urine samples were deconjugated by enzymatic hydrolysis and then the total (free and deconjugated) concentration of BPA were measured by a method for simultaneous quantitative determination of BPA and other simple phenols using isotope dilution TurboFlow-LC-MS/MS as previously described (Frederiksen et al., 2013). The limit of detection (LOD) for urinary BPA was 0.12 ng/ml. The samples were analyzed in 17 batches in two periods about a year apart. The first 200 randomly selected samples were analyzed from December 2011 to January 2012. The remaining samples were analyzed at the end of 2012 and were selected according to availability of questionnaire and clinical data. There was no difference in samples that were measured in the two measuring periods and the data has previously been published (Frederiksen et al., 2014). The osmolality (Osm/kg) of each individual urine sample, which is a measure of urinary dilution, was measured by the freezing point depression method using automatic cryosopic osmometer (Osmomat® 030 from Gonotec, Berlin, Germany). To assess the precision of the osmolality measurements a control standard urine pool was also measured. The mean urinary osmolality in this pool (n = 77) was 0.825 Osm/kg, with a relative standard deviation of 1.85%. The median (range) osmolality of all urine samples included in this study was 0.639 (0.094–1.117) Osm/kg (Lassen et al., 2013; Middleton et al., 2016).

2.3. Language development assessment

Language development was assessed using the validated Danish adaptation (Bleses et al., 2008) of the MacArthur-Bates Communicative Development Inventories (MB-CDI) (Fenson et al. (2007)). The parents completed an electronic version of the MB-CDI questionnaire (MB-CDI "Words and Sentences") regarding their child's current language skills, every third month between the age of 18 and 36 months. The questionnaires contained seven subscales. For our study, we chosed to focus on two of these, which are related to important aspects of language development at this age span, and which at the same time are known to be good predictors of later reading development (Bleses et al. (2016)). The two categories were: a) Vocabulary (725 items - 22 semantic categories) which focuses on the individual child's use of commonly used words for toddlers (lexicon), and b) Complexity (33 items) which focuses on the child's use of grammar and syntactic complex sentences (morphosyntax).

We included only data from the initial MB-CDI questionnaire filled

out for each child, as some parents only filled in few questionnaires and others many and at different ages. We generated a productive vocabulary summary score (number of produced words). Complexity data was used to generate a complexity summary score (number of produced complexity items), starting from the age of 30 months for boys and 26 months for girls, since more than 15% of the children scored zero before that age (Bleses et al., 2008). We then assigned each child a percentile language score according to the age and sex reference value from the Danish MB-CDI among 3714 children by comparing the obtained score for each individual child with the sex and age specific score for the reference population thereby obtaining a pertentile score. A percentile-score of ≤ 15 was considered as delayed language development (Bleses et al., 2008). In original validation of the Danish MB-CDI (Bleses et al., 2008), children whose parents had different ethnicity (which suggest that the child was reared in a bilingual family), whose parents were living apart, or who suffered from any chronic diseases or speech/speech-hearing problems were excluded. In contrast, we did not obtain information about these factors in this study and were therefore not able to exclude these children.

2.4. Child Behavior Checklist for ages 1½-5 (CBCL 1½-5)

ADHD related behavior was assessed using the parent-report questionnaire CBCL 1½–5 which consists of 100 questions. All items are rated on a 3-point Likert scale: 0 (not true), 1 (somewhat/sometimes true) and 2 (very true/often true). The purpose is to measure emotional and behavioral problems, including ADHD symptoms, in children between 1.5 and 5 years. A standardized version of CBCL 1½–5 translated into Danish is available (Kristensen et al., 2010). In this study, a ADHD problem scale (CBCL 1½–5 extracted) consisting of 6 questions (cannot concentrate, hyperactive, cannot wait, demands met immediately, quickly shifts, get into everything) with a maximum score of 12 was used as outcome. Good reliability and validity have been reported for the CBCL 1½–5 in both clinical and research settings (Kristensen et al., 2010). A score above 4 corresponded to being above the 85th percentile. We only included the ADHD related behavior from the CBCL questionnaires, as previous studies have suggested association between BPA exposure and especially AHDH symptoms (Braun et al., 2011; Casas et al., 2015; Philippat et al., 2017).

2.5. Ethics

The study was performed in accordance with the second Helsinki Declaration with written informed consent, and approved by the regional Ethical Committee (Project ID S-20090130) and the Danish Data Protection Agency (j.no. 2016-231-0188).

2.6. Statistical analysis

All samples with detectable BPA concentrations were corrected for variation in the urinary dilution by normalization to the median osmolality of all samples (0.639 Osm/kg). This was done by multiplying the individual urinary BPA concentration (ng/milliliter) with the median osmolality of all samples (osmoles/kilogram) and dividing the product with the individual urinary osmolality (osmoles/kilogram). Urinary BPA concentrations below the LOD were not adjusted for osmolality but were substituted by LOD divided by the square root of 2. Given that 15% of the concentrations were below the LOD and BPA was not normally distributed, osmolality-adjusted BPA concentrations were divided into tertiles.

Language scores and ADHD related behavior scores were also not normally distributed (see supplementary Figure 1 for distribution); medians and 25–75 percentiles, as well as categorized scores of respectively below the 15th and above the 85th percentile, were therefore calculated. Language scores below 15th percentiles and ADHD scores above 85th percentiles were compared among women and children with different characteristics by the use of Kruskal-Wallis and chi-square tests. Possible confounders were identified by careful review of the literature or selected if they differed in exposure (BPA) and/or outcome (language scores or ADHD related behavior).

Logistic regression analysis was undertaken to calculate the Odds-ratio (OR) for having a language score below the 15th or an ADHD related behavior score above the 85th percentiles across increasing tertiles of BPA concentrations, both unadjusted and adjusted for two potential confounders, i.e., maternal education and breastfeeding (even though the latter occurs after exposure). Maternal age, parity, smoking, BMI or prematurity were not included as they did not substantially change the ORs (did not change OR estimates 10%). We did not adjust for child age, as language scores were categorized according to age of a reference population and AHDH questionnaires were filled in at approximately the same age. Given the previously observed association between prenatal phthalate exposure and language development, we additionally adjusted for osmolality adjusted concentrations of MEP, the sum of DEHP metabolites (ΣDEHP) and the sum of DiNP metabolites ΣDiNP transformed by the natural logarithm as these were strongly correlated to BPA (Pearson correlation, $p < 0.01$).

Analyses were performed for all children and for boys and girls separately, since both language development and ADHD problem scores varied significantly according to sex even though the interaction term between BPA and sex was not statistically significant (data not shown). We conducted statistical tests for trends across tertiles of BPA exposure by inserting ordinal categorical variable indicators coded using integer values (1, 2, 3) in the regression model.

We evaluated the fit of the regression models by inspecting the residual plots for model assumption of homogeneity of variances. Results are presented with 95% confidence intervals (CIs); p-values < 0.05 were considered significant.

3. Results

3.1. Characteristics of the study population

A total of 2217 singletons of Caucasian origin are still enrolled in the cohort. Of these, 796 had BPA measured in maternal urine, 1360 responded to the MB-CDI subscales and 1707 responded to the CBCL-ADHD subscale (Fig. 1). The women with and without BPA measurements did not differ according to age, parity or gestational age at birth. However, the women with BPA measurements had higher BMI and less often smoked (data not shown). Responders of the MB-CDI did not differ from non-responders according to BMI and parity. However, the women who responded to the MB-CDI questionnaires were older, had fewer preterm births and fewer of them were smokers (data not shown).

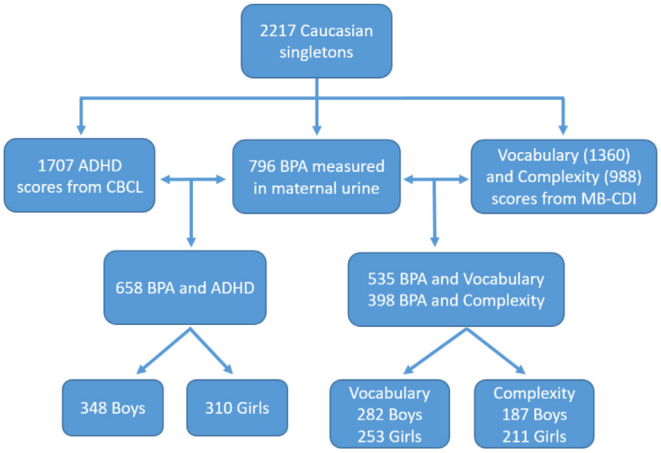

Fig. 1. Flow diagram of participants in the Odense Child Cohort and responding to ADHD or language questionnaires.

Table 1
Maternal and child characteristics according to 1) median (M) BPA concentrations (25–75 percentiles (25–75)) in maternal urine in gestational week 28; 2) percentages of children aged 2–4 years with ADHD score (CBCL 1.5–5) ≥ 85 percentile; 3) M and 25–75 vocabulary and complexity score of children aged 1.5–3 years in mother-child pairs from Odense Child Cohort.

Maternal and child characteristics	N (%)	Maternal median BPA ng/ml (25–75)	% with ADHD score ≥ 85 percentile		Median M-CDI vocabulary percentile score in the offspring				Median M-CDI complexity percentile score in the offspring			
			Boys, N = 348 Percent	Girls, N = 310 Percent	Boys		Girls		Boys		Girls	
					N	M (25–75)	N	M (25–75)	N	M (25–75)	N	M (25–75)
All	658 (100)	1.2 (0.5–2.4)	18	12	282	50 (25–75)	253	55 (25–80)	187	40 (15–75)	211	45 (15–70)
Age (years)												
< 25	61 (9)	1.3 (0.5–2.4)	29	23	28	40 (21–75)	22	53 (28–75)	20	45 (20–69)	18	50 (10–70)
25–34	475 (72)	1.2 (0.5–2.5)	17	11	200	55 (30–75)	190	55 (29–81)	123	40 (15–75)	164	50 (25–75)
≥35	122 (19)	1.2 (0.4–2.5)	17	8	54	45 (15–71)	41	40 (10–73)	44	18 (10–75)	29	35 (15–58)
Pre-pregnancy BMI (kg/m^2)												
< 20	62 (9)	1.0 (0.3–2.4)*	15	14	31	55 (25–75)	29	40 (18–75)	18	55 (20–78)	24	45 (15–60)
20–24.9	350 (53)	1.1 (0.4–2.1)*	20	12	137	50 (23–75)	138	55 (30–80)	84	40 (20–80)	115	50 (15–70)
≥25	246 (37)	1.6 (0.7–2.6)*	16	10	114	50 (25–75)	75	53 (19–75)	85	30 (10–75)	72	45 (18–70)
Smoking												
Yes	19 (3)	1.6 (0.7–2.7)	23	33	11	40 (20–40)	8	73 (56–94)	10	20 (3–45)*	7	45 (35–90)
No	639 (97)	1.2 (0.4–2.4)	18	11	271	50 (25–75)	245	50 (25–80)	177	40 (15–75)*	204	48 (15–70)
Education												
High school or less	177 (27)	1.5 (0.6–2.6)	28*	19*	78	40 (20–70)	65	40 (15–75)	53	35 (15–65)	54	45 (24–70)
High school + 1–4 years	346 (53)	1.2 (0.4–2.3)	14*	12*	155	55 (30–75)	123	55 (25–80)	97	40 (15–75)	105	50 (15–73)
High school + > 4 years	131 (20)	1.3 (0.3–2.2)	10*	3*	48	48 (20–85)	61	50 (33–83)	36	55 (10–89)	50	45 (24–71)
Parity												
Nulliparous	371 (56)	1.4 (0.4–2.6)	20	13	168	50 (25–75)	138	53 (25–80)	108	40 (16–75)	116	45 (15–70)
Multiparous	287 (44)	1.1 (0.5–2.2)	15	9	114	50 (20–75)	115	50 (25–75)	79	35 (15–75)	95	50 (25–80)
Inclusion (year)												
2010–11	380 (48)	1.4 (0.6–2.6)	17	9*	153	50 (20–73)	139	50 (25–75)	115	35 (15–75)	122	45 (19–70)
2012	327 (42)	1.2 (0.4–2.2)	20	12*	103	55 (25–75)	96	58 (30–85)	64	40 (15–80)	80	50 (15–74)
2013	89 (11)	1.2 (0.4–2.3)	12	25*	26	48 (34–81)	18	53 (23–85)	8	23 (3–75)	9	30 (13–73)
Birth weight (grams)												
< 3550	332 (51)	1.4 (0.5–2.5)	20	13	126	50 (25–75)	132	50 (25–75)	78	38 (15–75)	111	45 (15–70)
≥3550	326 (49)	1.2 (0.4–2.3)	16	10	156	50 (20–75)	121	65 (30–85)	109	40 (13–75)	100	50 (16–74)
Birth length (cm)												
≤52	366 (56)	1.3 (0.4–2.4)	17	13	139	50 (25–75)	149	50 (25–75)	93	40 (15–75)	122	48 (24–70)
> 52	288 (44)	1.2 (0.5–2.4)	19	9	140	50 (25–75)	102	60 (24–85)	92	35 (15–75)	87	45 (15–70)
Preterm (< 37 weeks)												
Yes	24 (4)	1.3 (0.4–2.3)	29	20	5	35 (8–68)	1	25	4	18 (8–61)	1	40
No	633 (96)	1.2 (0.5–2.4)	17	11	277	50 (25–75)	252	53 (25–80)	183	40 (15–75)	210	45 (15–70)
Exclusive breastfeeding (weeks)												
0	185 (30)	1.4 (0.4–2.3)	20	9	78	45 (24–71)	71	40 (15–75)	56	28 (10–59)*	60	40 (15–60)
1–12	212 (35)	1.2 (0.5–2.4)	19	14	96	50 (20–75)	73	60 (30–85)	67	45 (15–80)*	61	50 (18–70)
> 12	214 (35)	1.2 (0.4–2.4)	14	13	91	55 (35–85)	95	55 (30–85)	57	50 (23–78)*	78	50 (19–76)

* $p < 0.05$ Kruskal-Wallis (language) or Chi square (ADHD).

Responders to CBCL 1½-5 questions were older, had higher parity, were higher educated and less often smokers than non-responders (data not shown). The final sample sizes for the analyses of association between BPA and vocabulary, complexity and ADHD related behavior scores were 535, 398 and 658, respectively (Fig. 1).

BPA was detected in 85.3% of the urine samples and the median (25–75 percentile) concentration was 1.2 ng/ml (0.5–2.4). BPA concentration was higher among less educated and primiparous women, in overweight or obese women and among women who did not breastfed (although only statistically significant for pre-pregnancy BMI) (Table 1).

3.2. Language scores and ADHD related behavior scores

The initial MB-CDI questionnaires on Vocabulary were completed at a median age of 21 months (boys range 20–34, girls range 20–35). The median age of the boys when parents completed the Complexity subscale score was 31 months (30–36), and 27 months (26–35) for the girls. For the Vocabulary subscale, the boys had a median (25–75 percentile) percentile score of 50 (25–75), while girls had a median score of 50 (25–80). For Complexity, the boys had a percentile score median of 40 (15–75), while girls had a median score of 45 (15–70). The percentile language scores were lower among children of older and smoking mothers, and among those children who were not breastfed (Table 1). Moreover, children of younger mothers, and children of mothers with 1–4 years of additional education after high school had higher language scores, although these results were not statistically significant (Table 1).

CBCL 1½-5 questionnaires were filled in at a mean age of 2.7 (standard deviation 0.6) years and ADHD related behavior score split by the 85th percentile (score ≥4). A score above the 85th percentile was associated with lower maternal education (significant), maternal age and parity, smoking, low birth weight, preterm birth and not being breastfed (Table 1).

3.3. Associations between BPA and language scores or ADHD related behavior scores

In the unadjusted analyses, a borderline dose-response association between higher BPA tertile and having age standardized vocabulary

Table 2
Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for a vocabulary (N = 535) and complexity (N = 398) score below the age and sex standardized 15 percentile for tertiles of osmolality adjusted BPA exposure among 535 children from Odense Child Cohort and for boys and girls separately.

Osmolality adjusted BPA (ng/ml)	MB-CDI Vocabulary score below 15th percentile									MB-CDI Complexity score below 15th percentile								
	All (N = 535)			Boys (N = 282)			Girls (N = 253)			All (N = 398)			Boys (N = 187)			Girls (N = 211)		
	N ≤/ > 15th	OR	95% CI	N ≤/ > 15th	OR	95% CI	N ≤/ > 15th	OR	95% CI	N ≤/ > 15th	OR	95% CI	N ≤/ > 15th	OR	95% CI	N ≤/ > 15th	OR	95% CI
Unadjusted																		
1th tertile BPA[a]	23/159	Reference		9/88	Reference		14/71	Reference		36/95	Reference		13/46	Reference		23/49	Reference	
2th tertile BPA[b]	46/128	2.48	1.43–4.32	22/66	3.26	1.41–7.54	24/62	1.96	0.94–4.12	34/95	0.94	0.55–1.63	18/43	1.48	0.65–3.38	16/52	0.66	0.31–1.39
3th tertile BPA[c]	37/142	1.80	1.02–3.18	24/73	3.22	1.41–7.35	13/69	0.96	0.42–2.18	40/98	1.08	0.63–1.83	25/42	2.11	0.96–4.64	15/56	0.57	0.27–1.21
p-trend[d]		0.06			0.007			0.94			0.78			0.06			0.75	
Adjusted for maternal education and breastfeeding																		
1th tertile BPA[a]		Reference			Reference			Reference			Reference			Reference			Reference	
2th tertile BPA[b]		2.62	1.46–4.72		4.72	1.77–12.6		1.74	0.80–3.74		1.03	0.58–1.83		1.80	0.74–4.38		0.68	0.31–1.49
3th tertile BPA[c]		1.88	1.03–3.45		4.63	1.74–12.3		0.87	0.37–2.03		1.15	0.65–2.00		2.43	1.02–5.77		0.63	0.29–1.36
p-trend[d]		0.06			0.003			0.76			0.63			0.046			0.23	
Additionally adjusted for phthalate metabolites[5]																		
1th tertile BPA[a]		Reference			Reference			Reference			Reference			Reference			Reference	
2th tertile BPA[b]		2.69	1.46–4.95		4.10	1.52–11.1		2.19	0.97–4.96		0.95	0.52–1.73		1.55	0.61–3.90		0.71	0.32–1.60
3th tertile BPA[c]		1.87	0.99–3.55		3.70	1.34–10.2		1.08	0.44–2.67		1.09	0.60–1.99		2.25	0.88–5.74		0.68	0.30–1.55
p-trend[d]		0.08			0.02			0.88			0.76			0.09			0.35	

[5]Osmolality adjusted and ln transformed MEP, ΣMEHP and ΣDiNP.

[a] 1th tertile BPA ≤ 0.85 ng/ml.

[b] 2th tertile BPA 0.86–1.95 ng/ml.

[c] 3th tertile BPA ≥ 1.96 ng/ml.

[d] Trend tested by inserting the tertile osmolality adjusted BPA as a continuous variable.

Table 3
Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for a CBCL-ADHD score above the 85 percentile for tertiles of osmolality adjusted BPA exposure among 658 children from Odense Child Cohort and for boys and girls separately.

Osmolality adjusted BPA (ng/ml)	ADHD score above 85th percentile								
	All (N = 658)			Boys (N = 348)			Girls (N = 310)		
	N ≤/ > 85th	OR	95% CI	N ≤/ > 85th	OR	95% CI	N ≤/ > 85th	OR	95% CI
Unadjusted									
1th tertile BPA[a]	37/177	Reference		27/83	Reference		10/94	Reference	
2th tertile BPA[b]	24/194	0.59	0.34–1.03	13/103	0.39	0.19–0.80	11/91	1.14	0.46–2.81
3th tertile BPA[c]	37/189	0.94	0.57–1.54	22/100	0.68	0.36–1.28	15/89	1.58	0.68–3.71
p-trend[d]		0.81			0.22			0.28	
Adjusted for maternal education and breastfeeding									
1th tertile BPA[a]		Reference			Reference			Reference	
2th tertile BPA[b]		0.58	0.32–1.05		0.38	0.18–0.83		1.06	0.40–2.81
3th tertile BPA[c]		0.96	0.56–1.64		0.64	0.32–1.27		1.84	0.74–4.54
p-trend[d]		0.92			0.20			0.17	
Additionally adjusted for phthalate metabolites[e]									
1th tertile BPA[a]		Reference			Reference			Reference	
2th tertile BPA[b]		0.60	0.32–1.10		0.36	0.16–0.81		1.32	0.48–3.62
3th tertile BPA[c]		0.96	0.55–1.69		0.58	0.28–1.21		2.35	0.89–6.18
p-trend[d]		0.96			0.16			0.08	

[a] 1th tertile BPA ≤ 0.85 ng/ml.
[b] 2th tertile BPA 0.86–1.95 ng/ml.
[c] 3th tertile BPA ≥ 1.96 ng/ml.
[d] Trend tested by inserting the tertile osmolality adjusted BPA as a continuous variable.
[e] Osmolality adjusted and ln transformed MEP, MEHP and ΣDiNP

scores below the 15th percentile was found (p = 0.06, Table 2). Sex-stratified analyses revealed that this association was driven by boys (p = 0.007) and was not seen in girls (p = 0.94). Similarly, a dose-response association for complexity score among boys was found in unadjusted models (p = 0.06). Adjustment for maternal education and breastfeeding strengthened the finding for boys, and boys of mothers with BPA exposure in the highest tertile had an OR of 4.63 (95% CI 1.74–12.30) of being in the lowest 15th percentile of vocabulary score and an OR of 2.43 (1.02–5.77) of being in the lowest 15th percentile of complexity score compared to boys of mothers within the lowest tertile of BPA exposure (Table 2). Further adjustment for ln-transformed MEP, ΣDEHP and ΣDiNP moderately attenuated the associations for boys, although a significant association for vocabulary score remained (p = 0.02) and an almost marginally significant association for complexity score remained (p = 0.09). No significant associations were found for girls (Table 2).

The OR of having an ADHD score above the 85th percentile according to tertiles of urinary BPA concentrations is reported in Table 3. Generally, no significant trends were found in either sex neither in the unadjusted nor in the adjusted models. A tendency of a reduced OR for having a high ADHD score in boys and an increased OR in girls for the highest tertiles of BPA exposure was found, although this was only significant in the second tertile among boys (adjusted OR = 0.36, 95% CI 0.16–0.81) (Table 3).

4. Discussion

In the present study of mother-child pairs from the Odense Child Cohort, higher prenatal exposure to BPA was significantly associated with a higher risk of a language development score below the 15th percentile for vocabulary (number of words or lexicon) and complexity (morphosyntax) among toddler boys, but not among girls, as measured by the two corresponding subscales in the Danish MB-CDI parent report. Since we previously found associations between certain phthalate metabolites and language development scores in the same cohort of children (Olesen et al., 2018), we further adjusted for concentrations of phthalate metabolites. This attenuated the associations, although we still found a significant result for the vocabulary subscale, and a marginally significant result for the complexity scale, though only for boys. This suggests that BPA and phthalates may have independent — and possibly additive — effects on language development. Moreover, our results suggest a possible sex-specific effect of BPA on language development. Regarding associations between prenatal BPA and ADHD behavior related scores obtained from the CBCL 1½-5 test, a tendency towards reduced ORs for having a high ADHD related behavior scores among boys and increased ORs among girls in the higher tertile of BPA exposure was observed. However, the absence of a monotonic dose-response relationship, complicates the interpretation of this association.

To the best of our knowledge, this is the first study that has analyzed the association between prenatal BPA exposure and child language development. Differences in early language development between boys and girls have been described (Eriksson et al., 2012), and the importance of early language development relies on its predictive value for later school and educational success (Elbro et al., 2011; Hawa and Spanoudis, 2014). In this line, our findings suggest that prenatal exposure to the widespread endocrine disruptor BPA could increase the risk of language problems or delays among boys, which could have further repercussions on later children neuropsychological health, academic achievement, and ultimately quality of life (Bleses et al., 2016; Grandjean and Landrigan, 2014). Interestingly, hearing and language development are thought to begin around the third trimester of gestation (Mampe et al., 2009; Moon et al., 2013; Zimmer et al., 1993), exactly the timing in which we estimated prenatal BPA exposure. Although we are far from understanding the exact underlying mechanisms of hormones on language development, there is no doubt that hormones play an important role. For example, cord blood testosterone is a predictor of poor language development at age 4 years among boys (Hollier et al., 2013) and peripheral hormones are key regulators of vocal behavior towards language development during a transitory hormone-surge in the first months of life known as “mini-puberty” (Wermke et al., 2018).

Vocal and language development cannot be studied in animals but one of the most plausible mechanisms proposed for these sex-specific effects are epigenetic modifications related to the estrogen-androgen balance, given evidence that BPA affects the gene expression of several estrogen receptor subtypes (ERα, ERβ and ERγ) in a sex- and brain region-specific manner (Kundakovic et al., 2013). Hence, *in utero* BPA exposure could alter the responses of certain brain areas to steroid

hormones (Mustieles et al., 2018), and consequently could influence early language development among other human sex-dependent traits (Bao and Swaab, 2011; Berenbaum and Beltz, 2011).

The epidemiologic literature regarding BPA and neuropsychological development has been extensively reviewed in Mustieles et al. (2015, 2018). Three previously published birth cohorts have reported associations between prenatal urinary BPA concentrations and ADHD symptoms (Braun et al., 2011; Casas et al., 2015; Philippat et al., 2017). Braun et al. (2011) studied 249 mother-child pairs from the HOME Study (US) and found a positive association between prenatal urinary BPA concentrations and increased hyperactivity among 3 year-old girls, while observing the inverse for boys, using the Behavioral Assessment System for Children (BASC-2) and the Behavior Rating Inventory of Executive Function-Preschool (BRIEF-P) tests. On the contrary, Casas et al. (2015) studied 438 mother-child pairs from the INMA-Sabadell cohort (Spain), reporting a positive association between prenatal urinary BPA concentrations and the risk of ADHD among 4-year old children, but stronger in boys than girls. ADHD was assessed using the Criteria of Diagnostic and Statistical Manual of Mental Disorders-4th Edition (ADHD-DSM-IV) test (Casas et al., 2015). More recently, a French study (Philippat et al., 2017) among 464 mother-child pairs (only boys) (EDEN cohort) found a positive association between prenatal urinary BPA concentrations and worse hyperactivity-inattention scores among 5-year old boys, using the Strengths and Difficulties Questionnaire (SDQ) test. We found a tendency towards reduced risk for a high ADHD score in boys and increased risk in girls within the highest tertiles of BPA exposure, although only statistically significant in the second tertile among boys. This pattern of associations is particularly difficult to interpret, due to the non-monotonicity of the results among boys. While the present findings could share some similarities with Braun et al. (2011), an important aspect is that Odense toddlers were between 1.5 and 2.5 years of age, and it has been pointed out that externalizing problems become more prevalent at 5–7 years of age (Rosenfeld and Trainor, 2014). In addition, BPA exposure levels in our study were lower than previous studies (see below). Future follow-up of these children could help to elucidate this issue. Overall, we did not observe a deleterious effect of prenatal BPA exposure on the risk of ADHD symptoms. However, it is noteworthy to mention that a recent systematic review and meta-analysis of both animal and epidemiologic studies has concluded that early life BPA exposure is a presumed human hazard for the development of hyperactivity (Rochester et al., 2018).

Associations between prenatal BPA exposure and child behavior have thus been studied extensively, whereas associations between BPA and different cognitive domains have been less consistently studied (Braun et al., 2017a; Nakiwala et al., 2018; Stacy et al., 2017). Future works should investigate whether early language development is a more sensitive endpoint for BPA effects on the human brain compared to other cognitive domains. In addition, it will be important also to measure postnatal BPA exposure as this will become increasingly important as the children grow up and are exposed, as suggested by Stacy (Stacy et al., 2017). Given the ubiquity of the exposure, as well as the fact that BPA is currently in the spotlight for its effect on neurodevelopment, more epidemiologic studies assessing language skills are needed to confirm or contradict the associations we observed in the present study.

Median prenatal urinary BPA concentration in our cohort was 1.2 ng/ml, which is lower than other prospective birth cohorts such as the HOME Study (Geometric mean: 2.0 ng/ml) and the EDEN Study (Geometric mean: 2.5 ng/ml) (Braun et al., 2011; Casas et al., 2015; Philippat et al., 2017). Since all urine samples were collected as fasting morning spot urine, this may have contributed to lower BPA concentrations. Nevertheless, even within this low-level exposed pregnant population, associations between maternal BPA exposure and a higher risk of poorer language development were evident. We adjusted for osmolality instead of creatinine, however, this has been proven a valid adjustment for urine dilution (Middleton et al., 2016).

Among the strengths of this study are the access to a large Danish reference population for language development, the longitudinal design, the high number of mother-child pairs enrolled, and the large amount of socio-demographic and clinical information available. In addition, we used the validated MB-CDI, which allowed us to study and report for the first time the relationship between prenatal BPA exposure and child's language development. The MB-CDI language score is based on the parental reporting and their knowledge of their child's language and is therefore neither dependent on the child's current state, nor on the test setting or the examiner. Importantly, we were able to account for phthalate's co-exposure in the models.

Our study, however, also present some limitations. First, both MB-CDI and CBCL subscales were reported by parents, which may lead to misclassification of the child's current language developmental and ADHD problem score. However, this is likely non-differential, as the parents were not aware of their BPA exposure concentrations and BPA was not strongly associated with predictors of development like socioeconomic status. Also, the children were relatively young to assess ADHD symptoms and language development. However, early language development predicts later school and educational success (Elbro et al., 2011; Hawa and Spanoudis, 2014). Secondly, a single urine sample may not adequately reflect long-term BPA exposure levels, so use of more than a one urine sample would have been preferable since BPA has a high temporal intra-individual variability and the degree of exposure misclassification can be high (Mahalingaiah et al., 2008; Perera et al., 2016). However, this misclassification is unlikely to be associated to language development and will thereby produce a bias towards the null-hypothesis (Perrier et al., 2016). Also, we only measured BPA in third trimester, and it would have been preferable to include BPA measurements during all trimesters, as brain development occurs through pregnancy. Fourth, although known confounders were studied and included in the statistical models, we were not able to account for other covariates such as maternal IQ or home conditions, nor diet or lifestyle factors, so residual confounding cannot be ruled out. In addition, we adjusted for exposure to phthalates but not for exposure to other endocrine disrupting chemicals e.g. benzophenone-3 which may be associated to BPA exposure (Kim et al., 2017).

5. Conclusions

In this study of 535 mother-child pairs from the Odense Child Cohort, higher prenatal BPA concentrations were significantly and positively associated with a higher risk of poorer language skills among toddler boys, but not girls, suggesting a possible sex-specific effect of BPA on early language development. No evidence of a deleterious effect of prenatal BPA exposure on the risk of ADHD symptoms was observed. To the best of our knowledge, this is the first study that has addressed the association between prenatal BPA exposure and child language development. Since early language development is a relevant predictor of reading skills and educational success, more epidemiologic studies assessing language skills are needed to confirm the present associations.

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Declaration of interest

There is no conflict of interest of any author that could be perceived as prejudicing the impartiality of the research reported.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2018.12.055.

References

Bao, A.M., Swaab, D.F., 2011. Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. Front Neuroendocrinol. 32, 214–226.
Berenbaum, S.A., Beltz, A.M., 2011. Sexual differentiation of human behavior: effects of prenatal and pubertal organizational hormones. Front. Neuroendocrinol. 32, 183–200.
Bleses, D., Vach, W., Slott, M., Wehberg, S., Thomsen, P., Madsen, T.O., et al., 2008. The Danish communicative developmental inventories: validity and main developmental trends. J. Child Lang. 35, 651–669.
Bleses, D., Makransky, G., Dale, P.S., Højen, A., Aktürk Ari, B., 2016. Early productive vocabulary predicts academic achievement 10 years later. Appl. Psycholinguist. 37, 1461–1476.
Braun, J.M., Yolton, K., Dietrich, K.N., Hornung, R., Ye, X., Calafat, A.M., et al., 2009. Prenatal bisphenol a exposure and early childhood behavior. Environ. Health Perspect. 117, 1945–1952.
Braun, J.M., Kalkbrenner, A.E., Calafat, A.M., Yolton, K., Ye, X., Dietrich, K.N., et al., 2011. Impact of early-life bisphenol a exposure on behavior and executive function in children. Pediatrics 128, 873–882.
Braun, J.M., Muckle, G., Arbuckle, T., Bouchard, M.F., Fraser, W.D., Ouellet, E., et al., 2017a. Associations of prenatal urinary bisphenol a concentrations with child behaviors and cognitive abilities. Environ. Health Perspect. 125, 067008.
Braun, J.M., Yolton, K., Stacy, S.L., Erar, B., Papandonatos, G.D., Bellinger, D.C., et al., 2017b. Prenatal environmental chemical exposures and longitudinal patterns of child neurobehavior. Neurotoxicology 62, 192–199.
Casas, M., Forns, J., Martinez, D., Avella-Garcia, C., Valvi, D., Ballesteros-Gomez, A., et al., 2015. Exposure to bisphenol a during pregnancy and child neuropsychological development in the INMA-Sabadell cohort. Environ. Res. 142, 671–679.
Elbro, C., Dalby, M., Maarbjerg, S., 2011. Language-learning impairments: a 30-year follow-up of language-impaired children with and without psychiatric, neurological and cognitive difficulties. Int. J. Lang. Commun. Disord. 46, 437–448.
Eriksson, M., Marschik, P.B., Tulviste, T., Almgren, M., Perez Pereira, M., Wehberg, S., et al., 2012. Differences between girls and boys in emerging language skills: evidence from 10 language communities. Br. J. Dev. Psychol. 30, 326–343.
Evans, S.F., Kobrosly, R.W., Barrett, E.S., Thurston, S.W., Calafat, A.M., Weiss, B., et al., 2014. Prenatal bisphenol a exposure and maternally reported behavior in boys and girls. Neurotoxicology 45, 91–99.
Fenson, L., Marchman, V.A., Thal, D.J., Dale, P.S., Reznick, J.S., Bates, E., 2007. Macarthur-Bates Communicative Development Inventories: User's Guide and Technical Manual. Paul Brookes, Baltimore.
Frederiksen, H., Aksglaede, L., Sorensen, K., Nielsen, O., Main, K.M., Skakkebaek, N.E., et al., 2013. Bisphenol a and other phenols in urine from Danish children and adolescents analyzed by isotope diluted TurboFlow-LC-MS/MS. Int. J. Hyg. Environ. Health 216, 710–720.
Frederiksen, H., Jensen, T.K., Jorgensen, N., Kyhl, H.B., Husby, S., Skakkebaek, N.E., et al., 2014. Human urinary excretion of non-persistent environmental chemicals: an overview of Danish data collected between 2006 and 2012. Reproduction 147, 555–565.
Grandjean, P., Landrigan, P.J., 2014. Neurodevelopmental toxicity: still more questions than answers–Authors' response. Lancet Neurol. 13, 648–649.
Harley, K.G., Gunier, R.B., Kogut, K., Johnson, C., Bradman, A., Calafat, A.M., et al., 2013. Prenatal and early childhood bisphenol a concentrations and behavior in school-aged children. Environ. Res. 126, 43–50.
Hawa, V.V., Spanoudis, G., 2014. Toddlers with delayed expressive language: an overview of the characteristics, risk factors and language outcomes. Res. Dev. Disabil. 35, 400–407.
Hollier, L.P., Mattes, E., Maybery, M.T., Keelan, J.A., Hickey, M., Whitehouse, A.J., 2013. The association between perinatal testosterone concentration and early vocabulary development: a prospective cohort study. Biol. Psychol. 92, 212–215.
Hong, S.B., Hong, Y.C., Kim, J.W., Park, E.J., Shin, M.S., Kim, B.N., et al., 2013. Bisphenol a in relation to behavior and learning of school-age children. J. Child Psychol. Psychiatry 54, 890–899.
Kim, S., Kim, S., Won, S., Choi, K., 2017. Considering common sources of exposure in association studies - Urinary benzophenone-3 and DEHP metabolites are associated with altered thyroid hormone balance in the NHANES 2007–2008. Environ. Int. 107, 25–32.
Kristensen, S., Henriksen, T.B., Bilenberg, N., 2010. The child behavior checklist for ages 1.5-5 (cbcl/1(1/2)-5): assessment and analysis of parent- and caregiver-reported problems in a population-based sample of danish preschool children. Nord J. Psychiatry 64, 203–209.
Kundakovic, M., Gudsnuk, K., Franks, B., Madrid, J., Miller, R.L., Perera, F.P., Champagne, F.A., 2013. Sex-specific epigenetic disruption and behavioral changes following low-dose in utero bisphenol A exposure. Proc. Natl. Acad. Sci. USA 110, 9956–9961.
Kyhl, H.B., Jensen, T.K., Barington, T., Buhl, S., Norberg, L.A., Jorgensen, J.S., et al., 2015. The odense child cohort: aims, design, and cohort profile. Paediatr. Perinat. Epidemiol. 29, 250–258.
LaKind, J.S., Naiman, D.Q., 2015. Temporal trends in bisphenol a exposure in the United States from 2003–2012 and factors associated with BPA exposure: spot samples and urine dilution complicate data interpretation. Environ. Res. 142, 84–95.
Lassen, T.H., Frederiksen, H., Jensen, T.K., Petersen, J.H., Main, K.M., Skakkebaek, N.E., et al., 2013. Temporal variability in urinary excretion of bisphenol a and seven other phenols in spot, morning, and 24-h urine samples. Environ. Res. 126, 164–170.
Mahalingaiah, S., Meeker, J.D., Pearson, K.R., Calafat, A.M., Ye, X., Petrozza, J., et al., 2008. Temporal variability and predictors of urinary bisphenol a concentrations in men and women. Environ. Health Perspect. 116, 173–178.
Mampe, B., Friederici, A.D., Christophe, A., Wermke, K., 2009. Newborns' cry melody is shaped by their native language. Curr. Biol. 19, 1994–1997.
Maserejian, N., 2014. Possible association between dental sealants and urinary bisphenol a levels in children warrants additional biomonitoring and safety research. J. Evid. Based Dent. Pract. 14, 200–202.
Middleton, D.R., Watts, M.J., Lark, R.M., Milne, C.J., Polya, D.A., 2016. Assessing urinary flow rate, creatinine, osmolality and other hydration adjustment methods for urinary biomonitoring using NHANES arsenic, iodine, lead and cadmium data. Environ. Health 15, 68.
Moon, C., Lagercrantz, H., Kuhl, P.K., 2013. Language experienced in utero affects vowel perception after birth: a two-country study. Acta Paediatr. 102, 156–160.
Mustieles, V., Perez-Lobato, R., Olea, N., Fernandez, M.F., 2015. Bisphenol a: human exposure and neurobehavior. Neurotoxicology 49, 174–184.
Mustieles, V., Ocon-Hernandez, O., Minguez-Alarcon, L., Davila-Arias, C., Perez-Lobato, R., Calvente, I., et al., 2018. Bisphenol a and reproductive hormones and cortisol in peripubertal boys: the INMA-Granada cohort. Sci. Total Environ. 618, 1046–1053.
Nakiwala, D., Peyre, H., Heude, B., Bernard, J.Y., Beranger, R., Slama, R., et al., 2018. In-utero exposure to phenols and phthalates and the intelligence quotient of boys at 5 years. Environ. Health 17, 17.
Olesen, T.S., Bleses, D., Andersen, H.R., Grandjean, P., Frederiksen, H., Trecca, F., et al., 2018. Prenatal phthalate exposure and language development in toddlers from the Odense child cohort. Neurotoxicol Teratol. 65, 34–41.
Perera, F., Nolte, E.L., Wang, Y., Margolis, A.E., Calafat, A.M., Wang, S., et al., 2016. Bisphenol a exposure and symptoms of anxiety and depression among inner city children at 10-12 years of age. Environ. Res. 151, 195–202.
Perez-Lobato, R., Mustieles, V., Calvente, I., Jimenez-Diaz, I., Ramos, R., Caballero-Casero, N., et al., 2016. Exposure to bisphenol a and behavior in school-age children. Neurotoxicology 53, 12–19.
Perrier, F., Giorgis-Allemand, L., Slama, R., Philippat, C., 2016. Within-subject pooling of biological samples to reduce exposure misclassification in biomarker-based studies. Epidemiology 27, 378–388.
Philippat, C., Nakiwala, D., Calafat, A.M., Botton, J., De Agostini, M., Heude, B., et al., 2017. Prenatal exposure to nonpersistent endocrine disruptors and behavior in boys at 3 and 5 years. Environ. Health Perspect. 125, 097014.
Rochester, J.R., Bolden, A.L., Kwiatkowski, C.F., 2018. Prenatal exposure to bisphenol a and hyperactivity in children: a systematic review and meta-analysis. Environ. Int. 114, 343–356.
Roen, E.L., Wang, Y., Calafat, A.M., Wang, S., Margolis, A., Herbstman, J., et al., 2015. Bisphenol a exposure and behavioral problems among inner city children at 7-9 years of age. Environ. Res. 142, 739–745.
Rosenfeld, C.S., Trainor, B.C., 2014. Environmental health factors and sexually dimorphic differences in behavioral disruptions. Curr. Environ. Health Rep. 1, 287–301.
Schug, T.T., Janesick, A., Blumberg, B., Heindel, J.J., 2011. Endocrine disrupting chemicals and disease susceptibility. J. Steroid Biochem. Mol. Biol. 127, 204–215.
Schug, T.T., Blawas, A.M., Gray, K., Heindel, J.J., Lawler, C.P., 2015. Elucidating the links between endocrine disruptors and neurodevelopment. Endocrinology 156, 1941–1951.
Stacy, S.L., Papandonatos, G.D., Calafat, A.M., Chen, A., Yolton, K., Lanphear, B.P., et al., 2017. Early life bisphenol a exposure and neurobehavior at 8 years of age: identifying windows of heightened vulnerability. Environ. Int. 107, 258–265.
Vandenberg, L.N., Hauser, R., Marcus, M., Olea, N., Welshons, W.V., 2007. Human exposure to bisphenol a (bpa). Reprod. Toxicol. 24, 139–177.
Wermke, K., Quast, A., Hesse, V., 2018. From melody to words: the role of sex hormones in early language development. Horm. Behav.
Xue, J., Liu, W., Kannan, K., 2017. Bisphenols, benzophenones, and bisphenol a diglycidyl ethers in textiles and infant clothing. Environ. Sci. Technol. 51, 5279–5286.
Zimmer, E.Z., Fifer, W.P., Kim, Y.I., Rey, H.R., Chao, C.R., Myers, M.M., 1993. Response of the premature fetus to stimulation by speech sounds. Early Hum. Dev. 33, 207–215.