Environment International 146 (2021) 106160

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Association of urinary bisphenols during pregnancy with maternal, cord blood and childhood thyroid function

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ARTICLE INFO

Handling Editor: Martí Nadal

Keywords:
Endocrine disrupting chemicals
Thyroid function
Pregnancy
Cord blood
Child

ABSTRACT

Background: Most pregnant women are exposed to bisphenols, a group of chemicals that can interfere with various components of the thyroid system.
Objectives: To investigate the association of maternal urinary bisphenol concentrations during pregnancy with maternal, newborn and early childhood thyroid function.
Methods: This study was embedded in Generation R, a prospective, population-based birth cohort (Rotterdam, the Netherlands). Maternal urine samples were analyzed for eight bisphenols at early (<18), mid (18–25) and late (>25 weeks) pregnancy. Maternal serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and total thyroxine (TT4) were measured in early pregnancy and child TSH and FT4 were measured in cord blood and childhood.
Results: The final study population comprised 1,267 mothers, 853 newborns and 882 children. Of the eight bisphenols measured, only bisphenol A (BPA) was detected in >50% of samples at all three time-points and bisphenol S (BPS) at the first time-point. There was no association of BPA or the bisphenol molar sum with maternal thyroid function. Higher BPS concentrations were associated with a higher maternal TT4 (β [95% CI] per 1 (natural-log) unit increase: 0.97 [0.03 to 1.91]) but there was no association with TSH or FT4. Furthermore, higher BPS was associated with an attenuation of the association between maternal FT4 and TSH ($P_{interaction}$ = 0.001). There was no association of early or mid-pregnancy BPA or early pregnancy BPS with cord blood or childhood TSH and FT4. A higher late pregnancy maternal BPA exposure was associated with a higher TSH in female newborns ($P_{interaction}$ = 0.06) and a higher FT4 during childhood in males ($P_{interaction}$ = 0.08).
Discussion: Our findings show that exposure to bisphenols may interfere with the thyroid system during pregnancy. Furthermore, the potential developmental toxicity of exposure to bisphenols during pregnancy could affect the thyroid system in the offspring in a sex-specific manner.

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https://doi.org/10.1016/j.envint.2020.106160
Received 27 June 2020; Received in revised form 19 September 2020; Accepted 21 September 2020
Available online 14 October 2020

1. Introduction

Endocrine disrupting chemicals (EDCs) interfere with the endocrine system and have been linked to the disruption of various reproductive, metabolic and neuroendocrine systems (Diamanti-Kandarakis et al., 2009). Bisphenols are EDCs widely used in consumer products such as plastic water bottles, canned food and thermal receipts. A consequence of their widespread use is environmental contamination with ubiquitous human exposure (Diamanti-Kandarakis et al., 2009; Boas et al., 2012; Chen et al., 2016). Experimental studies indicate that various bisphenol analogues can disrupt the thyroid system, for example by altering the expression of thyroid related genes including thyroid hormone receptors, deiodinase enzymes and the sodium/iodine symporter (Zoeller et al., 2005; Moriyama et al., 2002; Molina-Molina et al., 2013; Fernandez et al., 2018; Lee et al., 2017; Lee et al., 2019; Zhang et al., 2017). Bisphenol A has been shown to exert thyroid receptor antagonistic properties (Zoeller et al., 2005; Moriyama et al., 2002). Recent regulations restrict the use of BPA, yet its replacement by other analogues such as bisphenol S (BPS) and bisphenol F (BPF) may also interfere with the hypothalamic-pituitary-thyroid axis (Rochester and Bolden, 2015; Derakhshan et al., 2019).

Pregnancy is a state of increased thyroid hormone demand, during which the fetus is dependent on the placental transfer of maternal thyroid hormone (Korevaar et al., 2017). Both disruption of the maternal thyroid system and bisphenol exposure during pregnancy are independently associated with adverse pregnancy and offspring neurodevelopmental outcomes (Mughal et al., 2018; Ghassabian and Trasande, 2018; Korevaar et al., 2018). Yet, the association between bisphenol exposure and thyroid function is less clear. Some studies have found associations of bisphenol exposure (predominantly BPA) with maternal thyroid function, but others have not detected such links (Derakhshan et al., 2019; Chevrier et al., 2013; Romano et al., 2015; Aung et al., 2017; Aker et al., 2018; Aker et al., 2019). BPA is detected in the placenta, amniotic fluid and cord blood (Lee et al., 2018; Ikezuki et al., 2002); thus, fetal exposure to these thyroid disruptors can potentially interfere with the development of the fetal thyroid gland and the hypothalamic-pituitary-thyroid axis, with subsequent effects on thyroid function in later life (Mallozzi et al., 2016). However, studies on the association of maternal bisphenol exposure and newborn or child thyroid function are scarce. The only two available studies identified a sex-specific association of higher BPA exposure in late pregnancy with cord blood thyroid stimulating hormone (TSH), one of which identified a higher TSH in boys, while the other showed a lower TSH in girls (Chevrier et al., 2013; Romano et al., 2015). To the best of our knowledge, no study has yet investigated the association of exposure to bisphenols during pregnancy with childhood thyroid function. Here, we investigated the association of maternal urinary concentrations of BPA, BPS and BPF with maternal, newborn and child serum TSH, free thyroxine (FT4) and/or total thyroxine (TT4) concentrations.

2. Methods

2.1. Study population

This study was embedded in the Generation R, a population-based prospective birth-cohort (Kooijman et al., 2016). Between April 2002 and January 2006, a total of 8,879 pregnant women were enrolled, of which 7,069 were enrolled in early pregnancy (gestational age $\leq$ 18 weeks). Thyroid function tests were performed in 5,793 (82%) women and bisphenol concentrations were measured in a subgroup of 1,405 with singleton pregnancies. All components of the Generation R Study were approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam, Netherlands. Written informed consent was obtained from all participants and/or parents or guardians (Kooijman et al., 2016).

2.2. Laboratory measurements

Maternal serum samples were acquired in early pregnancy (<18 weeks), cord blood samples shortly after birth, and child serum samples around the age of 5 years. All serum samples were stored at −80 °C after immediate processing. Maternal TSH, FT4 and TT4 were determined in samples using chemiluminescence assays (Vitros ECI; Ortho Clinical Diagnostics, Rochester, NY). The intra- and inter-assay coefficients of variation were <4.1% for TSH, <5.4% for FT4 and <6.4% for TT4. Thyroid peroxidase antibodies (TPOAbs) were measured using the Phadia 250 immunoassay (Phadia AB, Uppsala, Sweden) and were defined as positive when exceeding 60 IU/ml. Human chorionic gonadotropin (hCG) was analyzed in maternal serum using a solid-phase, two-site chemiluminescent immunometric assay, calibrated against World Health Organization Third International Standard 75/537, on an Immulite 2000 XPi system (Siemens Healthcare Diagnostics, Deerfield, IL). Child TSH and FT4 concentrations were determined using an electrochemiluminescence immunoassay on the Cobas e601 immunoanayzer (Roche Diagnostics). The intra- and inter-assay coefficients of variation were 1.1–3.0% for TSH at a range of 0.4–0.04 mU/L and 1.6–5.0% for FT4 at a range of 1.6–24.1 pmol/L. References ranges of maternal and offspring thyroid function within the Generation R study can be found elsewhere (Medici et al., 2012; Önsesveren et al., 2017).

We quantified concentrations of eight bisphenols in spot urine samples acquired from women during early, middle, and late pregnancy (<18, 18–25, >25 weeks gestational age). Urine samples were collected in 100 mL polypropylene urine containers, stored at 4 °C and transported within 24 h of receipt to the STAR-MDC laboratory before being distributed manually in 25 mL polypropylene vials to be frozen at −20 °C. The urine specimens were shipped on dry ice in 4 mL polypropylene vials to the Wadsworth Center, New York State Department of Health, Albany, New York for analysis of bisphenol concentrations. Quantitative detection of bisphenols was performed using a liquid-liquid extraction (LLE) method followed by enzymatic deconjugation of the glucuronidated bisphenols accompanied by high performance liquid chromatography electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS). Using $_{13}C_{12}$-BPA and $_{13}C_{12}$-BPS isotopically labeled internal standards, bisphenols were quantified with limits of detection in the range of 0.03 and 0.18 ng/ml. Samples were analyzed for creatinine utilizing HPLC-ESI-MS/MS, improved by incorporating $^{2}D_{3}$-creatinine. Further details of laboratory analyses are reported elsewhere (Philips et al., 2018). Values below the limit of detection (LOD) were imputed as LOD$\div\sqrt{2}$. Bisphenols that were detected in <20% of samples were not included in the analysis, leaving BPA, BPS and BPF. We only analyzed each specific bisphenol analogue if it was above the LOD for >50% of the samples. All measured values (if detected above LOD in >20% of cases) were used to calculate the bisphenol weighted molar sum as: [(BPA concentration in ng/mL) × (1/molecular weight of BPA)/1000)] + [(BPS concentration in ng/mL) × (1/molecular weight of BPS)/1000)] + [(BPF concentration in ng/mL) × (1/molecular weight of BPF)/1000)]. All bisphenol measurements, including the molar sum, were divided by urinary creatinine to adjust for urine dilution.

2.3. Covariates

Data on maternal age at enrollment, pre-pregnancy body mass index (BMI), ethnicity, education level smoking status as well as parity were obtained using questionnaires. Smoking status was defined as: non-smokers, past smokers and current smokers. Gestational age at blood sampling was determined based on fetal ultrasound data. Information on method of delivery, pregnancy outcome, date of birth, birth anthropometrics, and the sex of the child was acquired from community midwives, obstetricians, and hospital registries. Child age and weight measurements were performed during visit to the Generation R research center for blood sampling.

3. Statistical analysis

TSH and bisphenol concentrations were natural log-transformed to deal with their right skewed distribution or to reduce any outlier effects. We used Spearman correlation to assess the correlation between bisphenol concentrations and intraclass correlation was used to assess the correlation between BPA measurements in early, mid and late pregnancy. We used multivariable linear regression models to study the association of urinary bisphenols with thyroid function measurements, utilizing restricted cubic splines to assess potential non-linearity. First, we performed cross-sectional analyses assessing the association of early pregnancy urinary bisphenol concentrations with maternal TSH, FT4 or TT4. These models were adjusted for maternal age, pre-pregnancy BMI, parity, smoking status, education level, ethnicity, gestational age at the time of blood sampling, urinary creatinine, TPOAb positivity and hCG. Selection of the gestational age at the time of blood sampling was based on its association with the physiologic changes of thyroid function as well as glomerular filtration rate during pregnancy (Korevaar et al., 2017; Wiles et al., 2019). Moreover, TPOAb positivity and hCG were considered as potential confounders because of the evidence showing that TPOAb positive women have generally a higher TSH while the response of their thyroid gland to stimulation by hCG is impaired compared to TPOAb negative women (Korevaar et al., 2017). Next, we studied the association of three measurements of urinary bisphenols (that is early, mid or late pregnancy) as well as the mean exposure throughout pregnancy with cord blood and childhood TSH and FT4 concentrations. Models included all three measurements of BPA or molar sum of bisphenols during pregnancy simultaneously (mutually adjusted) to investigate any potential windows of vulnerability (Chen et al., 2015). Models with cord blood thyroid parameters were adjusted for fetal sex, fetal distress, method of delivery (spontaneous, caesarean section and/or breech extraction), parity, ethnicity, maternal education, BMI (kg/m^2), smoking status and urinary creatinine (Korevaar et al., 2016). Models for childhood thyroid function were adjusted for child's age (years), BMI (kg/m^2), ethnicity and sex as well as maternal education, smoking status and urinary creatinine (Önsesveren et al., 2017; Korevaar et al., 2016). The potential confounders for maternal, cord blood and child models were selected according to directed acyclic graphs based on previous studies of maternal exposure to bisphenols and maternal, cord blood and child thyroid function. In addition, biologically plausible associations between covariates and exposures and/or outcomes were considered for confounder selection (see Supplemental Figs. 1–3) (Textor et al., 2016; VanderWeele, 2019). The additional adjustment of all models for urinary creatinine while bisphenol concentrations were already standardized for the creatinine concentrations was according to the suggestion by O'Brien et al. to fully consider for urinary dilution (O'Brien et al., 2016). Relevant outliers of thyroid function measurements were identified based on visual assessment of the data using histograms and were permanently removed if initial exclusion resulted in >0.5% change of effect estimate.

Furthermore, based on previous studies showing that exposure to bisphenols can alter the function of hypothalamus-pituitary-thyroid axis, we investigated whether the association of maternal FT4 with TSH differed according to BPA or BPS concentrations by adding an interaction term (bisphenol*FT4) to the model with maternal TSH as dependent variable (Fernandez et al., 2018; Lee et al., 2017; Zhang et al., 2017; Gentilcore et al., 2013; Kaneko et al., 2008). Also, since previous studies suggested sex-specific effects (Chevrier et al., 2013; Romano et al., 2015), in a separate analysis, we added an interaction term (bisphenol*sex) to the cord blood and child regression models. Finally, we checked for potential effect modification by TPOAb status in the association of BPA or BPS with maternal TSH or FT4 by adding their interaction terms to the models. A P-value < 0.15 was considered as indicator of potential effect modification and stratified analyses were conducted accordingly to assess the relevance of potential differences in the effect estimates.

We used multiple imputation by chained equations to impute missing data of covariates. Ten sets were imputed and the results of analyses were pooled using Rubin's rules (Buuren et al., 2011). All statistical analyses were performed using R statistical software version 3.5.2 (packages mice, rms and visreg; https://www.r-project.org/).

4. Results

After exclusion of women with pre-existing thyroid disease or history of fertility treatment and children with chronic diseases, using thyroid medication or growth hormone, the final study population comprised 1,267 women, 853 newborns and 882 children (Fig. 1). The median (95% range) gestational age at enrollment was 12.9 (9.8–17) weeks, the mean (SD) maternal age at inclusion was 30.5 (4.8) years, and the study population consisted predominantly of non-smokers (949/1,267; 75.5%) that were of Western ethnical origin (671/1,267; 53.2%; Table 1). The mean (SD) newborn gestational age at birth was 40.1 (1.3) weeks, with a mean (SD) birth weight of 3,491 (462) grams of which 48.5% were female (Table 1). The mean (SD) age at the time of measurements during childhood was 5.9 (0.2) years (Table 1). Data on covariates was missing for maternal BMI (0.4%), smoking (9.7%), education level (4.7%), ethnicity (1.1%) and neonatal mode of delivery (5.8%). There were no meaningful differences in thyroid function or baseline characteristics when comparing pregnant women or their newborns based on the availability of bisphenol measurements (Supplemental Tables 1–3). BPA concentrations were above the LOD in 79%, 93% and 90% for early, mid and late pregnancy (Table 2). BPS was detected in 66.6% and BPF in 40.2% of the samples in early pregnancy but in <30% of samples in middle and late pregnancy (Table 2). Creatinine adjusted concentrations of bisphenols are provided in Supplemental Table 4. The intraclass correlation coefficient (95% CI) between three maternal urinary BPA measurements was −0.003 (−0.03 to 0.02, $P = 0.58$). Moreover, the Spearman correlation coefficients of BPA, BPS and BPF during pregnancy (when detected in more than 20% of samples) ranged from −0.05 to 0.32, with the strongest correlations between bisphenols measured in early pregnancy (Supplemental Fig. 4).

4.1. Maternal thyroid function during early pregnancy

There was no consistent association between early pregnancy BPA, BPS or the bisphenol molar sum with maternal TSH, FT4 or TT4 (Table 3). However, the inverse log-linear association of FT4 with TSH attenuated with a higher BPS concentration. Below the median BPS concentration (0.34 ng/mL), the β (95% CI) for the association of FT4 with ln-TSH was −0.04 (−0.05 to −0.03) while it was −0.02 (−0.03 to −0.01) for BPS above the median (P for interaction = 0.001; Fig. 2). However, we did not identify a similar attenuation for higher BPA concentrations (P for interaction = 0.95). There was no effect modification by TPOAb status in the association of BPA or BPS with TSH or FT4 (*Ps* for interaction ranged from 0.17 to 0.91).

4.2. Newborn thyroid function

A higher BPA and a higher molar sum of bisphenols during late pregnancy was associated with a higher cord blood TSH (β [95% CI]: 0.04 (0.007 to 0.07) and 0.04 (0.002 to 0.07), respectively; Table 4). Further analysis suggested that this association for late pregnancy BPA was only apparent in female newborns but not male newborns (P for interaction = 0.06, Supplemental Table 5). However, there was no association of early or mid-pregnancy bisphenol exposure with cord blood TSH. There was evidence for an association of higher late pregnancy molar sum of bisphenols with lower cord blood FT4 in newborn girls but not in newborn boys (P for interaction = 0.13; Supplemental Table5). Neither early pregnancy BPS, mean gestational exposure to BPA nor the early or middle pregnancy molar sum of bisphenols were associated with cord blood TSH or FT4.

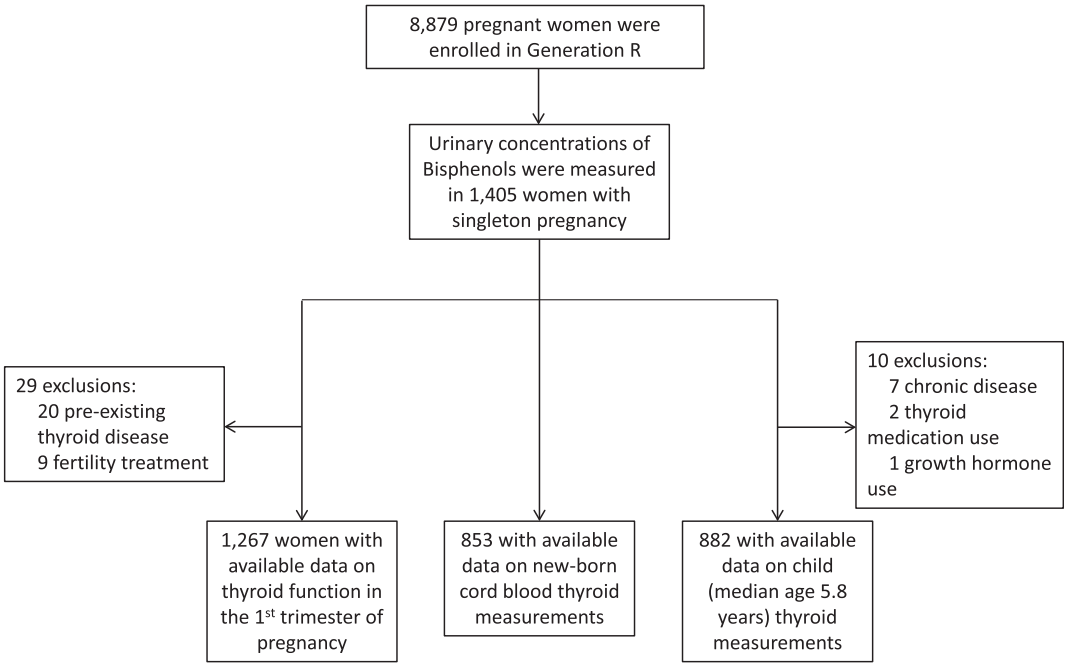

Fig. 1. Flowchart of the study population.

4.3. Childhood thyroid function

A higher BPA during late pregnancy, but not early or mid-pregnancy, was associated with a lower child FT4 (β [95% CI]: −0.11 [−0.21 to −0.01], Table 4), with evidence of a sex-specific association (β [95% CI]: −0.18 [−0.31 to −0.05] in males, −0.009 [−0.16 to 0.14] in females, *P* for interaction = 0.08; Supplemental Table 6). A higher late pregnancy molar sum of bisphenols was also associated with a lower child FT4, but there was no evidence of a sex-specific association (Table 4 and Supplemental Table 6). In addition, a higher mean exposure to BPA or mean molar sum of bisphenols during pregnancy was associated with a lower child FT4 (Table 4). There was no association of early pregnancy BPS with childhood thyroid function.

5. Discussion

We investigated the association of maternal urinary bisphenol concentrations with maternal, newborn and childhood thyroid function. We showed that a higher early pregnancy maternal BPS exposure was associated with an attenuation of the log-linear association of FT4 with TSH. Furthermore, higher maternal BPA exposure during late pregnancy was associated with a higher cord blood TSH in girls and lower childhood FT4 concentrations in boys.

Several experimental studies have shown that BPA can interfere with the thyroid system by altering the expression of genes related to thyroid hormone synthesis, metabolism and action (Lee et al., 2019; Gentilcore et al., 2013; Kaneko et al., 2008; Zoeller et al., 2005; Moriyama et al., 2002; Molina-Molina et al., 2013; Fernandez et al., 2018; Lee et al., 2018; Sheng et al., 2012; Wu et al., 2016). In this sample of pregnant women, we could not identify any association of maternal BPA with maternal TSH or FT4 concentrations. Previous epidemiological studies in pregnant populations showed inconsistent results. On one hand, of two smaller studies (N = 335 and N = 181) performed in the US, one showed that higher BPA exposure was associated with lower TT4 (Chevrier et al., 2013), while the other did not show any association of BPA with TSH, FT4 or free triiodothyronine (T3) (Romano et al., 2015). In the largest study to date, our group recently showed that higher urinary BPA concentrations were associated with a lower TT4 and a lower ratio of T4 to T3 in early pregnancy, possibly reflecting effects on deiodinase enzymes (Derakhshan et al., 2019). In contrast, the only study utilizing repeated measurements of BPA as well as TSH and FT4 concentrations during pregnancy (N = 439, 4 measurements) showed that higher BPA exposures were associated with a lower TSH and a higher FT4 (Aung et al., 2017). An overview of the exposure levels of bisphenols in pregnant populations from different countries shows that exposure to BPA in Generation R study is almost the same as pregnant women from the US or Sweden but lower than Puerto Rico and higher than Japan (Supplemental Table 7). Interpretation of whether or not human evidence is in line with findings from experimental studies is limited by the current heterogeneity of human studies regarding study population characteristics including bisphenol exposure levels but also the frequency and timing of bisphenol and/or thyroid function measurements.

In this study, a higher early pregnancy BPS was associated with an attenuation of the inverse association of FT4 with TSH. One explanation for the observed association can be that BPS exposure may alter the pituitary-thyroid axis homeostasis and that presents as the attenuation of the expected log-linear association of FT4 and TSH in pregnant women. Interestingly, *in vivo* and *in vitro* studies have shown that BPS can alter the gene expression of the thyroid hormone receptor β and proteins necessary for thyroid hormone synthesis such as thyroglobulin (Tg), sodium/iodide symporter (NIS) and thyroid peroxidase (Lee et al., 2017; Lee et al., 2019; Zhang et al., 2017). Thus, interference of BPS with thyroid system at two levels, i.e. thyroid hormone production together with reduced pituitary TSH response could be the underlying mechanism for the altered association of FT4 with TSH in the current study. Of note, experimental studies also showed similar effects for BPA (Gentilcore et al., 2013; Kaneko et al., 2008), however, we did not find a similar association for BPA. This is most likely due to a lower BPA exposure in pregnant women as compared to experimental settings. Interestingly, experimental data indicate that BPS can disrupt the thyroid system at a lower concentration than BPA (Lee et al., 2017).

We identified some evidence for fetal sex-specific associations of late pregnancy maternal urinary BPA with cord blood TSH and childhood FT4. The cord blood analyses were based on the notion that BPA crosses the placenta (Corbel et al., 2014) indicating the potential to affect the fetal and neonatal thyroid system. Interestingly, these associations were only identified for the BPA measurement that was closest to birth, but

Table 1
Characteristics of the study population.

Maternal Characteristics	N = 1,267
Thyroid stimulating hormone (mU/L)	1.30 (0.004–4.44)
Free thyroxine (pmol/L)	14.6 (10.1–21.7)
Total thyroxine (nmol/L)	137.5 (88.5–207.0)
Thyroid peroxidase antibody positivity, n (%)	78 (6.0)
Human chorionic gonadotropin (IU/L)	46,030 (14,771–108,812)
Gestational age at inclusion (weeks)	12.9 (9.8–17.0)
Age (years)	30.5 (4.8)
BMI (kg/m^2)	24.4 (4.3)
Parity, %	
0	768 (61.0)
1	343 (27.4)
≥2	149 (11.6)
Education level, n (%)	
None or primary only	106 (8.4)
Secondary education	537 (42.6)
Higher education	617 (48)
Smoking, n (%)	
Non-smokers	949 (75.5)
Past smokers	132 (10.2)
Current smokers	179 (14.3)
Ethnic origin, n (%)	
Western	671 (53.2)
Non-western	589 (46.8)
Newborn characteristics	**N = 853**
Thyroid stimulating hormone (mU/L)	9.57 (3.13–34.7)
Free thyroxine (pmol/L)	20.6 (14.8–31.0)
Gestational age at birth, weeks	40.1 (1.3)
Birth weight, grams	3,491 (462)
Fetal distress, %	52 (6.2)
Method of delivery, n (%)	
Spontaneous	755 (93)
Caesarean section	54 (6.5)
Breech extraction	3 (0.5)
Sex (female), n (%)	404 (48.5)
Child characteristics	**N = 882**
Thyroid stimulating hormone (mU/L)	2.33 (0.92–4.87)
Free thyroxine (pmol/L)	16.8 (13.7–20.9)
Age, (years)	5.9 (0.2)
Weight, (kg)	22.5 (3.37)
Sex, (female), n (%)	414 (47.2)

Data are shown as median (95% range), mean (SD) or percentages as appropriate.

not for the measurement time points of early and mid-pregnancy. This particular finding has also been reported by two previous studies (Chevrier et al., 2013; Romano et al., 2015), and could be explained by the fact that fetal thyroid gland becomes mature and functional after week 20 of gestation (Korevaar et al., 2017), thus any exposure to EDCs after this point could alter the function and sensitivity of the fetal thyroid gland rather than its development. While we found evidence that a higher late pregnancy BPA is associated with a higher cord blood TSH in girls, in the two previous studies, higher BPA, measured closest to birth, has been associated with a lower cord TSH in girls (Romano et al., 2015) or a lower heel prick TSH in boys (Chevrier et al., 2013). In addition, a recent study could not identify any association of cord blood BPA with cord blood TSH or FT4 (Minatoya et al., 2017). Based on the latter finding, it could be speculated that exposure to BPA during gestation and development (vulnerable time-window) rather than concurrent exposure (BPA measured in cord blood) can have lasting effects on offspring's thyroid function. The between-studies differences, such as opposite direction of associations, might arise from different methods of thyroid function measurements in newborns (cord blood vs. heel prick) or a lack of statistical power. These differences reflect the need for further research to shed light on the possible association of maternal urinary bisphenols with cord blood thyroid function with a focus on sex-specific effects.

To the best of our knowledge, this is the first study to investigate the association of maternal urinary bisphenols during pregnancy with thyroid function of the offspring during childhood. We showed that a higher late pregnancy maternal BPA was associated with a lower childhood FT4 concentration in boys but not in girls. BPA disrupts the endocrine system via various mechanisms and receptors, for example through its properties as a xenoestrogen with binding affinity for the estrogen receptors (Alonso-Magdalena et al., 2012). The development of neuroendocrine systems is controlled in a sex-specific manner by gonadal steroid hormones and disruption of this system by exposure to EDCs (mostly through epigenetic programming) can result in impairment of endocrine systems in later life (Walker and Gore, 2011). Therefore, the sex-specific effects shown in this study indicate that fetal exposure to BPA could potentially impair hypothalamic-pituitary development and impact the

Table 3
The association of early pregnancy urinary bisphenols with maternal TSH, FT4 and TT4.

	TSH	P value	FT4	P Value	TT4	P value
Bisphenol A	−0.007 (−0.02 to 0.007)	0.34	0.011 (−0.09 to 0.11)	0.81	0.12 (−0.93 to 1.18)	0.82
Bisphenol S	−0.004 (−0.01 to 0.008)	0.49	0.076 (−0.002 to 0.15)	0.08	0.97 (0.03 to 1.91)	0.04
Molar sum	−0.008 (−0.02 to 0.01)	0.33	0.049 (−0.07 to 0.17)	0.42	0.62 (−0.71 to 1.95)	0.35

Betas (95% CI) are per 1 natural log-transformed increase in creatinine-adjusted urinary bisphenols. Multivariable linear regression models were utilized for each bisphenol separately adjusting for gestational age at the time of sampling, maternal age, thyroid peroxidase antibodies, human chorionic gonadotropin, urinary creatinine concentrations, body mass index, education level, ethnicity, smoking status and parity. All bisphenols measurements as well as TSH were natural log-transformed for the analyses.

Table 2
Maternal urinary bisphenols and creatinine concentrations per trimester.

Maternal urinary measurements N = 1267	Early pregnancy	%>LOD	Middle pregnancy	%>LOD	Late pregnancy	%>LOD
Gestational age (weeks)	12.9 (9.9–17.0)	–	20.3 (18.9–22.7)	–	30.2 (28.7–32.5)	–
Bisphenol A (ng/mL)†	1.61 (<LOD-21.0)	79.0	1.47 (<LOD-21.2)	93.0	1.65 (<LOD-20.5)	90.0
Bisphenol S (ng/mL)†	0.34 (<LOD-8.83)	66.6	0.24 (<LOD-1.69)	29.8	NA	18.9
Bisphenol F (ng/mL)†	0.55 (<LOD-6.66)	40.2	NA	5.5	1.17 (<LOD −7.38)	23.3
Molar sum of bisphenols*	8.98 (1.21–95.1)	–	6.38 (0.59–85.2)	–	9.18 (1.09–98.7)	–
Creatinine (g/L)	1.02 (0.15–3.44)	–	1.17 (0.27–4.36)	–	0.94 (0.16–3.26)	–

Data are shown as median (95% range). Early, mid and late pregnancy correspond to <18, 18–25 and >25 weeks gestational age, respectively. LOD: Limit of detection.
† LOD for BPA, BPS and BPF were 0.15, 0.05 and 0.18 ng/mL, respectively.
* Values are grouped molar concentrations of bisphenols in nmol/L with non-detectable levels of separate bisphenols imputed as $LOD \div \sqrt{2}$. Bisphenols are included in the molar sum only if more than 20% of values was above the LOD.
NA: not applicable due to >80% below the limit of detection.

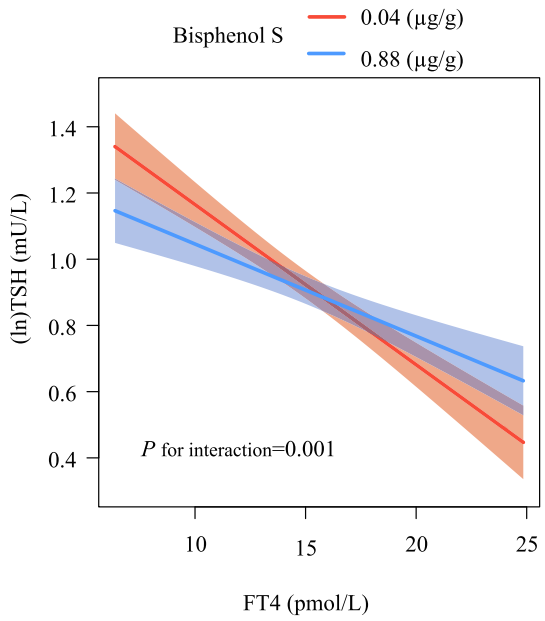

Fig. 2. Association of maternal FT4 with TSH according to urinary bisphenol S concentrations. Figure shows the association of maternal FT4 with natural log-transformed TSH according to 10th and 90th percentiles of the urinary bisphenol S (BPS) concentrations. A multivariable linear regression model was utilized containing the interaction term of FT4 and BPS adjusted for gestational age at the time of sampling, maternal age, thyroid peroxidase antibodies, human chorionic gonadotropin, urinary creatinine, body mass index, education level, ethnicity, smoking status and parity.

thyroid system during later life in a sex-specific manner. Interestingly, sex-differences have also been reported for maternal BPA exposure and offspring metabolic outcomes, such as higher adiposity and BMI only in boys or lower fat mass and BMI only in girls (Russ and Howard, 2016). In addition, in a study on pregnant ewes, BPA exposure increased thyroid gland weight in male, but not female fetuses (Vyas et al., 2019). Taking these data together with our results, we can suggest that late pregnancy BPA has a transient effect on cord blood TSH only in female newborns, while in the long term, exposure to BPA during the development of the fetal thyroid gland and programming of the hypothalamic-pituitary-thyroid axis may affect childhood thyroid function in males.

We were able to study the association of repeatedly measured maternal urinary bisphenols with maternal, newborn and childhood thyroid function in a large, prospective, population-based cohort with detailed data on potential confounders and effect modifiers. This study was limited by the fact that bisphenols were measured using single spot urine samples at all three time points during pregnancy. Furthermore, considering the short half-life and high intra-individual variability of bisphenols, and a low within-individual correlation between the three measurements of BPA in this study, we cannot dismiss the possibility that our results are affected by (non-differential) measurement error. Finally, we did not assess child postnatal bisphenol exposure, differences in which could be a reflection of maternal exposure during pregnancy and act as a potential positive or negative effect modifier.

In conclusion, we show that maternal urinary BPS was associated with an attenuation of the log-linear association of TSH with FT4, and that late pregnancy BPA exposure was associated with higher cord blood TSH and lower childhood FT4 in a sex-specific manner. Further studies are needed to replicate our results and investigate the potential long-term effects of bisphenol exposure on human thyroid function.

Table 4
The association of maternal urinary bisphenols with cord blood or childhood TSH and FT4.

	Cord blood			
	TSH		FT4	
	Beta (95% CI)	*P* value	Beta (95% CI)	*P* Value
Bisphenol A				
Early pregnancy BPA*	−0.008 (−0.03 to 0.02)	0.65	0.04 (−0.12 to 0.19)	0.64
Mid pregnancy BPA*	0.02 (−0.01 to 0.05)	0.26	0.09 (−0.07 to 0.30)	0.22
Late pregnancy BPA*	0.04 (0.007 to 0.07)	0.01	−0.14 (−0.34 to 0.04)	0.14
Mean exposure during pregnancy	0.03 (−0.02 to 0.07)	0.22	−0.07 (−0.30 to 0.17)	0.63
Molar sum of bisphenols				
Early pregnancy molar sum**	−0.01 (−0.04 to 0.01)	0.37	0.05 (−0.14 to 0.25)	0.58
Mid pregnanacy molar sum**	0.02 (−0.01 to 0.05)	0.19	0.12 (−0.08 to 0.31)	0.24
Late pregnancy molar sum**	0.04 (0.002 to 0.07)	0.04	−0.14 (−0.35 to 0.07)	0.22
Mean exposure during pregnancy	0.02 (−0.02 to 0.07)	0.36	−0.03 (−0.31 to 0.24)	0.81
	Childhood			
	TSH		FT4	
	Beta (95% CI)	*P* value	Beta (95% CI)	*P* Value
Bisphenol A				
Early pregnancy BPA*	−0.008 (−0.02 to 0.01)	0.36	−0.04 (−0.12 to 0.04)	0.28
Mid pregnancy BPA*	0.005 (−0.01 to 0.02)	0.66	−0.02 (−0.11 to 0.08)	0.70
Late pregnancy BPA*	0.007 (−0.01 to 0.03)	0.53	−0.11 (−0.21 to −0.01)	0.02
Mean exposure during pregnancy	−0.01 (−0.04 to 0.01)	0.34	−0.15 (−0.28 to −0.02)	0.01
Molar sum of bisphenols				
Early pregnancy molar sum**	−0.002 (−0.02 to 0.02)	0.85	−0.007 (−0.11 to 0.09)	0.88
Mid pregnancy molar sum**	0.006 (−0.01 to 0.03)	0.59	−0.03 (−0.13 to 0.07)	0.55
Late pregnancy molar sum**	0.01 (−0.01 to 0.04)	0.27	−0.16 (−0.27 to −0.05)	0.004
Mean exposure during pregnancy	−0.004 (−0.03 to 0.03)	0.80	−0.16 (−0.30 to −0.01)	0.03

Betas (95% CI) are calculated using multivariable linear regression for 1 natural log-transformed increase in creatinine-adjusted urinary bisphenols. All cord blood models were adjusted for fetal sex, fetal distress, method of delivery (spontaneous, caesarean section and/or breech extraction), parity, ethnicity, maternal education, BMI, smoking status and urinary creatinine. All child models were adjusted for age (years), BMI (kg/m^2), ethnicity and sex as well as maternal education, smoking status and urinary creatinine concentrations. Bisphenol measurements as well as TSH were natural log-transformed.
* or ** were simultaneously adjusted in one regression model.

CRediT authorship contribution statement

Arash Derakhshan: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Elise M. Philips:** Methodology, Formal analysis, Investigation, Data curation, Writing - review & editing. **Akhgar Ghassabian:** Conceptualization, Methodology, Writing - review & editing, Funding acquisition. **Susana Santos:** Conceptualization, Methodology, Writing - review & editing. **Alexandros G. Asimakopoulos:** Methodology, Resources, Data curation, Writing - review & editing. **Kurunthachalam Kannan:** Methodology, Resources, Data curation, Writing - review & editing. **Andreas Kortenkamp:** Conceptualization, Methodology, Writing - review & editing, Funding acquisition. **Vincent W.V. Jaddoe:** Project administration, Conceptualization, Methodology, Resources, Writing - review & editing, Funding

acquisition. **Leonardo Trasande:** Project administration, Conceptualization, Methodology, Resources, Writing - review & editing, Funding acquisition. **Robin P. Peeters:** Project administration, Supervision, Conceptualization, Methodology, Resources, Writing - review & editing, Funding acquisition. **Tim I.M. Korevaar:** Supervision, Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Visualization, 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.

Acknowledgments

We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam. This project has been supported by grant RO1ES022972 and RO1ES029779-01 from the National Institutes of Health, USA. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health. In addition, this study was supported by the Exchange in Endocrinology Expertise (3E) program of the European Union of Medical Specialists (UEMS), Section and Board of Endocrinology and the European Union's Horizon 2020 Programme for research, technological development and demonstration under grant agreement no. 825161. Dr. Ghassabian's work was supported by grant UH3OD023305 from the Environmental influences on Child Health Outcomes Program (National Institutes of Health).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106160.

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