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Association of urinary bisphenols and triclosan with thyroid function during early pregnancy

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ABSTRACT

Background: Bisphenols and triclosan are considered as potential thyroid disruptors. While mild alterations in maternal thyroid function can result in adverse pregnancy and child developmental outcomes, there is still uncertainty whether bisphenols or triclosan can interfere with thyroid function during pregnancy.
Objectives: We aimed to investigate the association of urinary bisphenol A (BPA), bisphenol S (BPS), bisphenol F (BPF) and triclosan with early pregnancy thyroid function.
Methods: This study was embedded in the Swedish Environmental Longitudinal, Mother and child, Asthma and allergy study (SELMA), a population-based prospective pregnancy cohort. In total, 1996 participants were included in the current study. Maternal urinary concentrations of three bisphenols and triclosan, collected at median (95% range) 10 (6–14) weeks of pregnancy as well as serum concentrations of thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), total thyroxine (TT4), and total triiodothyronine (TT3) were measured.
Results: Higher BPA levels were associated with lower TT4 concentrations (non-monotonic, $P = 0.03$), a lower FT4/FT3 ratio (β [SE] -0.02 [0.01], $P = 0.03$) and a lower TT4/TT3 ratio (β [SE] -0.73 [0.27], $P = 0.008$). Higher BPF levels were associated with a higher FT3 (β [SE] 0.01 [0.007], $P = 0.04$). There were no associations between other bisphenols or triclosan and absolute TSH, (F)T4 or (F)T3 concentrations. The association of BPA with thyroid function differed with gestational age. The negative association of BPA with FT4/FT3 and TT4/TT3 ratios was only apparent in early but not late gestation (P for interaction: 0.003, 0.008, respectively).
Conclusion: These human data during pregnancy substantiate experimental findings suggesting that BPA could potentially affect thyroid function and deiodinase activities in early gestation.

1. Introduction

Bisphenols, a group of organic compounds belonging to the class of phenols, are utilized for the production of commonly used plastics such as epoxy resins in food and water containers, thermal receipts, toys and plastic bags. Consequently, there is widespread environmental contamination and constant human exposure to bisphenols (LaKind and Naiman, 2015; Rochester and Bolden, 2015). These compounds are detected in surface water, sediments, indoor dust and are also commonly identified in human serum, urine, placenta, umbilical cord blood, and breast milk (LaKind and Naiman, 2015; Rochester and Bolden, 2015; Lee et al., 2018a). Bisphenols are considered as endocrine disruptors because in vitro and animal studies show that they can interfere with estrogen as well as thyroid hormone action and regulation at multiple levels (Rochester and Bolden, 2015; Boas et al., 2012; Mughal et al., 2018; Ermler et al., 2011). Bisphenol A (BPA) is one of the most produced and well-studied subtypes which has been shown to interfere with thyroid hormone signaling and action via various

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mechanisms, including inhibition of the sodium/iodide symporter and altering the expression of thyroid function related genes (Wu et al., 2016; Lee et al., 2017; Gentilcore et al., 2013; Zhang et al., 2017). In response to regulatory interventions that restrict its use, BPA is increasingly substituted with rather similar chemicals such as bisphenol S (BPS) and bisphenol F (BPF). However, human data about the effects of these substitutes remains scarce and their potential to disrupt the thyroid system remains unknown. Furthermore, the thyroid hormone disruptive potential of triclosan, another widely used phenolic compound has mainly been studied in animals but requires confirmation in human studies (Weiss et al., 2015; Dann and Hontela, 2011; Paul et al., 2012; Johnson et al., 2016).

Disruption of the thyroid system may have more pronounced consequences in periods of increased demand for thyroid hormone, such as pregnancy. Adequate thyroid hormone availability is essential for a normal pregnancy and optimal development of the fetus, especially the fetal brain. In the last two decades, it has been demonstrated that even mild maternal thyroid dysfunction (such as subclinical hypothyroidism and hypothyroxinemia) is associated with a higher risk of adverse pregnancy and child developmental outcomes (Korevaar et al., 2017a). Maternal/fetal exposure to bisphenols has also been associated with pregnancy outcomes including impaired fetal growth, low birth weight, spontaneous preterm delivery, newborn hypothalamic-pituitary-adrenal axis dysfunction and adverse childhood neurodevelopmental outcomes (Mughal et al., 2018; Snijder et al., 2013; Huo et al., 2015; Lee et al., 2014; Behnia et al., 2016; Giesbrecht et al., 2017; Ghassabian and Trasande, 2018; Pergialiotis et al., 2017). However, available data on the association of exposures to bisphenols or triclosan with thyroid function in pregnant women is confusing. Some studies showed positive, some revealed negative associations with thyroid function, and yet other studies did not find any associations at all (Chevrier et al., 2013; Aung et al., 2017; Aker et al., 2016; Braun et al., 2018; Romano et al., 2015; Aker et al., 2018; Aker et al., 2019).

In this study, we aim to investigate the association of maternal urinary concentrations of BPA, BPS, BPF and triclosan with thyroid function during pregnancy in a large population-based cohort.

2. Methods

2.1. Study population

This study included mothers from the Swedish Environmental Longitudinal, Mother and child, Asthma and allergy study (SELMA), a population-based prospective pregnancy cohort. SELMA has been established to investigate the effects of early life exposure to environmental toxicants, in particular potential endocrine disrupting chemicals, on pregnancy outcomes and child health and development (Bornehag et al., 2012). Pregnant women were enrolled at median gestational week of 10 (with 95% of the women recruited before week 14) in the county of Värmland (Sweden) between September 2007 and March 2010. Participating families gave written consent for collection of blood and urine samples and participation in the SELMA study. The SELMA study has been approved by the regional ethical committee, Uppsala, Sweden (2007-05-02, Dnr: 2007/062) (Bornehag et al., 2012).

2.2. Laboratory measurements

Maternal blood samples were obtained and centrifuged during the first prenatal visit at the antenatal care centers. Serum samples were frozen at −80° Celsius and stored in a bio-bank at the Central Hospital in Karlstad. Serum thyroid stimulating hormone (TSH), free thyroxine (FT4), total thyroxine (TT4), free triiodothyronine (FT3), total triiodothyronine (TT3), thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) were measured using electrochemiluminescence assays (Cobas® e601; Roche Diagnostics, Mannheim, Germany) at the Department of Clinical Chemistry, Máxima Medical Center (Veldhoven, The Netherlands). Inter and intra-assay coefficients of variation were 2.1%, 3.5%, 3.8%, 3.8%, and 7.7% for TSH, FT4, TT4, FT3 and TT3, respectively. TPOAb positivity and TgAb positivity were defined as TPOAb > 34 IU/mL or TgAb > 115 IU/mL (manufacturer cut-offs), and the coefficients of variation were 12.4% and 7.1% for TPOAb at 33 or 100 IU/mL, respectively, 10.9% and 8.6% for TgAb at 76 and 218 IU/mL, respectively. Human chorionic gonadotropin (hCG) was measured in lithium-heparin plasma by electrochemiluminescence assays (Cobas® e601; Roche Diagnostics, Mannheim, Germany).

In addition, cotinine, a biomarker of tobacco exposure, was analyzed in serum according to Lindh et al. (2012), where 100 µL aliquots were added with 25 µL of a water:acetonitrile (50:50) solution with labeled internal standards and 200 µL acetonitrile, to precipitate proteins. Samples were shaken for 30 min, followed by centrifugation.

2.3. Bisphenols and triclosan measurement

First void morning urine samples were obtained during the first prenatal visit. Samples were stored at −20 °C before being processed at the Laboratory of Occupational and Environmental Medicine at Lund University, Lund, Sweden. The urine samples were analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS) as described in Gyllenhammar et al. to quantify BPA, BPS, BPF and triclosan (Gyllenhammar et al., 2017). Briefly, 0.1 mL of ammonium acetate and 0.01 mL of β-glucuronidase (*Escherichia coli*) was added to aliquots of 0.2 mL of urine and then incubated at 37 °C for 30 min and thereafter added with labeled internal standards for each analyzed compound. The samples were analyzed in a randomized order and in duplicate. The limit of detection (LOD) was defined as the concentration corresponding to a peak area ratio of three times the standard deviation of the chemical blanks, and were for BPA, BPS, BPF and triclosan, 0.22, 0.03, 0.03 and 0.1 ng/mL, respectively (Gyllenhammar et al., 2017). For concentrations below the LOD, reported concentrations were used. See appendix of the paper by Berge et al. for a detailed explanation of the methods used for bisphenols analysis, including measures taken to avoid contamination (Berge et al., 2017). Creatinine was used to standardize for urinary dilution, and determined by an enzymatic method (Mazzachi et al., 2000). The laboratory is a reference laboratory for analyses of urinary bisphenol in the Erlangen intercomparison program and participates in the comparison program for triclosan.

2.4. Covariates

During the visit to one of the antenatal care centers, data on ethnicity, education level and maternal height were determined by questionnaires. Weight of the participants was derived from the Swedish National Birth Register and body mass index (BMI) was calculated as weight (kg) divided by squared height (m). Participants were categorized as non-smoker, passive smoker or active smoker according to serum cotinine levels as follows: below 0.2 ng/mL, 0.2–15 ng/mL or higher than 15 ng/mL, respectively.

2.5. Statistical analysis

We used histogram of the thyroid function tests (outcomes) to visually asses the data and identify and exclude outliers. The identified outliers for each thyroid function test corresponded with the following percentiles: > 99.7th for TSH, < 0.1st or > 99.9th for FT4, FT3 and TT3 and < 0.1st or > 99.8th for TT4. TSH, bisphenols and triclosan concentrations were natural log-transformed due to their right skewed distribution. We assessed the correlations between urinary bisphenol concentrations using Spearman's correlation coefficients. We used multivariable linear regression to study the association of urinary bisphenols with thyroid function measurements, utilizing restricted cubic splines with 3 knots to assess potential non-linearity. All analyses were

adjusted for potential confounders including maternal age, BMI, parity, smoking status according to serum cotinine concentrations, education level, ethnicity, gestational age at the time of blood sampling, TPOAbs and TgAbs and hCG concentrations. In addition to the creatinine-standardized bisphenols and triclosan as described in the laboratory measurements methods, urinary creatinine was also included as a covariate in all models, according to the methods presented by O'Brien et al., to fully take into account the urinary dilution (O'Brien et al., 2016).

Potential windows of vulnerability to bisphenols and triclosan exposure during pregnancy were investigated by including interaction terms of each chemical compound with gestational age at the time of sampling in regression models. Furthermore, findings from several experimental studies suggest that bisphenols can interfere with the hypothalamic-pituitary-thyroid axis by altering thyroid hormone receptors gene transcriptions (Lee et al., 2017; Gentilcore et al., 2013; Zhang et al., 2017; Fernandez et al., 2018; Kaneko et al., 2008). Thyroid function homeostasis is maintained by the hypothalamic-pituitary-thyroid axis which is controlled by the negative feedback loop: FT4 binds to thyroid hormone receptors of pituitary and thus controls the secretion of TSH and this is reflected by the physiologic log-linear association of TSH and FT4 (Korevaar et al., 2017b; Rothacker et al., 2016); therefore, we hypothesized that higher concentrations of BPA, BPS or BPF, through the explained mechanism, might alter this log-linear association and we investigated this by adding interaction terms of each bisphenol with FT4 to the linear regression models with natural log-transformed TSH as outcome. Finally, due to impairment of hCG mediated stimulation of the thyroid in TPOAb positive women during pregnancy, all analyses of TSH and/or FT4 were additionally checked by adding the interaction term of TPOAb positivity status with bisphenols or triclosan to the models (Korevaar et al., 2017c).

We used multiple imputation by chained equations to impute missing data of covariates, pooling 25 imputed datasets for analyses (Buuren and Groothuis-Oudshoorn, 2011). All statistical analyses were done using R statistical software version 3.5.2 (packages “mice: Multivariate Imputation by Chained Equations”, “rms: Regression Modeling Strategies” and “visreg: Visualization of Regression Models”; https://www.r-project.org/).

3. Results

After exclusions, the final study population comprised 1996 pregnant women (Fig. 1). Characteristics of the study population are shown in Table 1. The median gestational age of the participants at the time of sampling was 10 weeks (95% range: 6–14 weeks). BPA, BPS, BPF and triclosan were detected with measurements above the LOD in 99.1%, 80.2%, 88% and 92.5% of the study population and their median (95% range) creatinine adjusted levels were 1.38 (0.35–7.5), 0.06 (0.1–0.63), 0.11 (0.1–6.4) and 0.69 (0.004–600) μg/g, respectively. Spearman's correlation coefficients between bisphenols ranged from 0.17 to 0.33 ($P < 0.001$).

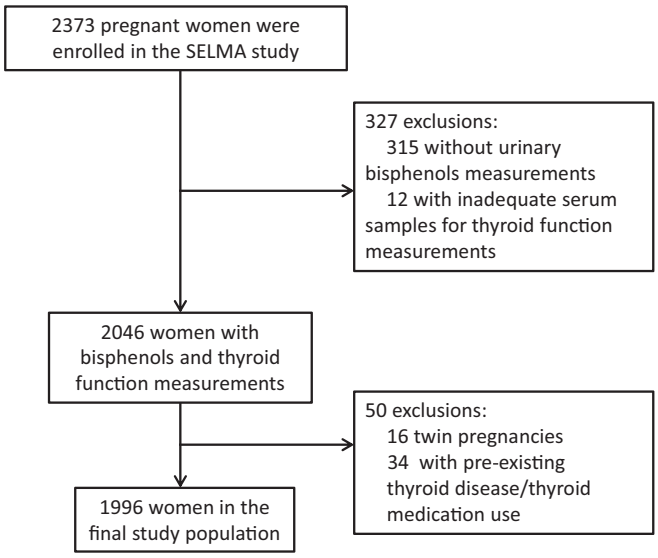

Fig. 1. Flowchart of the study population.

Table 1
Characteristics of the study population.

Characteristics	$N = 1996$
Bisphenol A (ng/mL)	1.51 (0.34–9.36)
Bisphenol S (ng/mL)	0.08 (0.03–0.88)
Bisphenol F (ng/mL)	0.15 (0.03–7.88)
Triclosan (ng/mL)	0.88 (0.12–706)
Thyroid-stimulating hormone (mU/L)	1.31 (0.11–4.14)
Free thyroxine (pmol/L)	15.0 (11.4–19.5)
Total thyroxine (nmol/L)	118 (81–166)
Free Triiodothyronine (pmol/L)	4.67 (3.72–5.96)
Total Triiodothyronine (nmol/L)	1.93 (1.27–2.90)
Thyroid peroxidase antibodies (IU/mL)	12.2 (6.3–247)
Thyroglobulin antibodies (IU/mL)	10.9 (10–415)
Human chorionic gonadotropin (IU/L)	69,778 (9724-167,949)
Urinary creatinine (g/L)	1.09 (0.37–2.47)
Gestational age (weeks)	10 (6–14)
Age	30.9 (4.9)
BMI	24.8 (4.5)
Parity, n (%)	
0	905 (45)
1	730 (37)
≥2	361 (18)
Ethnicity, n (%)	
Western	1935 (97)
Non-Western	61 (3)
Serum cotinine levels, n (%)	
Non-smoker: < 0.2 ng/mL	1699 (85.1)
Passive smoker: 0.2–15 ng/mL	117 (5.9)
Active smoker: > 15 ng/mL	180 (9)
Education level, n (%)	
Low	83 (4)
Medium	716 (36)
High	1197 (60)

Data are median (95% range), mean (SD) or number (percentage) as appropriate.

Higher urinary BPA levels were associated with lower TT4 (non-monotonic, $P = 0.03$, Fig. 2) and higher BPF with increased FT3 ($P = 0.04$, Table 2). Higher BPA levels were also associated with lower FT4/FT3 and TT4/TT3 ratios ($P = 0.03$ and 0.008, respectively; Fig. 2, Tables 2 and 3). There was no association between BPS or triclosan with absolute TSH, (F)T4 or (F)T3 concentrations.

We conducted sensitivity analyses to identify potential vulnerability windows and investigated the relationship between BPA and thyroid hormone levels at different gestational ages. The association of BPA with FT3 differed according to gestational age at the time of sampling (P for interaction = 0.02), but there was no difference for TSH, FT4, TT4 or TT3 (Fig. 3). During earlier pregnancy (mean 7 weeks), there was a positive association of BPA with FT3 which was no longer present during mean week of 12. Furthermore, there was a negative association of BPA with the FT4/FT3 and TT4/TT3 ratios during earlier but not later gestation (P for interaction = 0.003 and 0.008, respectively; Fig. 3). The association of BPS, BPF or triclosan with thyroid function did not differ according to gestational age at the time of sampling. In general, the association of bisphenols or triclosan with TSH or FT4 did not differ according to TPOAb status (P for interaction = 0.08 to 0.94). Moreover, the association of FT4 with TSH did not differ according to bisphenols or triclosan concentrations (P for interactions = 0.11 to 0.99).

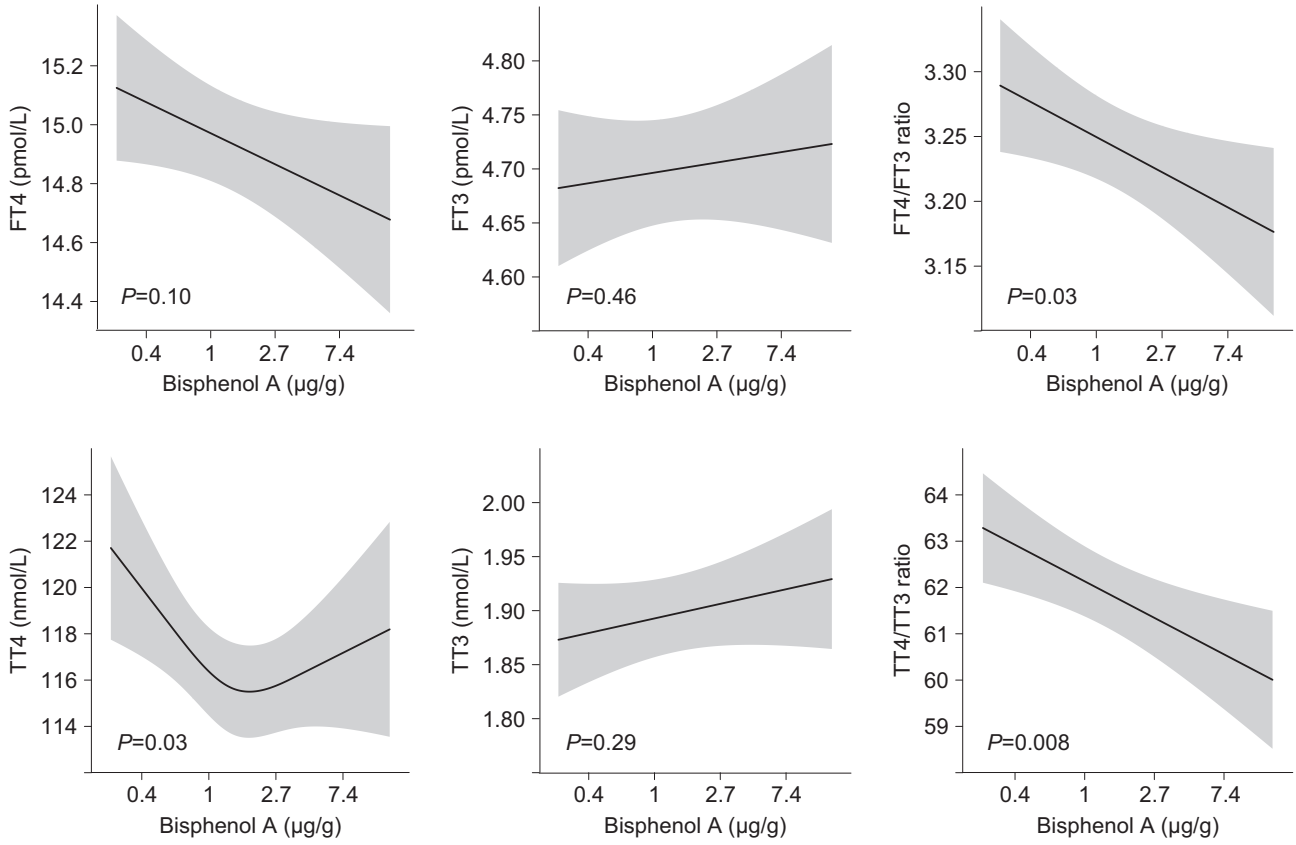

Fig. 2. Association of bisphenol A with FT4, FT3, TT4, TT3 and the corresponding ratios.
Figure shows the association of bisphenol A (µg/g urinary creatinine) with free and total thyroxine (FT4 and TT4) and free and total triiodothyronine (FT3 and TT3) concentrations and (F)T4/(F)T3 ratios. All analyses were adjusted for maternal age, thyroid peroxidase antibodies, thyroglobulin antibodies, human chorionic gonadotropin, urinary creatinine, smoking status (according to serum cotinine), body mass index, education, ethnicity and parity.

4. Discussion

In the current study, we investigated the association of urinary BPA, BPS, BPF and triclosan concentrations with thyroid function during pregnancy and we show that a higher exposure to BPA is associated with a lower TT4 and a higher exposure to BPF is associated with a higher FT3. Furthermore, we identified evidence of gestational age-specific effects of BPA on thyroid function, particularly on the (F)T4/(F)T3 ratios. There was no association of BPS or triclosan with serum thyroid hormone levels.

A consistent finding among experimental studies is that bisphenols can disrupt thyroid hormone signaling and action by altering the transcription of thyroid function related genes such as TSH-β, TRs and all three types of deiodinase. However, the molecular mechanism of these disruptions are complex and multifactorial, with different non-monotonic and dose-dependent effects in presence of thyroid hormones and estradiol (Wu et al., 2016; Lee et al., 2017; Gentilcore et al., 2013; Zhang et al., 2017; Zoeller et al., 2005; Lee et al., 2018b; Moriyama et al., 2002; Lu et al., 2018; Huang et al., 2016). This complexity hampers any efforts to translate results from these experimental studies to the human situation.

In the current study, we show that a higher BPA is associated with a lower TT4 and a lower FT4/FT3 and TT4/TT3 ratio. Since the (F)T4/(F)T3 ratio is a marker of peripheral thyroid hormone metabolism (which is regulated by three types of deiodinase enzyme), we hypothesize that this BPA effect could be mediated via alterations in deiodinase activity. Several experimental studies have shown that the expression of genes associated with thyroid hormone synthesis and metabolism, including different types of deiodinase genes, is affected by BPA (Xu et al., 2019; Lee et al., 2019). This hypothesis is supported by a recent animal study that identified evidence of potential disruption of deiodinase activity since exposure to BPA resulted in a higher (reverse)T3/TT4 ratio in pregnant ewe (Guignard et al., 2017). An alternative explanation for the differences in the (F)T4/(F)T3 ratio would be

Table 2
The association of urinary concentrations of bisphenols and triclosan with maternal thyroid function.

	TSH	*P* value	FT4	P value	FT3	P value	FT4/FT3 ratio	P value
Bisphenol A	−0.01 (0.02)	0.44	−0.09 (0.05)	0.10	0.01 (0.01)	0.46	−0.02 (0.01)	0.03
Bisphenol S	0.01 (0.01)	0.52	0.06 (0.04)	0.14	0.003 (0.01)	0.77	0.007 (0.01)	0.42
Bisphenol F	−0.01 (0.01)	0.33	0.02 (0.02)	0.36	0.01 (0.007)	0.04	−0.004 (0.005)	0.43
Triclosan	0.001 (0.007)	0.81	0.0 (0.01)	0.99	−0.003 (0.005)	0.45	0.001 (0.003)	0.64

Betas (SE) are calculated using a multi-variable linear regression model for natural log-transformed bisphenols and triclosan (per gram urinary creatinine) separately, adjusted for gestational age at the time of sampling, maternal age, thyroid peroxidase antibodies, thyroglobulin antibodies, human chorionic gonadotropin, urinary creatinine, smoking status (according to serum cotinine), body mass index, education, ethnicity and parity. TSH, thyroid stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine.

Table 3
The association of urinary concentrations of bisphenols and triclosan with TT4, TT3 and TT4/TT3 ratios.

	TT4	P value	TT3	P value	TT4/TT3 ratio	P value
Bisphenol A	Non-linear	0.03	0.01 (0.01)	0.29	−0.73 (0.27)	0.008
Bisphenol S	0.03 (0.47)	0.94	−0.008 (0.01)	0.92	0.11 (0.21)	0.60
Bisphenol F	−0.43 (0.29)	0.14	−0.001 (0.005)	0.75	−0.14 (0.13)	0.30
Triclosan	−0.12 (0.19)	0.51	−0.005 (0.003)	0.17	0.11 (0.08)	0.18

Betas (SE) are calculated using a multi-variable linear regression model for natural log-transformed bisphenols and triclosan (per gram urinary creatinine) separately, adjusted for gestational age at the time of sampling, maternal age, thyroid peroxidase antibodies, thyroglobulin antibodies, human chorionic gonadotropin, urinary creatinine, smoking status (according to serum cotinine), body mass index, education, ethnicity and parity. TT4, total thyroxine; TT3, total triiodothyronine.

that BPA affects the intrathyroidal iodine content, since studies in rat thyroid microsomes have shown that BPA is a noncompetitive inhibitor of the sodium/iodide symporter (NIS) (Wu et al., 2016). Inhibition of NIS will cause lower thyroidal iodine uptake, which could result in a higher secretion of T3 over T4 by the thyroid gland (Larsen and Zavacki, 2012).

Another main result in the current study is that the effect of BPA on the T4/T3 ratio was only present during very early pregnancy. One possible explanation may be that this difference in effect according to gestational age is due to the physiological changes related to hCG concentrations which result in an increase in thyroid hormone production and secretion by the thyroid gland from about the 6th week onwards peaking at week 8–12. This increase in thyroidal stimulation also requires an increase in iodine uptake, and potential inhibitory effects of BPA on NIS may have more apparent effects on the T4/T3 ratio in the phase of increased thyroid hormone production (Korevaar et al., 2017a; Laurberg et al., 2016). This might indicate that very early pregnancy is a window of vulnerability for BPA exposure. Because fetal thyroid hormone availability fully depends on the placental transfer of maternal thyroid hormones until the 14th week of pregnancy, these gestational age-specific effect warrant further studies.

In the current study, there was a positive association of BPF with FT3 but not with other markers of thyroid function, and we did not find any association of BPS with thyroid function. The thyroid disrupting potential has been shown for both BPF and BPS in experimental studies, mostly by interfering with thyroid specific gene expressions (Lee et al., 2019; Zhang et al., 2018). One possible reason that we did not identify other associations between BPF and BPS with thyroid function may have been due to the fact that exposure to BPF and BPS was still relatively low (median concentration 1.51 ng/ml vs 0.08 ng/ml and 0.15 ng/ml, respectively). Considering the gradual move of the industry to substitute BPA with other analogs, future studies on these substitutes, including BPS and BPF are essential to exclude a potential effect on thyroid function.

The results of previous human studies on the association of BPA or BPS with thyroid function during pregnancy are inconclusive. In two recent studies within the same population, a higher BPA was associated with a higher TSH after week 20 of pregnancy whereas BPS above the LOD was associated with lower thyroid function in the first 15 weeks of pregnancy (Aung et al., 2017; Aker et al., 2018). In other studies, there was either no association of BPA with thyroid function or there was a positive or negative association with FT4 or TT4, respectively (Chevrier et al., 2013; Aker et al., 2016; Romano et al., 2015; Aker et al., 2019). In the current study, our results indicate that BPA may affect thyroid function during very early gestation (e.g. around 7 weeks) before the pregnancy-specific physiological changes in thyroid function occur, but

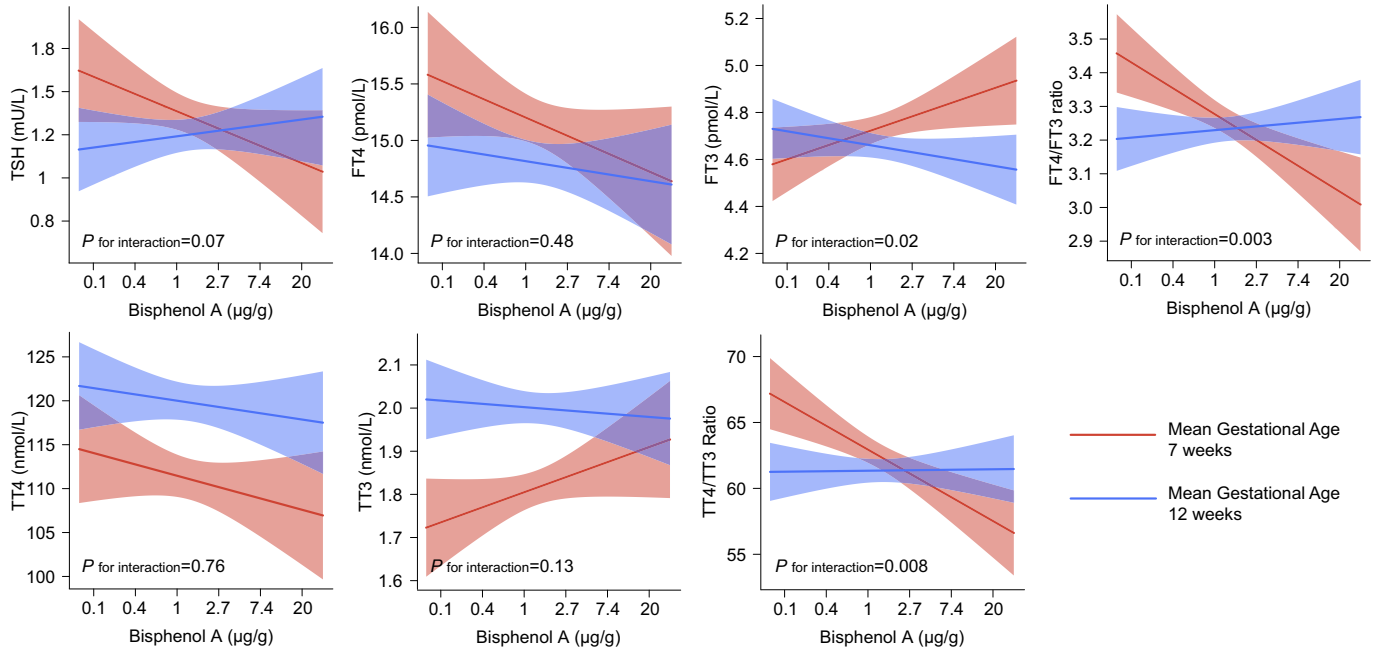

Fig. 3. Association of bisphenol A with thyroid function according to gestational age.
Figure shows the association of bisphenol A (μg/g urinary creatinine) with thyroid function according to gestational age at the time of blood sampling; categorized as mean 7th or 12th weeks of gestation, red and blue lines, respectively. All analyses were adjusted for maternal age, thyroid peroxidase antibodies, thyroglobulin antibodies, human chorionic gonadotropin, urinary creatinine, smoking status (according to serum cotinine), body mass index, education, ethnicity and parity. TSH, thyroid stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; TT4, total thyroxine; TT3, total triiodothyronine. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

not during later pregnancy (Korevaar et al., 2017a; Laurberg et al., 2016). This could partially explain some of the discrepancies between studies on the thyroid disrupting effects of bisphenols in humans which have been performed in different gestational ages and mostly not in early pregnancy.

In Sweden, use of triclosan in products has been decreasing, resulting in lower exposure levels compared to other countries (Larsson et al., 2014). In the current study there was no association of triclosan with thyroid function measurements. Although experimental studies have shown that triclosan can disrupt thyroid function (Wu et al., 2016; Paul et al., 2012), results of the human and epidemiological studies are inconclusive. In a randomized intervention of allocating wash products with or without triclosan to pregnant women, exposure to triclosan did not affect maternal thyroid function (Ley et al., 2017). In some epidemiological studies in pregnant women, triclosan had no association with thyroid hormones (Aker et al., 2016; Braun et al., 2018) while triclosan has been associated with thyroid hormone concentrations in other studies (Aker et al., 2018; Aker et al., 2019; Berger et al., 2018). These discrepancies between results may be due to different exposure levels among populations and advocate the need for more detailed studies in pregnant women on the potential thyroid disrupting activity of triclosan.

To the best of our knowledge, this is the first study to investigate the association of BPA, BPS and BPF as well as triclosan with a wide range of thyroid function measurements during pregnancy in a large prospective population-based cohort while taking into account thyroid autoimmunity and hCG. In addition, in the current study, the effects of exposure to tobacco smoke, which is a well-known disruptor of thyroid function, has been taken into account using serum cotinine measurements. A potential limitation of this study is that bisphenol exposure was based on a single spot urine sample, which may not represent the average long-term exposure of women to bisphenols due to the short half-life and high within-person variability of bisphenols in vivo (Townsend et al., 2013). In addition, the interpretation of the results of this study is limited by its observational nature.

In conclusion, our results indicate that that BPA can affect thyroid hormone concentrations and homeostasis during very early pregnancy. Considering the vulnerability of the fetus during pregnancy, further studies are required to replicate our findings, further elucidate any (patho)physiological mechanisms and translate these findings to study whether maternal or fetal thyroid disruption by bisphenol exposure during pregnancy could adversely affect later-life outcomes.

Disclosure

The authors have nothing to disclose.

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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.

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