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Blood and urinary biomarkers of prenatal exposure to disinfection byproducts and oxidative stress: A repeated measurement analysis

Chong Liu[a,b], Yi-Xin Wang[a,c,1,*], Ying-Jun Chen[a], Yang Sun[d,e], Li-Li Huang[f], Ying-Hui Cheng[g], Er-Nan Liu[h], Wen-Qing Lu[a,b,1,*], Carmen Messerlian[d,e,1]

[a] Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, and State Key Laboratory of Environmental Health (incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, PR China
[b] Department of Occupational and Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, PR China
[c] Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[d] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[e] Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[f] School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[g] Department of Gynecology and Obstetrics, Xiaonan Maternal and Child Care Service Centre, Xiaogan City, Hubei, PR China
[h] Wuhan Center for Disease Prevention and Control, Wuhan, Hubei, PR China

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ABSTRACT

Background: Toxicological studies have demonstrated that disinfection by-products (DBPs) can induce oxidative stress, a proposed mechanism that is relevant to adverse birth outcomes.
Objective: To examine the associations of blood trihalomethanes (THMs) and urinary haloacetic acids (HAAs) with urinary biomarkers of oxidative stress among pregnant women.
Methods: From 2015 to 2017, a total of 4150 blood and 4232 urine samples were collected from 1748 Chinese women during pregnancy. We determined concentrations of 4 blood THMs [chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM)] and 2 urinary HAAs [dichloroacetic acid (DCAA) and trichloroacetic acid (TCAA)]. The summary measures of exposure for brominated THMs (Br-THMs; a molar sum of BDCM, DBCM, and TBM) and total THMs (TTHMs; a molar sum of TCM and Br-THMs) were also calculated. Associations of categorical (i.e., tertiles) and continuous measures of DBPs with urinary concentrations of oxidative stress (OS) biomarkers, 8-hydroxy-2-deoxyguanosine (8-OHdG), 4-hydroxy-2-nonenal-mercapturic acid (HNE-MA), and 8-*iso*-prostaglandin $F_{2\alpha}$ (8-isoPGF$_{2\alpha}$), were assessed using linear mixed regression models.
Results: After adjusting for relevant confounding factors, we observed positive dose-response relationships between blood Br-THM tertiles and urinary HNE-MA (P for trend < 0.001). We also found positive associations between tertiles of blood TCM and TTHMs and urinary 8-OHdG and HNE-MA (all P for trend < 0.05). Urinary HAAs were also positively associated with 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ in a dose-response manner (all P for trend < 0.001). These associations were further confirmed when we modeled DBP exposures as continuous variables in linear mixed regression models, as well as in penalized regression splines based on generalized additive mixed models.
Conclusions: Exposure to DBPs during pregnancy may increase maternal OS status.

1. Introduction

Chlorine is a cost-effective disinfectant used globally to kill disease-causing microbes in drinking water. However, disinfection by-products (DBPs) are unintentionally generated when chlorine reacts with natural organic matter in raw water. Among 700 identified DBPs, trihalomethanes (THMs) and haloacetic acids (HAAs) are the two most prevalent by-products (Richardson et al., 2007). Humans can be exposed to

* Corresponding authors at: Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, and State Key Laboratory of Environmental Health (incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, PR China.
E-mail addresses: yixinwang@hsph.harvard.edu (Y.-X. Wang), luwq@mails.tjmu.edu.cn (W.-Q. Lu).
[1] These authors jointly supervised this work: Yi-Xin Wang, Wen-Qing Lu and Carmen Messerlian.

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Table 1
Geometric mean (standard deviation) concentrations of OS biomarkers (μg/g Cr) according to selected characteristics (N = 1748).

Characteristics	N (%) or mean ± SD	8-OHdG	HNE-MA	8-isoPGF$_{2\alpha}$
Gestational age at sample collection (weeks)				
Early pregnancy (< 14 weeks, reference)	9.2 ± 2.3	9.9 (2.3)	77.7 (6.6)	2.5 (3.1)
Middle pregnancy (14–27 weeks)	17.1 ± 2.3	8.2 (1.8)*	34.5 (5.3)*	2.0 (2.6)*
Late pregnancy (> 27 weeks)	31.8 ± 2.8	7.4 (1.8)*	86.9 (4.0)	1.8 (3.2)*
Age (years)				
< 25 (reference)	658 (37.6%)	8.6 (2.0)	62.0 (5.4)	2.2 (2.9)
25–29	741 (42.4%)	8.6 (2.0)	63.0 (5.9)	2.1 (3.0)
≥30	349 (20.0%)	8.8 (2.1)	62.1 (5.8)	2.1 (3.1)
Pre-pregnancy BMI (kg/m^2)				
< 18.5 (reference)	367 (21.2%)	9.2 (2.0)	59.4 (5.8)	2.2 (2.9)
18.5–24.9	1131 (65.4%)	8.5 (2.0)*	61.2 (5.7)	2.1 (3.0)
≥25	232 (13.4%)	7.6 (2.0)*	67.8 (5.0)	2.2 (2.8)
Education				
Junior school and below (reference)	1094 (62.9%)	8.7 (2.0)	63.2 (5.6)	2.2 (3.0)
High school	416 (23.9%)	8.4 (2.0)	61.2 (5.7)	2.0 (3.0)
Above high school	229 (13.2%)	9.0 (2.0)	60.7 (5.6)	2.3 (2.8)
Income (Yuan/month)				
< 3000 (reference)	707 (40.6%)	8.3 (2.0)	64.5 (5.6)	2.1 (2.9)
3000–4999	798 (45.9%)	8.8 (2.0)*	62.5 (5.8)	2.2 (3.1)
≥5000	235 (13.5%)	8.7 (2.0)	61.1 (5.6)	2.1 (3.0)
Gravidity				
1 (reference)	798 (45.7%)	8.6 (2.0)	60.0 (5.8)	2.1 (2.9)
> 1	949 (54.3%)	8.7 (2.0)	64.6 (5.6)	2.1 (3.1)
Infant sex				
Girl (reference)	863 (52.3%)	8.6 (2.0)	60.5 (6.0)	2.1 (3.1)
Boy	786 (47.7%)	8.7 (2.0)	64.2 (5.4)	2.2 (2.9)
Time varying factors				
Urine collection time				
07:00–08:59 (reference)	2905 (69.3%)	8.2 (1.9)	42.1 (5.1)	1.9 (2.8)
09:00–11:59	870 (20.8%)	9.3 (2.1)*	116.2 (5.6)*	2.5 (3.3)*
12:00–15:30	417 (9.9%)	10.9 (2.2)*	264.6 (3.6)*	3.6 (3.1)*
Season of collection				
Spring (reference)	1075 (25.5%)	9.0 (2.0)	64.6 (6.0)	2.0 (3.3)
Summer	1534 (36.4%)	8.8 (2.1)	55.9 (6.4)	2.1 (3.0)
Autumn	496 (11.8%)	8.2 (2.0)*	60.1 (5.2)	2.2 (2.8)*
Winter	1113 (26.4%)	8.2 (1.9)*	71.7 (4.6)	2.4 (2.8)*
BMI at each visit (kg/m^2)				
< 18.5 (reference)	554 (13.4%)	9.9 (2.2)	53.1 (6.6)	2.3 (3.1)
18.5–24.9	2754 (66.5%)	8.8 (2.0)*	60.6 (5.8)	2.2 (2.9)
≥25	833 (20.1%)	7.3 (1.9)*	76.7 (4.7)*	1.9 (3.1)*
Vegetable consumption (times/week)				
< 7 (reference)	745 (17.6%)	8.5 (1.9)	62.6 (5.9)	2.0 (3.0)
≥7	3478 (82.4%)	8.7 (2.0)	62.2 (5.6)	2.2 (3.0)

* *P*-value < 0.05 for significant difference in biomarker concentration from reference category, estimated from linear mixed models with a random intercept for subject identification.

DBPs through ingestion, dermal absorption, and inhalation during daily water-use activities (Nieuwenhuijsen et al., 2000).

Toxicological studies have demonstrated that THMs and HAAs adversely affect fetal growth in rodent species, manifested as reduced birth weight/length (Murray et al., 1979; Ruddick et al., 1983; Smith et al., 1989; Narotsky et al., 2015), decreased survival rate (Murray et al., 1979; Ruddick et al., 1983; Smith et al., 1989; Narotsky et al., 2015), and increased congenital defects (Smith, et al., 1989; Narotsky et al., 2011). Growing evidence from humans has associated markers of exposure to THMs and HAAs with stillbirth (King et al., 2000; Toledano et al., 2005), congenital anomalies (Cedergren et al., 2002; Chisholm et al., 2008), low birth weight (Lewis et al., 2006; Zhou et al., 2012; Cao et al., 2016), and small for gestational age (SGA) (Wright et al., 2004; Cao et al., 2016). However, underlying mechanisms remain poorly understood.

Oxidative stress (OS) is proposed to play a critical role in the pathoetiology of adverse fetal development (Biberoglu et al., 2016; Rashid et al., 2018). In humans, high levels of maternal urinary OS biomarkers, including 8-hydroxy-2-deoxyguanosine (8-OHdG) and malondialdehyde (MDA), have been associated with pre-eclampsia (Aouache et al., 2018), preterm birth (Ferguson et al., 2015), and intrauterine growth retardation (Kamath et al., 2006; Hracsko et al., 2008). Meanwhile, THMs and HAAs were also found to induce OS both *in vivo* (Abbassi et al., 2010; Hassoun et al., 2010; Hassoun et al., 2014) and *in vitro* (Beddowes et al., 2003). Epidemiological studies have further revealed higher levels of OS biomarkers in exhaled breath condensate and blood of swimmers exposed to chlorinated water (Varraso et al., 2002; Morissette et al., 2016). However, no study to date has investigated the associations between exposure to drinking-water DBPs and OS biomarkers during pregnancy. These potential associations constitute particular concern given the gestational vulnerability of fetal growth and development.

Blood THMs and urinary HAAs are identified as useful markers of exposure to drinking water DBPs, which represent integrative measures of exposure from different sources and routes (Gangler et al., 2018; Chen et al., 2019). Nevertheless, our recent variability study showed high within-individual variability in blood THMs and urinary HAAs over the course of pregnancy (Wang et al., 2019); high within-individual variability of HAAs and OS biomarkers in urine was also exhibited among healthy adult men (Wang et al., 2014; Wang et al., 2019), and school-aged children (Li et al., 2019). To reduce measurement error, we used repeated specimens collected during early, middle, and late pregnancy from 1748 pregnant women to assess the associations of blood THMs and urinary HAAs with 8-OHdG, 4-hydroxy-2-

Table 2
Distribution of blood THMs, urinary HAAs and urinary OS biomarkers.

Compounds	Overall				Early pregnancy		Middle pregnancy		Late pregnancy	
	% > LOD/LOQ	Geometric mean	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range
THMs (ng/L)										
Number of samples quantified			4150		1659		1373		1118	
TCM	92.5	9.4	10.2	6.0–15.7	10.0	5.8–15.8	9.6	5.7–14.7	11.2	6.9–16.7
BDCM	79.5	0.80	0.81	0.56–1.1	0.79	0.53–1.2	0.80	0.55–1.08	0.88	0.60–1.2
DBCM	42.7	0.74	< LOD	< LOD–1.1	< LOD	< LOD–1.0	< LOD	< LOD–1.1	< LOD	< LOD–1.1
TBM	49.0	4.5	< LOD	< LOD–10.1	< LOD	< LOD–8.7	< LOD	< LOD–9.6	< LOD	< LOD–15.3
Br-THM	–	7.1	4.0	2.8–12.2	3.9	2.7–10.6	3.7	2.8–11.5	4.7	2.8–17.2
TTHM	–	20.4	17.2	10.9–29.2	16.6	10.4–28.4	16.2	10.5–26.8	18.9	12.2–36.5
HAAs (μg/g Cr)										
Number of samples quantified			4080		1546		1395		1139	
DCAA	96.2	8.5	8.6	5.9–12.8	8.5	5.5–14.6	8.0	5.6–11.5	9.3	7.0–12.8
TCAA	91.5	2.3	2.1	1.4–3.4	2.3	1.4–4.2	1.9	1.3–3.0	2.1	1.5–3.1
OS (μg/g Cr)										
Number of samples quantified			4232		1682		1402		1148	
8-OHdG	99.6	8.6	8.4	5.8–12.4	9.5	6.3–15.0	8.2	5.8–11.8	7.2	5.2–10.0
HNE-MA	98.3	61.6	61.0	19.9–217.8	90.2	22.8–311.8	27.9	17.4–92.8	90.5	34.8–240.8
8-isoPGF$_{2\alpha}$	94.8	2.1	2.3	1.4–3.9	2.6	1.4–4.8	2.1	1.4–3.3	2.3	1.2–3.8

Abbreviations: THMs, trihalomethanes; HAAs, haloacetic acids; OS, oxidative stress biomarkers; LOD, limit of detection; LOQ, limits of quantification; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Br-THM, brominated THM; TTHM, total THM; DCAA, dichloroacetic acid; TCAA, trichloroacetic acid; 8-OHdG, 8-hydroxy-2-deoxyguanosine; HNE-MA, 4-hydroxy-2-nonenal-mercapturic acid; 8-isoPGF$_{2\alpha}$, 8-*iso*-prostaglandin F$_{2\alpha}$.

nonenal-mercapturic acid (HNE-MA), and 8-*iso*-prostaglandin F$_{2\alpha}$ (8-isoPGF$_{2\alpha}$).

2. Methods and materials

2.1. Research design

From 2015 to 2017, we recruited a total of 1876 pregnant women before 14 gestational weeks at the Maternal and Child Health Care Service Center of Xiaonan District in Hubei province, China (Chen et al., 2019; Wang et al., 2019). Women were included if they were between 18 and 40 years of age, resided in Xiaogan City, and had a singleton pregnancy. Women were followed throughout the duration of pregnancy. Research staff collected mothers' demographic and anthropometric data (e.g., height, education level, income, age, and gravidity) at recruitment. Maternal body weight, water-use activities (e.g., sources of drinking water and time interval since the last bathing/showering) and biological specimens (i.e., blood and urine) were collected during early (< 14 gestational weeks), middle (14–27 gestational weeks), and late pregnancy (> 27 gestational weeks). Birth outcome data (birth weight, gestational age, infant sex) were ascertained at delivery from medical records. After excluding 116 participants with stillbirths (n = 18), therapeutic termination (n = 33), malformations (n = 2), or spontaneous abortions (n = 63), and 12 women with insufficient urine volume for determination of HAAs or OS biomarkers, 1748 participants with singleton livebirths were retained in our analysis. Our study protocol was approved by the Ethics Committee of Tongji Medical College. All women signed an informed consent before participation.

2.2. Sample collection and quantification of THMs and HAAs

Sample collection and quantification have been described previously (Wang et al., 2019). Briefly, venous blood samples throughout pregnancy were drawn from the cubital vein using an anticoagulant blood collection tube. We determined blood concentrations of chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM) using a headspace solid-phase microextraction gas chromatography method. Spot urine samples were collected during pregnancy using a polypropylene container. Urinary dichloroacetic acid (DCAA) and trichloroacetic acid (TCAA) were pretreated by liquid-liquid extraction and then quantified by an Agilent Technologies 6890N gas chromatograph with an electron capture detector (Agilent Technologies, Palo Alto, USA). The limits of detection (LODs) for TBM, DBCM, BDCM, TCM, DCAA, and TCAA, were 2.00 μg/L, 0.68 μg/L, 0.45 μg/L, 1.95 μg/L, 1.0 μg/L, and 0.5 μg/L, respectively. Urinary creatinine (Cr) was determined by an automated clinical chemistry analyzer (Mindray Medical International Ltd., Shenzhen, China) (Wang et al., 2019). Urinary specific gravity (SG) was measured using the UriSed LabUMat urine analyzer at the Maternal and Child Health Care Service Center of Xiaonan District (Wang et al., 2019).

2.3. Quantification of OS biomarkers

Urinary concentrations of 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ were measured using established methods (Wang et al., 2019). In brief, the urine sample was centrifugated at 10,000 rpm for 10 min. A 100-μL supernatant was diluted with 2.4-mL deionized water, spiked with 50 μL of isotope-labeled standards (100 ng/mL), and then purified using solid-phase extraction. The resulting eluent was evaporated to dryness and re-dissolved in 200-μL 5% methanol/water. The mixture was separated by a Phenomenex Gemini-NX-C18 column (3 μm, 100 × 2 mm) and detected by Agilent 6460 triple quadrupole mass spectrometer. The limits of quantification (LOQs) of 8-OHdG, HNEMA, and 8-isoPGF$_{2\alpha}$ were 0.08, 0.03, and 0.06 ng/mL, respectively. One blank and two quality controls (5 ng/mL and 25 ng/mL standards added in the pooled samples) were analyzed within each batch. The concentrations of analytes in all blank samples were below the LOQs; the recoveries of spiked specimens ranged from 87% to 102%. We also evaluated the intra-batch precision by analyzing 5 replicated samples within a single day; the inter-batch precision was assessed by analyzing replicated samples in 5 different batches. The average intra- and inter-batch variability were 6.9% and 8.4%, respectively.

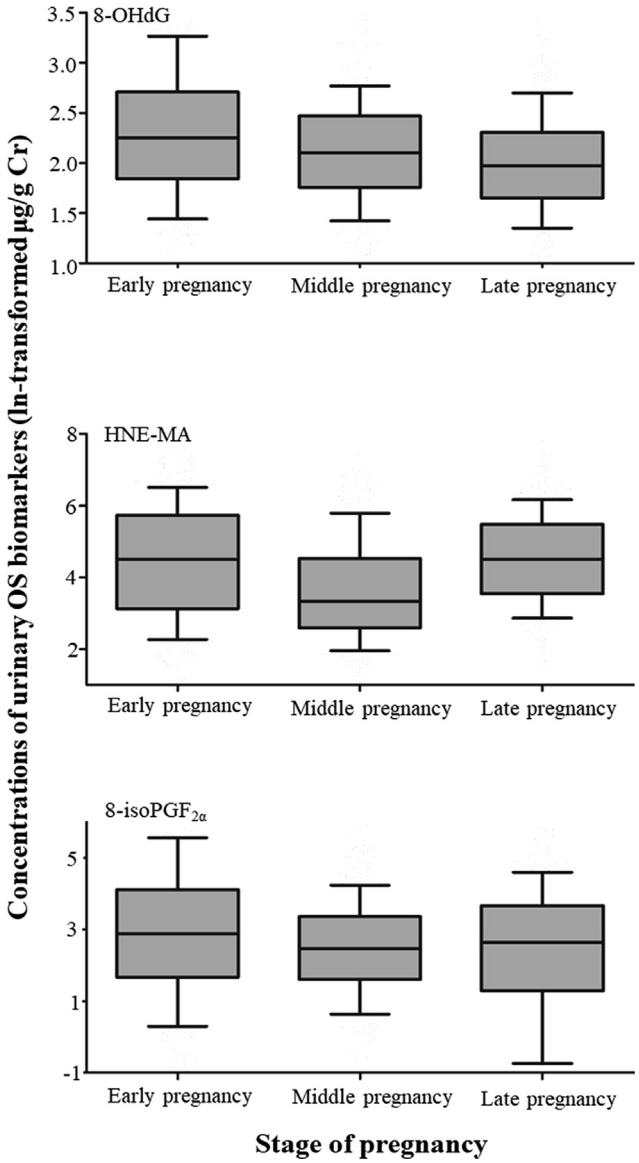

Fig. 1. Distribution of urinary OS biomarkers (ln-transformed, μg/g creatinine) during early, middle, and late pregnancy. The displayed values are the 10th (bottom whisker), 25th percentile (bottom of the box), median (line in box), 75th percentile (top of the box), and 90th (top whisker) of the concentrations.

2.4. Data analysis

Descriptive statistics were performed for baseline maternal characteristics (e.g., education level, income, age, and gravidity) and time-varying factors [e.g., gestational body mass index (BMI), time of sample collection, and water-use activities]. Concentrations of THMs, HAAs, and OS biomarkers in biospecimens lower than the LODs/LOQs were replaced by LOD/LOQ/√2 (Cao et al., 2016). A summary estimate of blood brominated THM (Br-THM, μg/L) was calculated as the sum of TBM, BDCM, and DBCM concentrations. We also estimated total blood THM (TTHM, μg/L) as the sum of Br-THM and TCM concentrations. To account for urine dilution, creatinine-adjusted concentrations of urinary HAAs and OS biomarkers were calculated by dividing the crude HAA concentration values (μg/L) by creatinine concentrations (g/L). We also calculated the SG-corrected concentrations of HAAs and OS biomarkers using the formula: $Pc = P[(SGmean - 1)/(SG - 1)]$, where Pc was SG-corrected concentrations, P was the crude concentrations, and SGmean was the mean SG of the overall participants from this study (Wang et al., 2019). We used the creatinine-adjusted values in the main analyses due to missing urinary SG measurements on 222 participants. Because of the skewed distributions of THMs, HAAs, and OS biomarkers, ln-transformed values were used for the analyses that required a normal distribution.

Table 3
The variance decomposition of ln-transformed concentrations of OS biomarkers (μg/g Cr) in repeated samples collected during pregnancy.OS biomarkers.

	Number of samples[a]	Between women[b]		Within women[b]		ICCs[b]
		Variance (SE)	%[c]	Variance (SE)	%[c]	
8-OHdG						
All subjects	4013	0.055 (0.010)	12	0.423 (0.012)	0.12	0.12
Subjects with 3 measures	2883	0.047 (0.009)	11	0.386 (0.012)	0.11	0.11
HNE-MA						
All subjects	4013	0.019 (0.055)	1	3.000 (0.086)	0.01	0.01
Subjects with 3 measures	2883	0.019 (0.054)	1	2.857 (0.092)	0.01	0.01
8-isoPGF$_{2\alpha}$						
All subjects	4013	0.012 (0.022)	1	1.170 (0.034)	0.01	0.01
Subjects with 3 measures	2883	0.009 (0.021)	1	1.119 (0.036)	0.01	0.01

Abbreviations: OS, oxidative stress; ICCs, intraclass correlation coefficients; 8-OHdG, 8-hydroxy-2-deoxyguanosine; HNE-MA, 4-hydroxy-2-nonenal-mercapturic acid; 8-isoPGF$_{2\alpha}$, 8-*iso*-prostaglandin F$_{2\alpha}$.

[a] Actual number of samples used in the mixed regression models.

[b] Ln-transformed concentrations of 8-OHdG, 8-isoPGF$_{2\alpha}$, and HNE-MA were treated as the dependent variables in mixed models with a random intercept; models were adjusted for time in weeks since conception.

[c] Percentage of the total variance.

We compared the differences in the geometric mean concentrations of OS biomarkers across the categorical covariates based on linear mixed models (Ferguson et al., 2015). The variability of creatinine-adjusted concentrations of 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ in repeated urine samples was evaluated by calculating intraclass correlation coefficients (ICCs).

We assessed the associations between DBP exposures measured in early, middle, and late pregnancy and urinary OS biomarkers from the same stage of pregnancy using linear mixed regression models with subject-specific random intercepts. We modeled each individual DBP biomarkers as well as the summary estimates (Br-THM and TTHM) both as tertile categories and continuous variables in the regression models. Blood DBCM and TBM were excluded in further analysis because of their limited detection rates (< 50%). To evaluate the non-linear associations of THMs and HAAs with urinary OS biomarkers, we conducted penalized regression splines based on generalized additive mixed models (GAMMs) with adjustment for the same set of covariates as in the linear mixed regression models. We also separately assessed the cross-sectional associations between DBP exposures and OS biomarkers in early, middle, and late pregnancy to investigate potential windows of susceptibility by gestational periods. Finally, we stratified data to examine whether the associations between DBP exposures and OS biomarkers were modified by maternal BMI (≤25 kg/m^2 vs. > 25 kg/m^2) or infant sex (male vs. female).

Potential confounders were selected based on biological and statistical considerations, which were further tested for inclusion if they produced a > 10% change in the effect estimates for the associations between exposures and OS biomarkers (Greenland, 1989). Mixed regression models were adjusted for age (continuous), gestational body mass index (BMI, time-varying; continuous), time in weeks since conception (time-varying; continuous), gravidity (1 vs. > 1), infant sex (male vs. female), education level (junior school or below, high school, or above high school), income (< 3000, 3000–4999, or ≥5000 Yuan/month), and the sampling time of day (time-varying; 07:00–08:59, 9:00–11:59, or 12:00–15:30).

Table 4
Percent changes (95% CI) in OS biomarker concentrations associated with blood THMs and urinary HAAs based on linear mixed models.[a]

DBPs	8-OHdG[b]	HNE-MA[b]	8-isoPGF$_{2\alpha}$[b]
THMs (ng/L)			
TCM			
T1 (< 7.45)	ref	ref	ref
T2 (7.45–13.53)	3.9 (–1.5, 9.6)	18.3 (4.3, 34.3)	9.0 (0.17, 18.6)
T3 (> 13.53)	7.7 (2.2, 13.6)	29.9 (14.5, 47.5)	2.9 (–5.4, 12.0)
P for trend	0.006	< 0.001	0.51
Continuous[c]	5.1 (2.6, 7.7)	13.9 (7.5, 20.7)	4.3 (0.33, 8.4)
BDCM			
T1 (< 0.66)	ref	ref	ref
T2 (0.66–1.00)	–3.2 (–8.2, 2.1)	–9.8 (–20.5, 2.4)	1.9 (–6.3, 10.9)
T3 (> 1.00)	–0.89 (–6.0, 4.5)	6.9 (–5.9, 21.4)	–4.2 (–12.0, 4.3)
P for trend	0.74	0.31	0.32
Continuous[c]	–0.18 (–3.9, 3.7)	2.6 (–6.2, 12.3)	–2.1 (–7.8, 3.9)
Br-THM			
T1 (< 3.01)	ref	ref	ref
T2 (3.01–7.93)	–3.0 (–8.0, 2.3)	14.2 (0.64, 29.6)	2.8 (–5.5, 11.9)
T3 (> 7.93)	4.0 (–1.4, 9.7)	24.0 (9.3, 40.7)	1.5 (–6.7, 10.4)
P for trend	0.16	< 0.001	0.73
Continuous[c]	1.3 (–0.36, 3.0)	3.8 (–0.23, 8.0)	0.85 (–1.8, 3.5)
TTHM			
T1 (< 12.84)	ref	ref	ref
T2 (12.84–23.77)	4.3 (–1.1, 9.9)	28.0 (12.9, 45.3)	8.4 (–0.32, 18.0)
T3 (> 23.77)	7.1 (1.5, 13.0)	36.2 (20.0, 54.6)	6.0 (–2.6, 15.3)
P for trend	0.01	< 0.001	0.18
Continuous[c]	3.6 (1.4, 5.8)	9.4 (4.0, 15.1)	2.4 (–1.0, 5.9)
HAAs (μg/g Cr)			
DCAA			
T1 (< 6.81)	ref	ref	ref
T2 (6.81–10.99)	31.8 (25.4, 38.4)	28.7 (13.4, 46.1)	20.1 (10.4, 30.6)
T3 (> 10.99)	91.0 (81.7, 100.8)	99.9 (76.0, 127.1)	66.6 (53.1, 81.2)
P for trend	< 0.001	< 0.001	< 0.001
Continuous[c]	43.3 (39.5, 47.2)	46.5 (36.8, 56.9)	34.3 (28.4, 40.5)
TCAA			
T1 (< 1.60)	ref	ref	ref
T2 (1.60–2.79)	21.6 (15.5, 27.9)	51.5 (33.5, 71.9)	21.1 (11.3, 31.7)
T3 (> 2.79)	65.7 (57.3, 74.6)	97.9 (74.0, 125.3)	56.5 (43.6, 70.4)
P for trend	< 0.001	< 0.001	< 0.001
Continuous[c]	35.8 (32.2, 39.5)	48.9 (39.4, 59.1)	33.2 (27.5, 39.2)

Abbreviations: THMs, trihalomethanes; HAAs, haloacetic acids; OS, oxidative stress; T, tertile; TCM, chloroform; BDCM, bromodichloromethane; Br-THM, brominated THM; TTHM, total THM; DCAA, dichloroacetic acid; TCAA, trichloroacetic acid; 8-OHdG, 8-hydroxy-2-deoxyguanosine; HNE-MA, 4-hydroxy-2-nonenal-mercapturic acid; 8-isoPGF$_{2\alpha}$, 8-*iso*-prostaglandin F$_{2\alpha}$.

[a] The models were adjusted for age, education level, income, gravidity, infant sex, gestational BMI, time in weeks since conception, and sampling time of day.

[b] The values were ln-transformed and then back-transformed {100*[exp (beta)-1]} to obtain percent changes.

[c] Ln-transformed values.

Several sensitivity analyses were performed. First, we assessed the associations between DBP exposures and urinary OS biomarkers by restricting the analysis among women who had a normal range of urinary creatinine (i.e., > 0.3 to < 3 g/L). Second, we reanalyzed the aforementioned associations by excluding women who ever consumed tobacco or alcohol during pregnancy. Third, we re-analyzed the penalized regression splines based on generalized additive mixed models using SG-corrected concentrations in the subset of participants for whom we had SG measured. All statistical analyses were performed using Statistical Package for Social Science (version 21.0, SPSS, Inc., USA), or R software (version 3.1.2, R Foundation for Statistical Computing, Austria). A *P*-value < 0.05 was considered to be statistically significant.

3. Results

3.1. Participant characteristics

Most of the study participants were aged < 30 years (80.0%), had an income of < 6000 Yuan/month (86.5%), and reported educational background as junior school or below (62.9%) at recruitment (Table 1). Nearly half of the participants were in their first pregnancy (45.7%), and 65.4% had a normal pre-pregnancy BMI (18.5–24.9 kg/m^2). Geometric mean concentrations (μg/g Cr) of OS biomarkers stratified by mothers' characteristics are also shown in Table 1. Higher concentrations of 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ were observed in the samples that were collected in early pregnancy or after 9:00 pm. We observed lower levels of 8-OHdG and 8-isoPGF$_{2\alpha}$ among women whose gestational BMI was ≥25 kg/m^2.

3.2. Distribution of blood THMs, urinary HAAs, and OS biomarkers

Blood THMs (TCM, BDCM), urinary THMs (DCAA, TCAA), and OS biomarkers (8-OHdG, HNE-MA, 8-isoPGF$_{2\alpha}$) were detected in ≥79.5% of the specimens (Table 2). The geometric mean concentrations of TCM, BDCM, DCAA, TCAA, 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ were 9.4 ng/L, 0.80 ng/L, 8.5 μg/g Cr, 2.3 μg/g Cr, 8.6 μg/g Cr, 61.6 μg/g Cr, and 2.1 μg/g Cr, respectively (Table 2). A total of 1659, 1373 and 1118 blood samples were obtained during early, middle, and late pregnancy, respectively. For urine samples, 1682, 1402, and 1148 specimens were gathered during early, middle, and late pregnancy, respectively.

3.3. Variability of urinary OS biomarkers

Fig. 1 showed that urinary concentrations of 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ varied substantially across early, middle, and late pregnancy. Mixed-effect models further demonstrated that the within-women variance of repeated measures of 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ was much higher than the between-women variance (Table 3), indicating high temporal variability (ICCs = 0.01–0.12). The variance decompositions were substantially unchanged when the analyses were restricted among women who had all 3 measurements of OS biomarkers during pregnancy.

3.4. Associations between DBP exposures and urinary OS biomarkers

After adjusting for age, education level, income, gravidity, infant sex, gestational BMI, time in weeks since conception, and time of day of sample collection, we observed positive dose-response relationships between tertiles of blood TCM and TTHM and urinary 8-OHdG, and between tertiles of blood TCM, Br-THM, and TTHM and urinary HNE-MA (all *P* for trend ≤0.01) (Table 4). Percent changes in OS biomarkers comparing the highest vs. lowest tertiles ranged from 7.1% to 36.2%. For urinary HAAs, both DCAA and TCAA were positively associated with 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ (all *P* for trend < 0.001); percent changes in OS biomarkers comparing the highest vs. lowest tertiles of DCAA and TCAA ranged from increases of 57.6% to 95.6%. These associations were largely unchanged when DBP exposures were modeled continuously. We also evaluated the aforementioned significant dose-response relationships using GAMMs; smooth plots showed that most of the associations were monotonous linear with the exception of Br-THM and TTHM with HNE-MA, which showed inverse U-shaped relationships (Figs. 2 and 3). When gestational period-specific associations were tested, we found that the positive relationships between THMs and OS biomarkers were stronger during middle pregnancy than early and late pregnancy and that the positive relationships between urinary HAAs and OS biomarkers were stronger during early pregnancy (Figs. S1 and S2).

There was no evidence of interaction between exposures and infant sex or pre-pregnancy BMI (all *P* for interaction > 0.05; Tables S1 and

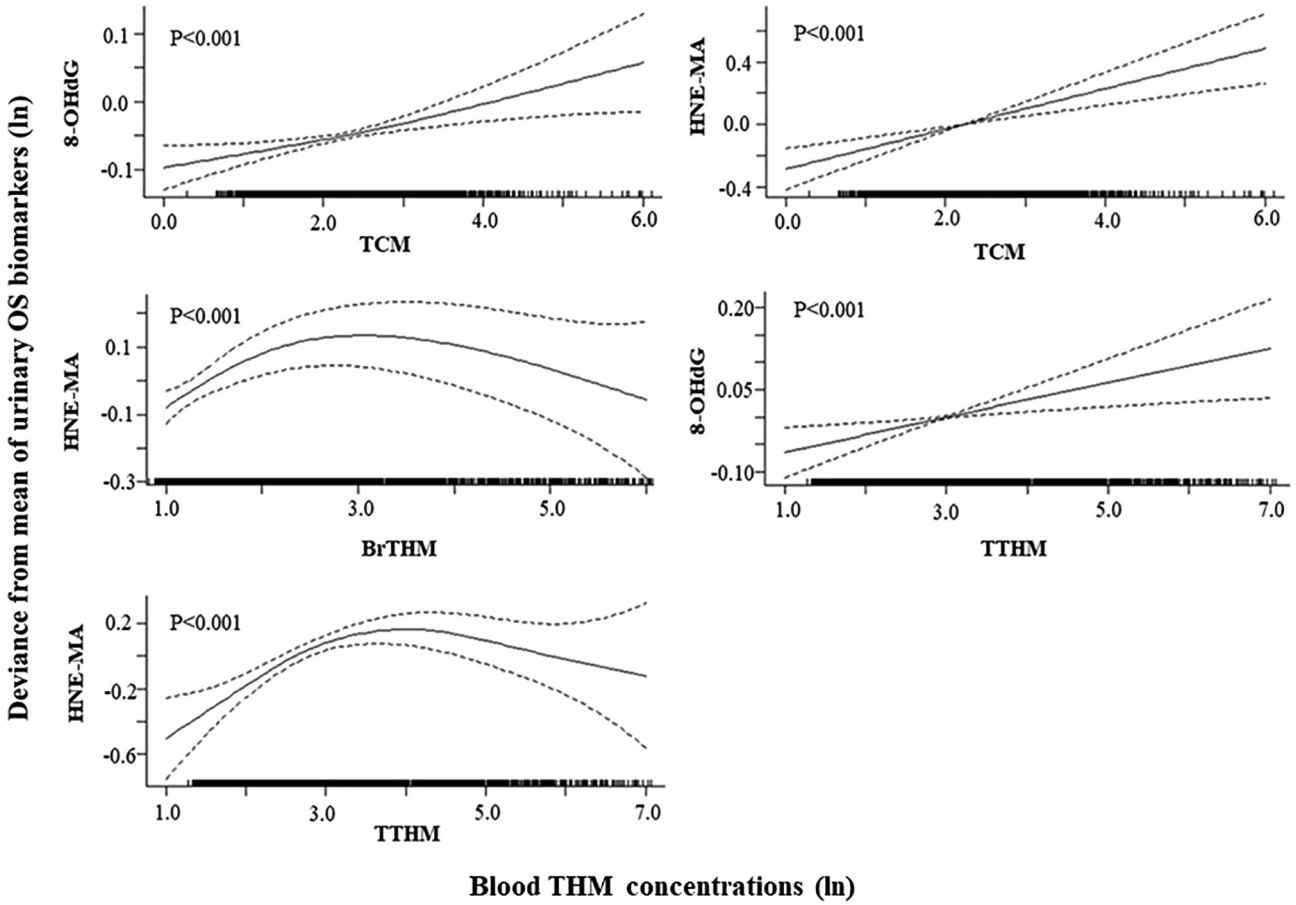

Fig. 2. Penalized regression splines for blood trihalomethane (THMs) in relation to OS biomarker concentrations based on generalized additive mixed models (GAMMs). The models were adjusted for age, education level, income, gravidity, infant sex, gestational BMI, time in weeks since conception, and sampling time of day.

S2). The associations between DBP concentrations and OS biomarkers were not substantially changed after restricting the analysis among women who had a normal range of urinary creatinine (i.e., > 0.3 to < 3 g/L) (Table S3), or among women without tobacco or alcohol consumption during pregnancy (Table S4). Most of the positive associations between DBP concentrations and OS markers were further confirmed in our sub-analysis when SG-corrected concentrations were used in the GAMMs (Figs. S3 and S4).

4. Discussion

Among 1760 Chinese pregnant women, we found high variability in urinary concentrations of 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ across gestational periods. Using a repeated measurement design, we found positive dose-response relationships between concentrations of blood THMs (i.e., TCM, Br-THM, and TTHM) and urinary HAAs (i.e., DCAA and TCAA) and urinary 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$. These associations were further confirmed when the exposure biomarkers were modeled as continuous variables in linear mixed models and in GAMMs. Stratified analysis showed that the associations between exposures and OS biomarkers were not modified by infant sex or pre-pregnancy BMI.

In accordance with our results, Ferguson et al. (2015) reported high variability (ICC = 0.32) in urinary 8-OHdG concentrations among 482 pregnant women. In a recent study from our group of 11 healthy adult men, we observed high degrees of within-subject variability in urinary concentrations of 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ in spot, first morning, and 24-hour samples (ICCs ≤ 0.37) (Wang et al., 2019). OS biomarkers also exhibited high within-individual variability in other biological fluids, such as blood, saliva, and nipple aspirate fluid (Kato et al., 2006; Alajbeg et al., 2017). The high variability of urinary OS biomarker concentrations during pregnancy is not unexpected, because they are readily affected by changes in diet (Kim et al., 2011; Aalami-Harandi et al., 2015), lifestyle factors (e.g., physical activity) (Matsuzaki et al., 2014; Cid and Gonzalez, 2016), and external exposures during pregnancy (Ferguson et al., 2015; Watkins et al., 2015). Physiological and metabolic status changes during pregnancy have also been linked to altered OS status (Hung et al., 2010; Loy et al., 2013; Moore et al., 2019).

Existing evidence from *in vitro* and *in vivo* studies has well-documented that THMs and HAAs can induce OS. For instance, TCM was found to induce OS in rat liver, as manifested by elevating MDA and metallothionein, and depleting glutathione (GSH) levels (Abbassi et al., 2010). DCAA and TCAA were reported to induce superoxide anion production, lipid peroxidation, and superoxide dismutase (SOD), whereas impair antioxidant capability in rodent species (Hassoun et al., 2010; Hassoun and Cearfoss, 2011; Hassoun and Cearfoss, 2014). The underlying mechanisms may be related to the metabolism of DBPs that can accelerate free radical production (Hassoun et al., 2014). THMs are metabolized and bioactivated through cytochrome P450 pathway, through which free radical and oxidized intermediates (e.g., phosgene) are generated (Lilly et al., 1997; Beddowes et al., 2003). HAAs are metabolized via a reductive dechlorination pathway, which can generate free radicals and further elicit a lipoperoxidative response (Larson and Bull, 1992). A recent *in vivo* study showed that the mixture of DCAA and TCAA exhibited an additive effect on ROS production via decreasing hepatic glutathione S-transferase zeta activity. Of interest, we found no evidence of interactions between DBP exposures and infant sex or maternal BMI, suggesting that the relationships between DBP

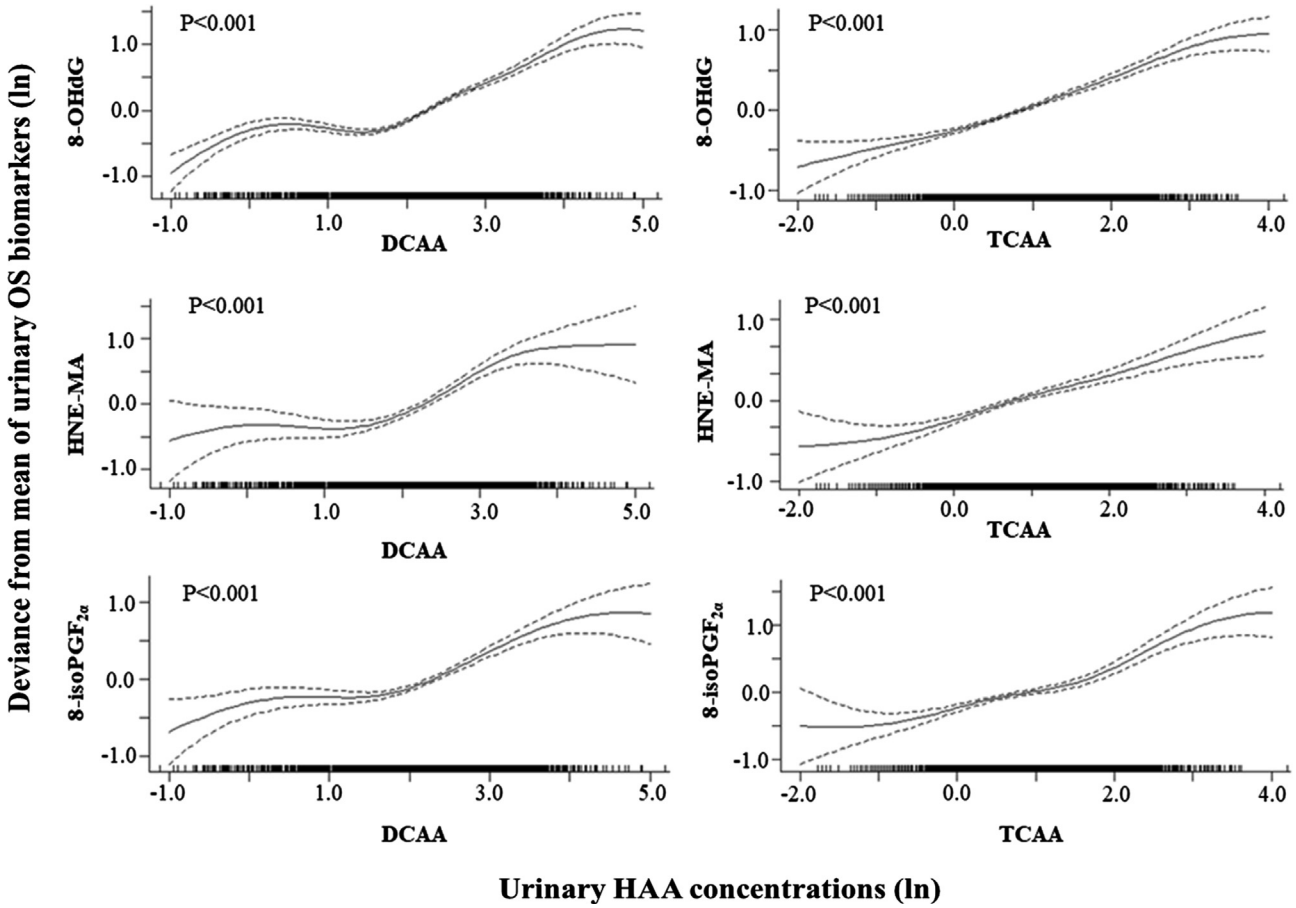

Fig. 3. Penalized regression splines for urinary haloacetic acides (HAAs) in relation to OS biomarker concentrations based on generalized additive mixed models (GAMMs). The models were adjusted for age, education level, income, gravidity, infant sex, gestational BMI, time in weeks since conception, and sampling time of day.

exposures and OS biomarkers were not modified by these two factors.

To date, few human studies have investigated the associations between DBP exposures and OS biomarkers, and the results are divergent. In support of our findings, Varraso et al. (2002) found higher blood levels of OS biomarkers (e.g., Cu^{++}/Zn^{++} SOD activity and GSH-Px) among 16 male swimmers after training in a chlorinated pool; Morissette et al. (2016) revealed that 8-isoprostane levels in exhaled breath condensate were increased in 23 athletes after swimming in a chlorinated pool. However, a lack of association between THMs in exhaled breath condensate and 8-isoprostane was also reported among 48 healthy nonsmoking adults who swam for 40 mins in a chlorinated swimming pool (Font-Ribera et al., 2010). The inconsistency between studies may be related to the difference in sample size, population characteristics, and measures of DBP exposures and OS biomarkers. Moreover, all prior studies measured OS and DBP markers at a single time point, which may have resulted in measurement error due to high within-individual variability.

Of interest, when we separately assessed the cross-sectional associations between DBP exposures and OS biomarkers in early, middle, and late pregnancy, the positive associations of HAAs and THMs with OS biomarkers were stronger during early or middle pregnancy. Previous studies have demonstrated that placenta, which plays an important role in producing oxidative stress during pregnancy (Hung et al., 2010), is highly vulnerable to toxicant exposures in the early stage of pregnancy (Wong et al., 2015; Wu et al., 2016). A stronger association in the early stage of pregnancy could also be related to the variations in antioxidant capacity. As pregnancies progress, a combination of increased placental antioxidant protective mechanisms and decreased lipid peroxidation markers may lead to a lower OS status (Basu et al., 2015). Differences in exposure levels and sample size in early, middle, and late pregnancy may also lead to the variations in effect estimation across gestational periods.

Growing evidence has shown that excessive oxidative stress plays a critical role in the pathogeny of adverse fetal development (Biberoglu et al., 2016; Rashid et al., 2018). For instance, excessive oxidative DNA damage, reflected by increased 8-OHdG production, can inhibit placental vascularization and consequently affect fetal health (Potdar et al., 2009; Basu et al., 2018). Lipid peroxidation, indicated by HNE-MA and 8-isoPGF$_{2\alpha}$, has also been associated with preterm birth, preeclampsia and intrauterine growth retardation (Challis et al., 2009; Fisher, 2015; Biberoglu, et al., 2016). In the current analysis, we revealed a strong association between DBP exposures and increased urinary concentrations of 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ among pregnant women, supporting a potential mediating role of oxidative stress in the previously observed associations between DBP exposures and adverse birth outcomes.

The strength of this study includes its relatively large sample size, the application of two classes of internal exposure biomarkers, and the repeated measurements of both exposures and OS biomarkers at different stages of pregnancy. However, our study also had some limitations. First, a single specimen (urine and blood) was collected during each stage of pregnancy (i.e., early, middle, and late pregnancy), which restricts our capability to capture all of the variability in concentrations of exposures and OS biomarkers. Second, our positive associations between blood THMs, urinary HAAs, and urinary OS biomarkers may have been confounded by other unmeasured covariates such as diet and lifestyle factors (e.g., physical activity), which may influence both DBP exposures and OS status (Riederer et al., 2014; Ferguson et al., 2015;

Watkins et al., 2015; Powers et al., 2016; Dashner-Titus et al., 2018; Wang et al., 2019). Third, a high proportion of women in this study were from a low socioeconomic position and had relatively low DBP exposure levels (Wang et al., 2019), which limits the generalizability of our findings.

5. Conclusions

Our results showed that urinary 8-OHdG, 8-isoPGF$_{2\alpha}$, and HNE-MA varied greatly across pregnancy, highlighting the importance of adopting a repeated sampling strategy to improve oxidative stress status estimation among pregnant women. Additionally, we found positive dose-response associations between concentrations of blood THMs and urinary HAAs and urinary 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ using a repeated measurement design. These associations are particularly relevant to adverse birth outcomes, which emphasize the importance of reducing the impact of DBPs in drinking water.

CRediT authorship contribution statement

Chong Liu: Conceptualization, Formal analysis, Investigation, Data curation, Methodology, Writing - original draft, Writing - review & editing. **Yi-Xin Wang:** Conceptualization, Formal analysis, Investigation, Data curation, Methodology, Writing - original draft, Writing - review & editing, Supervision. **Ying-Jun Chen:** Data curation, Investigation, Validation, Writing - review & editing. **Yang Sun:** Investigation, Validation, Writing - review & editing. **Li-Li Huang:** Data curation, Investigation, Validation, Writing - review & editing. **Ying-Hui Cheng:** Funding acquisition, Resources, Writing - review & editing. **Er-Nan Liu:** Investigation, Writing - review & editing. **Wen-Qing Lu:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing - review & editing. **Carmen Messerlian:** Conceptualization, Methodology, Writing - review & editing, Supervision.

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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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105518.

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