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Trimester-specific associations of maternal exposure to disinfection by-products, oxidative stress, and neonatal neurobehavioral development

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ABSTRACT

Background: Toxicological studies suggest that maternal exposure to disinfection by-products (DBPs) can impair fetal neurodevelopment. However, evidence from epidemiological studies is scarce and the underlying mechanisms remain unclear.

Objective: To explore the trimester-specific associations between maternal blood trihalomethane (THM) and urinary haloacetic acid (HAA) concentrations and neonatal neurobehavioral development, and the potential mediating role of oxidative stress (OS).

Methods: We included 438 pregnant Chinese women from the Xiaogan Disinfection By-Products (XGDBP) birth cohort. Biospecimens were repeatedly collected across trimesters and measured for blood THMs, urinary HAAs, and urinary OS biomarker concentrations. On the third day after birth, the Neonatal Behavioral Neurological Assessment (NBNA) test was administered to newborns. Associations of trimester-specific DBP measurements and OS biomarkers with neonatal NBNA scores were assessed using linear regression models with generalized estimating equations. The potential mediating role of maternal OS biomarkers was also investigated using mediation analyses.

Results: After adjusting for potential confounders, blood bromodichloromethane (BDCM) concentrations in the first trimester were inversely associated with NBNA scores [percent change comparing the extreme BDCM tertiles = –28.1% (95% CI: –55.2%, –0.88%); p for trend = 0.043]. Besides, third-trimester urinary trichloroacetic acid (TCAA) concentrations were inversely associated with NBNA scores [percent change comparing the extreme TCAA tertiles = –32.9% (95% CI: –64.7%, –1.0%); p for trend = 0.046]. These inverse associations differed across pregnancy trimesters (Type 3 p-value = 0.066 and 0.053, respectively) and were stronger in male infants and mothers aged ≥25 years. There was no evidence of mediating effect by 8-hydroxy-2-deoxyguanosine (8-OHdG), 4-hydroxy-2-nonenal-mercapturic acid (HNE-MA), or 8-*iso*-prostaglandin $F_{2\alpha}$ (8-isoPGF$_{2\alpha}$).

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Conclusions: Higher prenatal BDCM and TCAA concentrations during specific pregnancy trimesters were associated with lower NBNA scores. However, additional research is required to investigate underlying mechanisms.

1. Introduction

Neurodevelopmental disabilities such as attention deficit hyperactivity disorder, conduct problems, sensorimotor impairments, autism spectrum disorders, intellectual disability, and learning disorders constitute a major socioeconomic burden (Bennett et al., 2016; Lyons-Ruth et al., 2017), which affect about 52·9 million (8·4%) children worldwide (Global Research on Developmental Disabilities Collaborators, 2018). The intrauterine environment plays a critical role in early neural processes because the fetal brain develops dramatically as structures and connections form, providing the foundation for all future development (Bellanger et al., 2015; Wang et al., 2018). Besides well-documented risk factors for fetal neurodevelopment (e.g., folate deficiency, thyroid dysfunction, and preterm birth) (Cheong et al., 2017; Korevaar et al., 2016; Naninck et al., 2019), accumulating evidence indicates that prenatal exposure to environmental pollutants is associated with neurodevelopmental and neuropsychiatric disorders (Grandjean and Landrigan, 2014; Nie et al., 2019; Shah-Kulkarni et al., 2020; van den Dries et al., 2020).

Disinfection by-products (DBPs) are generated during the reaction between chlorine disinfectants and natural organic matters during the water treatment process. Among various identified DBPs in drinking water, trihalomethanes (THMs) and haloacetic acids (HAAs) are the two leading species (Richardson et al., 2007). Pregnant women are exposed to DBPs through ingestion of water or inhalation and absorption during daily water-use activities including showering and bathing (Wang et al., 2019b). Toxicological studies have shown that some DBPs can pass through the placenta (Christian et al., 2001; Danielsson et al., 1986), which can further impair fetal neurodevelopment. For instance, HAAs, including dichloroacetic acid (DCAA) and dibromoacetic acid, were found to cause limb weakness, gait and righting reflex deficits, hypotonia, and sensorimotor depression in rats (Moser et al., 1999; Moser et al., 2004). Guariglia and colleagues reported that a mixture of chloroform (TCM), bromoform (TBM), and tetrachloroethylene can induce autistic-like behaviors in male mice (Guariglia et al., 2011). Several human studies also showed that prenatal exposures to THMs and HAAs were associated with elevated risks of neural tube defects and impaired cognitive function in offspring (Bove et al., 2002; Chowdhury et al., 2010; Klotz and Pyrch, 1999; Villanueva et al., 2018). We recently assessed neonatal neurobehavioral development among 451 infants and found an inverse association between first-trimester blood bromodichloromethane (BDCM) concentrations and total Neonatal Behavioral Neurological Assessment (NBNA) scores (Chen et al., 2019). However, the critical windows of vulnerability during pregnancy remain unclear, which could facilitate the study of modes of action and the establishment of more stringent regulatory guidelines to protect the fetus. Besides, no human study has assessed trimester-specific associations between non-volatile HAAs, another leading species of DBPs, and neonatal neurodevelopment. More importantly, the mechanisms underlying the associations between maternal DBP exposures and fetal neurodevelopment are also poorly understood.

Growing evidence shows that oxidative stress (OS) is associated with the development of neurodevelopmental disorders and neurodegenerative diseases (Bjorklund et al., 2020; Kabir et al., 2020; Lin and Beal, 2006; Steullet et al., 2017), by potentially disrupting thyroid hormone homeostasis and the metabolism of micronutrients (e.g., folate and fatty acid) (Assies et al., 2014; Mancini et al., 2016). Meanwhile, both *in vivo* and *in vitro* studies have demonstrated that THMs and HAAs can induce OS response and impair antioxidant defense (Beddowes et al., 2003; Hassoun and Cearfoss, 2014; Hassoun et al., 2010). In a previous analysis, we found a positive association between higher DBP concentrations and OS biomarkers among 1760 pregnant women (Liu et al., 2020). To refine and extend our previous work (Chen et al., 2019), we aimed to investigate the trimester-specific associations between maternal blood THM and urinary HAA concentrations and neonatal neurobehavior development and to explore the potential mediating role of OS biomarkers.

2. Materials and methods

2.1. Study population

Our study population came from the Xiaogan Disinfection By-Products (XGDBP) birth cohort, which has been described in detail previously (Sun et al., 2020). Xiaogan City is located in Hubei Province, China, which is served by a single water treatment plant. The arithmetic mean concentrations of chloroform (TCM), total trichloromethane (TTHMs), trichloroacetic acid (TCAA), and dichloroacetic acid (DCAA) in the tap water of Xiaogan City were 4.3, 7.4, 10.1, and 3.5 μg/L, respectively (Wang et al., 2019b). We recruited 1760 women at the Maternal and Child Health Care Service Center of Xiaonan District if they were aged between 18 and 40 years, were <14 weeks of gestation, had a singleton pregnancy, had no self-reported psychiatric or laboratory-confirmed endocrine diseases (e.g., diabetes and thyroid diseases), and permanently lived in Xiaogan City. All participants completed a questionnaire, had venous blood drawn, provided a single urine sample, and underwent physical examination during the first (gestational age <14 weeks), second (gestational age 14–27 weeks), and third trimester (gestational age >27 weeks). All NBNA tests were conducted on the third day after birth only for infants who were delivered at the Maternal and Child Health Care Service Center of Xiaonan District (n = 569). The pregnant women who delivered their babies in other hospitals (e.g., Xiaogan Central Hospital, Xiaogan First People Hospital, and Hangtian Hospital) were excluded (n = 1191) because no certificated pediatricians were available for the NBNA test (Chen et al., 2019). We further excluded 19 mother-neonate pairs due to serious comorbid conditions (e.g., meningitis, cleft palate, Down's syndrome, and severe neonatal jaundice), 99 due to refusal to undergo the NBNA testing, 5 due to insufficient specimen volumes for the determination of urinary HAAs and OS biomarkers, 1 due to missing gestational age at delivery, and 7 due to preterm birth, leaving 438 pairs in the current analysis (Fig. 1). The characteristics of mother-infant pairs included in the current analysis were mostly similar to that of the whole population, except for age and education levels. Compared with the total study population, the women included in the current analysis were slightly younger (mean ± SD: 25.9 ± 3.9 vs. 26.4 ± 4.2 years) and had lower education levels (70.5% vs. 62.8% reporting education levels as primary and below) (**Table S1**). Our study protocol was approved by the Ethics Committee of Tongji Medical College, and all participants provided written informed consent at recruitment.

2.2. Covariates

At enrollment, the research staff collected the basic characteristics of study participants, including age, ethnicity, marital status, occupation, height, household income, education background, and medical history. At enrollment and during follow-up visits, all pregnant women provided information on lifestyle factors (e.g., alcohol and tobacco consumption), second-hand smoke exposure, diet, and water-use activities (e.g., water sources, tap water consumption per day, boiled and filtered water usage,

frequency of swimming, washing, bathing, and showering, and time interval since the last bathing/showering). The research staff recorded the time when specimens were collected. Maternal weight during each visit was measured using multifunctional anthropometric instruments. We calculated the maternal body mass index (BMI) by dividing the weight (kg) by the square of height (m).

2.3. Specimen collection and analysis

Sample collection and quantification procedures have been previously described in detail elsewhere (Wang et al., 2019b). In short, venous blood samples across pregnancy trimesters were drawn in anticoagulant blood collection tubes and stored at 4 °C until THM analysis. Blood TCM, BDCM, dibromochloromethane (DBCM), and bromoform (TBM) were determined using a headspace solid-phase microextraction gas chromatography equipped with an electron capture detector (ECD) (Bonin et al., 2005; Cao et al., 2016). Spot urine samples across pregnancy trimesters were collected using polypropylene containers. Urinary TCAA and DCAA were purified with liquid-liquid extractions and then quantified by gas chromatography equipped with an ECD (Wang et al., 2014). Urinary OS biomarkers, namely 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 determined using liquid chromatography-tandem mass spectrometry (Wang et al., 2019c). Information on pretreatment, instrumental analysis, and quality control was presented in **Supplemental Material**. We determined urinary creatinine (Cr) concentrations using an automated clinical chemistry analyzer (Mindray Medical International Ltd., Shenzhen, China) (Liu et al., 2020).

2.4. Birth outcomes and NBNA test

Neonatal birth data such as birth weight, infant sex, delivery mode, and gestational age were abstracted from the hospital medical system by research staff. On the third day after birth, the Chinese-adapted version of the NBNA test was administered to neonates as formulated by Bao and colleagues (Bao et al., 1991). This neurobehavioral test is based on the method of Brazelton and Amiel-Tison, which has been demonstrated to be highly reliable in the Chinese population (Bao et al., 1993; Wang et al., 2018, 2019a). The test consists of five clusters, namely behavior (6 items), passive tone (4 items), active tone (4 items), primary reflexes (3 items), and general assessment (3 items). Each item is rated on a three-point Likert-type scale (0, 1, or 2). The total NBNA score is the sum score of these five clusters. The maximum attainable scores of behavior, passive tone, active tone, primary reflexes, general assessment, and total NBNA score are 12, 8, 8, 6, 6, and 40 points, respectively. Infants with NBNA score <37 were considered to be a-typically developing and at risk (Yu et al., 2014). In our study, the NBNA test was performed by two certificated pediatricians who were blinded to maternal DBP exposure and OS status and birth outcomes (Chen et al., 2019).

2.5. Statistical analysis

We performed descriptive analysis for maternal baseline characteristics, DBP and OS biomarker concentrations, neonatal birth outcomes, and NBNA scores. We used the Student *t*-test or Chi-square test to examine the differences in basic characteristics of our study population and the overall cohort volunteers. Brominated THMs (Br-THMs, ng/L) were the sum concentrations of BDCM, DBCM, and TBM; and total THMs (TTHMs, ng/L) were the sum concentrations of Br-THMs and TCM. Samples with concentrations of DBP and OS biomarkers lower than the LODs and LOQs were replaced by LOD/$\sqrt{2}$ and LOQ/$\sqrt{2}$, respectively (Hornung and Reed, 1990). To account for urine dilution, we divided urinary HAA and OS biomarker concentrations (μg/L) by creatinine concentrations (g/L). Urinary TCAA, DCAA, 8-OHdG, 8-isoPGF$_{2\alpha}$, and HNE-MA and blood TCM, BDCM, Br-THMs, and TTHMs were categorized into tertiles based on all measurements across pregnancy trimesters. Because of the limited detection rates for blood DBCM and TBM

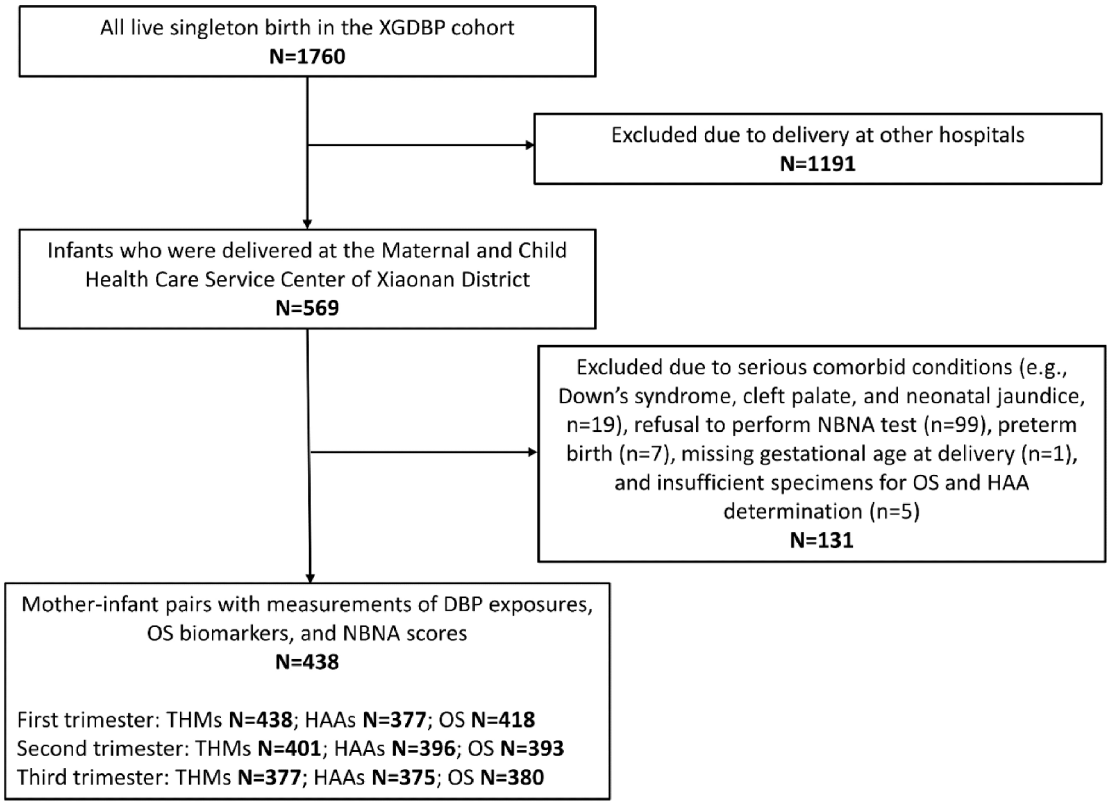

Fig. 1. Flow chart for the study population.

(≤45.1%), we created a three-level ordinal variable using <60th, 60th–80th, and >80th percentiles (Sun et al., 2020).

We explored trimester-specific associations of maternal blood THM and urinary HAA concentrations and OS biomarkers with neonatal NBNA scores using multiple informant models with generalized estimating equations (Sanchez et al., 2011). This model retains the interpretation of a set of separate multiple regressions for each trimester and also tests the differences in associations across pregnancy trimesters by jointly estimating the regression models using Type 3 tests based on the number of the observations across different exposure windows (Sanchez et al., 2011), which allows the number of measurement occasions for the exposure to vary across participants. Given the relatively low power of interaction tests (Greenland et al., 2016; Kaufman and Maclehose, 2013), a Type 3 *p*-value <0.10 was considered as an indication that associations differed across pregnancy trimesters. We used the lowest tertiles (or categories) as the reference group, and *p* for trends were calculated by modeling the tertiles (or categories) of DBP and OS biomarkers as ordinal variables using integer values (0, 1, 2). Because of the potential effect modification by infant sex and maternal age on the association between environmental pollutants and neonatal neurobehavioral development (Guo et al., 2020; Hyland et al., 2019; Moreno-Gimenez et al., 2021), we performed the stratified analyses by maternal age (<25 vs. ≥25 years of age) and infant sex (female vs. male). The *p*-values for interaction were calculated using the Wald test (Kaufman and Maclehose, 2013).

The potential covariates were initially selected based on biological and statistical considerations and then included in the final models if they resulted in a >10% change in the effect estimates for the aforementioned associations (Greenland, 1989). The final models were adjusted for maternal age (continuous), BMI at enrollment (continuous), smoking status (never vs. ever), alcohol intake (never vs. ever), folic acid usage during pregnancy (yes vs. no), delivery mode (caesarean vs. eutocia), infant sex (female vs. male), and education background (primary school and below, high school, or college and above).

We explored the potential mediation effect of OS biomarkers on the associations between DBP concentrations and neonatal NBNA scores using the "*mediation*" package in R software (Dustin et al., 2014). The mediation effects are established based on the following assumptions: a) significant relationships between an exposure and outcomes; b) significant relationships between exposures and the mediators, and c) significant relationships between the mediators and health outcomes (Valeri and Vanderweele, 2013).

We also performed several sensitivity analyses to test the robustness of our results. Firstly, we further adjusted for the gestational week at delivery in the association analyses. Secondly, we reanalyzed the above-mentioned associations after excluding infants with low birth weight (i.e., <2500 g, n = 2) or small-for-gestational-age (i.e., gender-specific birth weight <10th percentile for gestational age in a representative Chinese referent population, n = 11) (Chen and Jin, 2011; Sun et al., 2020). Finally, to assess the influence of recent peak exposure events such as bathing and showering (Ashley et al., 2020; Nuckols et al., 2005), we additionally included the time interval since last showering/bathing as a covariate in regression models. All statistical analyses were conducted using Statistical Analysis Software (SAS, version 9.4, SAS Institute Inc., Cary, NC) and R software (version 3.1.2, R Foundation for Statistical Computing, Austria).

3. Results

3.1. Information about mother-infant pairs

The characteristics of mother-infant pairs in the current analysis are presented in Table 1. More than half of our participants were ≥25 years old (56.6%), had a normal range of BMI (18.5–25 kg/m^2) at enrollment (68.8%), attained primary education or lower (70.5%), and used folic acid supplementation during pregnancy (92.9%). Regarding their infants, 52.8% were boys and 65.5% were delivered by caesarean section.

Table 1
Characteristics of mother-infant pairs (N = 438).[a]

Characteristics	N (%)
Mothers	
Age (years)	
<25	190 (43.4)
≥25	248 (56.6)
BMI at enrollment (kg/m^2)	
<18.5	95 (21.9)
18.5–25	298 (68.8)
>25	40 (9.3)
Gravidity	
1	216 (49.3)
>1	222 (50.7)
Education level	
Primary school and below	308 (70.5)
High school	77 (17.6)
College and above	52 (11.9)
Income (Yuan/month)	
<3000	190 (43.6)
3000–4999	191 (43.8)
≥5000	55 (12.6)
Smoking status	
Ever	4 (0.9)
Never	434 (99.1)
Alcohol use	
Ever	18 (4.1)
Never	420 (95.9)
Second-hand smoke exposure	
Ever	130 (29.8)
Never	306 (70.2)
Folic acid usage during pregnancy	
Yes	407 (92.9)
No	31 (7.1)
Infants	
Sex	
Male	231 (52.8)
Female	207 (47.2)
Delivery mode	
Caesarean	287 (65.5)
Eutocia	151 (34.5)
Birth weight (g)	
<3000	70 (16.0)
3000–3999	334 (76.3)
≥4000	34 (7.7)
Gestational age at delivery (weeks)	
<39	164 (37.4)
39–40	156 (35.6)
>40	118 (26.9)
Small for gestational age	
Yes	11 (2.5%)
No	427 (97.5%)

[a] A total of 5 women were missing for BMI at enrollment, 1 for education level, 2 for income, 2 for second-hand smoke exposure.

3.2. Distribution of DBP and OS biomarker concentrations

Maternal concentrations of DBP and OS biomarkers are shown in Table 2. Blood TCM and BDCM were detectable in >75% of the specimens, whereas the detection rates of blood DBCM and TBM were ≤45.1% across pregnancy trimesters. Urinary TCAA, DCAA, 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ were detected in >83% of urine samples. The median concentrations of blood Br-THMs and urinary TCAA, 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ were highest in the first trimester (3.8 ng/L, 2.3 μg/g Cr, 9.6 μg/g Cr, 115.0 μg/g Cr, and 2.6 μg/g Cr, respectively), while the median blood concentrations of TTHMs and urinary DCAA were highest in the third trimester (16.4 ng/L and 8.9 μg/g Cr).

Table 2
Distribution of blood THMs, urinary HAAs, and urinary OS biomarkers in different stages of pregnancy (N = 438).[a.]

Compounds	First trimester				Second trimester				Third trimester			
	N	%>LOD/LOQ	Median	IQR	N	%>LOD/LOQ	Median	IQR	N	%>LOD/LOQ	Median	IQR
THMs (ng/L)												
TCM	438	90.6	9.1	5.0–16.7	401	90.9	8.5	5.2–12.4	377	95.1	10.4	6.4–15
BDCM	438	75.6	0.79	0.51–1.2	401	77.0	0.80	0.52–1.1	377	78.6	0.81	0.54–1.1
DBCM	438	40.6	<LOD	<LOD–1.0	401	43.4	<LOD	<LOD–1.0	377	40.1	<LOD	<LOD–1.0
TBM	438	45.1	<LOD	<LOD–5.8	401	41.4	<LOD	<LOD–5.9	377	44.0	<LOD	<LOD–7.1
Br-THMs	438	–	3.8	2.8–7.7	401	–	3.4	2.7–7.8	377	–	3.6	2.7–8.6
TTHMs	438	–	15.5	9.6–25.0	401	–	13.9	9.2–21.2	377	–	16.4	11.1–25.4
HAAs (μg/g Cr)												
DCAA	377	90.4	8.5	5.4–14.9	396	99.5	8.0	5.6–11.1	375	99.2	8.9	6.8–12.6
TCAA	377	83.9	2.3	1.0–4.9	396	97.1	1.9	1.3–3.1	375	95.3	2.1	1.5–3.0
OS (μg/g Cr)												
8-OHdG	418	100	9.6	6.0–16.8	393	100	7.6	5.6–11.1	380	99.7	7.4	5.4–10.1
HNE-MA	418	98.4	115.0	26.7–339.6	393	98.7	31.0	13.3–113.4	380	99.0	105.8	38.6–290.3
8-isoPGF$_{2\alpha}$	418	94.4	2.6	1.5–4.7	393	97.5	2.0	1.2–3.1	380	93.0	2.5	1.2–4.1

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

[a] The LODs of TCM, BDCM, DBCM, TBM, DCAA and TCAA are 1.95 ng/L, 0.45 ng/L, 0.68 ng/L, 2.00 ng/L, 0.5 μg/L, and 1.0 μg/L, respectively. The LOQs of 8-OHdG, 8-isoPGF$_{2\alpha}$, and HNE-MA were 0.08 μg/L, 0.06 μg/L, and 0.03 μg/L, respectively.

Table 3
Distribution of neonatal NBNA scores (N = 438).

Items	The maximum attainable scores	Mean	Median	10th–90th	% of infants having The maximum attainable scores
Behavior	12	11.6	12	11–12	70.8
Primary reflexes	8	7.9	8	8–8	90.9
Active tone	8	7.2	7	6–8	39.3
Passive tone	6	5.8	6	5–6	78.5
General reaction	6	5.9	6	5–6	90.4
Total NBNA score	40	38.4	39	37–40	21.2

Abbreviations: NBNA, neonatal behavioral neurological assessment.

3.3. Neonatal NBNA scores

The NBNA scores of newborns on the third day after birth are shown in Table 3. The arithmetic means of behavior, primary reflexes, active tone, passive tone, general assessment, and total NBNA scores were 11.6, 7.9, 7.2, 5.8, 5.9, and 38.4, respectively.

3.4. Associations between maternal DBP concentrations and neonatal NBNA scores

Trimester-specific associations of maternal blood concentrations of THMs and urinary HAAs with neonatal NBNA scores are shown in Table 4. After adjusting for confounders, we found that higher blood BDCM concentrations in the first trimester were associated with lower neonatal NBNA scores (p for trend = 0.043); the percent change comparing the highest vs. lowest BDCM tertiles was –28.1% (95% CI: –55.2%, –0.88%). Besides, urinary TCAA concentrations in the third trimester were also inversely associated with neonatal NBNA scores (p for trend = 0.046); the percent change comparing the highest vs. lowest TCAA tertiles was –32.9% (95% CI: –64.7%, –1.0%). Type 3 tests indicated that the inverse associations of blood BDCM and urinary TCAA concentrations with NBNA scores differed across pregnancy trimesters (Type 3-p values = 0.066 and 0.053, respectively). Stratified analysis showed that the inverse associations of blood BDCM and urinary TCAA concentrations with NBNA scores were stronger in male infants and pregnant women aged ≥25 years (Fig. 2).

3.5. Associations between maternal OS biomarkers and neonatal NBNA scores and mediation analysis

There was no evidence of any dose–response relationships between concentrations of OS biomarkers across pregnancy trimesters and neonatal NBNA scores (all p for trends >0.05). However, we noted lower total NBNA scores among women with third-trimester urinary HNE-MA in the medium tertile, compared with women in the lowest tertile (–35.4%; 95% CI: –68.9%, –1.9%; Table 5). No evidence of mediation by OS biomarkers was observed in the associations between BDCM or TCAA concentrations and NBNA scores (**Table S2**). The associations between maternal DBP exposures, OS biomarkers, and NBNA scores were not materially changed when we additionally included the gestational week at delivery or time interval since last showering/bathing as a covariate in the regression models or when we excluded infants with low birth weight (i.e., <2500 g) or small-for-gestational-age (**Table S3–S6**).

4. Discussion

Results from this prospective investigation showed inverse associations of maternal concentrations of blood BDCM during the first trimester and urinary TCAA during the third trimester with neonatal NBNA scores. These associations were stronger in male infants and among women aged ≥25 years. While maternal blood BDCM and urinary TCAA concentrations were associated with OS biomarkers (Liu et al., 2020), as well as neonatal NBNA scores in this same cohort (Chen et al., 2019), in this analysis we found no evidence of mediating effects by urinary 8-OHdG, 8-isoPGF$_{2\alpha}$, or HNE-MA concentrations.

Toxicological studies have shown that BDCM and TCAA exposure can induce neurotoxicity in rodent species. For instance, Balster and colleagues reported altered operant behaviors after exposing adult male mice to 100 mg/kg/day of BDCM (120 mg/L in water) for 60 days (Balster and Borzelleca, 1982). Similarly, Moser and colleagues reported that oral exposure to 720 mg/L BDCM (72 mg/kg/day) in drinking water resulted in pathological changes of arousal and touch responses and sciatic nerve axonopathy in the midthigh region of F-344 rats (Moser

Table 4
Associations between tertiles of blood THM and urinary HAA concentrations and neonatal NBNA scores by pregnancy trimesters.[a]

Compounds	First trimester		Second trimester		Third trimester		Type 3*p* values
	N	Percent change (95% CI)	N	Percent change (95% CI)	N	Percent change (95% CI)	
THMs (ng/L)							
TCM							
T1 (<6.8)	151	0	147	0	107	0	0.316
T2 (6.8–12.3)	126	–3.4 (–32.3, 25.5)	153	9.9 (–17.5, 37.3)	127	16.2 (–15.0, 47.5)	
T3 (>12.3)	161	–10.3 (–37.4, 16.8)	101	3.1 (–27.5, 33.7)	143	25.7 (–4.5, 55.8)	
P for trend		0.457		0.783		0.097	
BDCM							
T1 (<0.62)	153	0	131	0	121	0	0.066
T2 (0.62–0.98)	128	–9.9 (–38.2, 18.5)	148	25.4 (–3.1, 54.0)	129	–5.3 (–35.3, 24.7)	
T3 (>0.98)	157	**–28.1 (–55.2, –0.88)**	122	25.3 (–4.4, 55.0)	127	13.7 (–16.5, 44.0)	
P for trend		**0.043**		0.091		0.369	
DBCM							
<60th (<0.74)	269	0	229	0	232	0	0.690
60th–80th (0.74–1.1)	85	5.0 (–24.5, 34.5)	90	8.6 (–21.0, 38.1)	68	–17.9 (–50.7, 15.0)	
>80th (>1.1)	84	–12.4 (–42.3, 17.6)	82	–17.2 (–47.6, 13.2)	77	–2.7 (–34.0, 28.6)	
P for trend		0.525		0.393		0.675	
TBM							
<60th (<2.8)	264	0	243	0	223	0	0.142
60th–80th (2.8–8.6)	89	–12.2 (–41.6, 17.1)	83	9.7 (–20.4, 39.7)	71	–16.2 (–49.0, 16.7)	
>80th (>8.6)	85	26.1 (–3.8, 56.0)	75	27.0 (–4.2, 58.3)	83	–11.8 (–42.4, 18.7)	
P for trend		0.187		0.091		0.361	
Br-THMs							
T1 (<2.9)	135	0	141	0	132	0	0.471
T2 (2.9–7.9)	163	0.56 (–27.2, 28.3)	128	–0.29 (–29.2, 28.7)	112	–10.9 (–41.44, 19.56)	
T3 (>7.9)	140	8.8 (–20.0, 37.6)	132	13.8 (–15.0, 42.6)	133	–17.27 (–46.7, 12.1)	
P for trend		0.547		0.352		0.249	
TTHMs							
T1 (<12.8)	147	0	150	0	107	0	0.591
T2 (12.8–23.8)	133	–7.5 (–36.0, 21.0)	140	3.8 (–24.3, 31.8)	134	27.3 (–3.6, 58.2)	
T3 (>23.8)	158	5.3 (–22.1, 32.7)	111	4.1 (–25.5, 33.7)	136	19.8 (–10.8, 50.4)	
P for trend		0.703		0.770		0.236	
HAAs (μg/g Cr)							
DCAA							
T1 (<6.8)	148	0	139	0	95	0	0.745
T2 (6.8–10.4)	89	11.2 (–20.5, 43.0)	149	–7.8 (–35.4, 19.8)	145	3.5 (–27.6, 34.7)	
T3 (>10.4)	140	0.34 (–27.6, 28.3)	108	–6.2 (–36.4, 24.0)	135	–12.8 (–44.5, 18.9)	
P for trend		0.978		0.605		0.339	
TCAA							
T1 (<1.7)	171	0	151	0	114	0	0.053
T2 (1.7–2.8)	101	–15.4 (–47.4, 16.7)	128	–15.0 (–43.2, 13.1)	154	–2.2 (–31.3, 27.0)	
T3 (>2.8)	159	–2.2 (–31.0, 26.5)	117	24.5 (–4.2, 53.3)	107	**–32.9 (–64.7, –1.0)**	
P for trend		0.953		0.135		**0.046**	

Abbreviations: NBNA, neonatal behavioral neurological assessment; CI, confidence interval; T, tertiles; THMs, trihalomethanes; HAAs, haloacetic acids; TCM, chloroform; BDCM, bromodichloromethane; DBCM, dibromochloromethane; TBM, bromoform; Br-THMs, brominated THMs; TTHMs, total THMs; Cr, creatinine; DCAA, dichloroacetic acid; TCAA, trichloroacetic acid.

[a] The models were adjusted for maternal age, educational level, BMI at enrollment, smoking status, alcohol intake, folic acid usage during pregnancy, delivery mode, and infant sex.

et al., 2007). Notwithstanding, to date, no toxicological study has evaluated prenatal exposure to THMs at low doses in relation to neurobehavior. For HAAs, 2000 mg/L of TCAA in drinking water was found to cause reduced neurological enzyme activity in rats (Celik et al., 2010); pregnant rats exposed to 1200 mg/kg/day of TCAA were found to induce hydrocephalus, neuropil vacuolation, altered choroids plexus architecture, and enhanced neuronal cell apoptosis in their offspring (Singh, 2006). However, these exposed doses in animal studies were much higher than the concentrations in the tap water of this cohort population (BDCM, 1.7 μg/L; TCAA, 8.2 μg/L) (Wang et al., 2019b). More toxicological studies are needed to examine the neurological effects of DBPs at environmental levels. In human studies, Villanueva and colleagues found that total and brominated THM uptakes from ingestion, showering, and bathing during pregnancy were inversely associated with general cognitive scores among 1855 children aged 4–5 years (Villanueva et al., 2018).

This present study refines and extends our previous evidence showing an inverse association between first-trimester blood BDCM concentrations and neonatal NBNA scores (Chen et al., 2019). We identified that the inverse associations between BDCM and neonatal NBNA scores differed across pregnancy trimesters, providing new evidence of a potentially critical window of susceptibility. Besides, we found an inverse association between urinary TCAA concentrations in the third trimester and neonatal NBNA scores, which did not persist when urinary TCAA concentrations in the first and second trimesters were evaluated. The underlying mechanisms are largely unknown, and these associations do not seem to be mediated by the OS biomarkers investigated. Animal studies have shown that BDCM can lead to histological changes in the thyroid gland (Chu et al., 1982; NTP, 1987), which may negatively affect the differentiation, proliferation, and migration of neuron cells during early gestation (de Graaf-Peters and Hadders-Algra, 2006). TCAA, however, was found to induce inflammation response and enhance neuron cell apoptosis (Prochazka et al., 2019; Singh, 2006), which could be linked to an altered maturation of axon, synapse, and glial cell in the late stage of pregnancy (Rock and Patisaul, 2018). TCAA was also reported to alter the calcium-binding protein level in glial cells, which can further induce neurotoxicity in late pregnancy (Zungun et al., 2013). These findings suggest that BDCM and TCAA may affect thyroid gland or neuron cells differently throughout pregnancy. Future studies should validate these trimester-

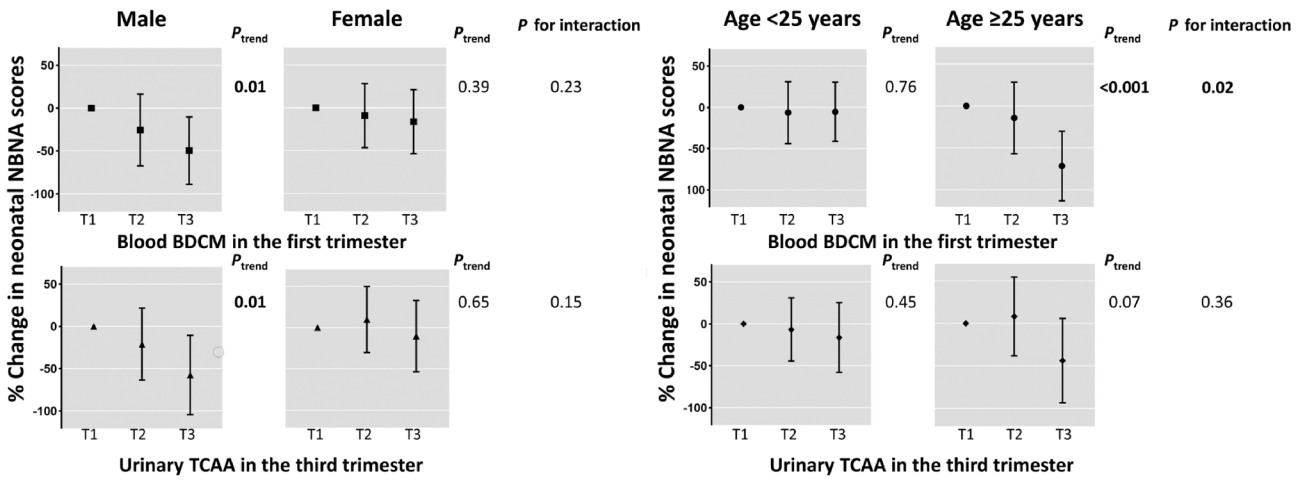

Fig. 2. Associations of blood BDCM in the first trimester and urinary TCAA in the third trimester with neonatal NBNA scores stratified by infant sex (male vs. female) and maternal age (<25 vs. ≥25 years). The models were adjusted for maternal age, educational level, BMI at enrollment, smoking status, alcohol intake, folic acid usage during pregnancy, and delivery mode.

Table 5
Associations between tertiles of urinary OS biomarker concentrations and neonatal NBNA scores by pregnancy trimesters.[a]

OS biomarkers	First trimester		Second trimester		Third trimester		Type 3*p* values
	N	Percent change (95% CI)	N	Percent change (95% CI)	N	Percent change (95% CI)	
8-OHdG							
T1 (<6.4)	113	0	137	0	147	0	0.401
T2 (6.4–10.4)	113	11.0 (–20.6, 42.6)	141	3.9 (–24.5, 32.2)	143	–16.7 (–44.6, 11.3)	
T3 (>10.4)	192	6.5 (–21.8, 34.8)	115	1.4 (–28.5, 31.2)	90	–22.7 (–54.7, 9.4)	
P for trend		0.717		0.830		0.116	
HNE-MA							
T1 (<32.3)	119	0	203	0	75	0	0.643
T2 (32.3–168.4)	124	–13.9 (–44.0, 16.2)	112	6.6 (–21.1, 34.2)	161	**–35.4 (–68.9, –1.9)**	
T3 (>168.4)	175	–9.8 (–38.0, 18.3)	78	–15.8 (–47.1, 15.5)	144	–21.3 (–55.5, 12.9)	
P for trend		0.541		0.460		0.409	
8-isoPGF$_{2\alpha}$							
T1 (<1.7)	117	0	153	0	127	0	0.557
T2 (1.7–3.2)	127	13.0 (–17.2, 43.2)	146	–4.6 (–31.9, 22.8)	124	4.1 (–26.1, 34.3)	
T3 (>3.2)	174	12.2 (–16.1, 40.5)	94	–10.4 (–41.1, 20.4)	129	12.7 (–17.2, 42.6)	
P for trend		0.462		0.508		0.403	

Abbreviations: NBNA, neonatal behavioral neurological assessment; CI, confidence interval; T, tertiles; Cr, creatinine; 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 maternal age, educational level, BMI at enrollment, smoking status, alcohol intake, folic acid usage during pregnancy, delivery mode, and infant sex.

specific findings and investigate other potential modes of action.

Stratified analysis showed that the associations of BDCM and TCAA with neonatal NBNA scores were stronger in male neonates. In support of our findings, Villanueva and colleagues also observed a stronger association between maternal total and brominated THM intake and child cognition in boys (Villanueva et al., 2018). It is well-known that testosterone is elevated in male fetuses between gestational weeks 8 and 24, leading to a masculinization of specific brain areas (Hines et al., 2015). Some DBPs have been shown to affect reproductive hormone levels in both rabbits and humans (Veeramachaneni et al., 2007; Zeng et al., 2013). Although the mechanisms behind these effects are poorly understood, damage to Leydig cells in response to DBP exposure could lead to reduced fetal testosterone levels during early pregnancy, in turn influencing male neurobehavioral development (Lombardo et al., 2012; Wallen and Hassett, 2009). However, it should be noted that the toxicological literature for DBP-related neurological effects is scarce. We thus call for new studies, particularly focused on prenatal effects at low DBP doses, and additionally investigating molecular endpoints to identify biomarkers of DBP-related neurotoxicity. Interestingly, the associations of BDCM and TCAA with neonatal NBNA scores were also stronger in mothers aged ≥25 years, which might be related to reduced activities of certain DBP metabolic enzymes (e.g., cytochrome P450 and glutathione S-transferase) as age increases, consequently accelerating the adverse effect of DBP exposures.

Growing evidence indicates that OS plays an important role in the development of neurodevelopmental disorders and neurodegenerative diseases (Bjorklund et al., 2020; Kabir et al., 2020; Lin and Beal, 2006; Steullet et al., 2017). For instance, Bharadwaj and colleagues reported an inverse association between maternal total antioxidant status and poor neuro-motor outcomes at 1 year of age (Bharadwaj et al., 2018). Similarly, Rommel and colleagues reported an inverse association between urinary prostaglandin-F$_{2\alpha}$ (PGF$_{2\alpha}$) and 8-isoPGF$_{2\alpha}$ in the third trimester with child behavioral outcomes at 4 years of age (Rommel et al., 2020). However, a lack of association between urinary 8-OHdG and malondialdehyde (MDA) and infants' neurodevelopmental performance was also reported (Al-Saleh et al., 2016). In the present study, we only found lower total NBNA scores among women with third trimester urinary HNE-MA in the medium tertile, compared to the women in the lowest tertile. Moreover, there was no evidence of mediating effect by OS. The discrepancies between studies could be largely related to the differences in OS markers, neurodevelopmental assessment scales, age at assessment, study design, and population characteristics. Besides OS

pathways, both *in vitro* and human studies also suggested that DBP exposures were associated with disrupted immune and inflammation function (Prochazka et al., 2019; Vlaanderen et al., 2017), which, in turn, play an important role in fetal brain development (Goeden et al., 2016; Suchdev et al., 2017; Tomlinson et al., 2019). Finally, DBP exposures were also reported to affect the synthesis of vitamin B12-dependent methionine and folate metabolism (Alston, 1991; Dow and Green, 2000), both of which are crucial to fetal neurodevelopment (Mitchell et al., 2014; Naninck et al., 2019).

The strengths of this study included its prospective study design, the repeated measurements of DBP exposures and OS biomarkers throughout pregnancy, and the use of blood THMs and urinary HAAs as exposure biomarkers. However, our study also had several limitations. First, blood THMs and urinary HAAs and OS biomarkers were measured at a single time point during each trimester. Given that blood THMs and urinary HAAs and OS biomarker concentrations varied greatly across pregnancy trimesters in this cohort (all interclass correlation coefficients $\leq$0.13) (Liu et al., 2020; Wang et al., 2019b), and exposure misclassification cannot be fully ruled, some associations of moderate magnitude may have been attenuated toward the null. Besides, although our results were materially unchanged after adjusting for time interval since last showering/bathing in sensitivity analyses, we cannot rule out other recent water-use activities such as hand washing and dishwashing that can influence blood THM concentrations (Ashley et al., 2005; Ashley et al., 2020; Nuckols et al., 2005). Second, our results may be confounded by other unmeasured covariates, such as maternal intelligence quotient (IQ) (Meador et al., 2011), dietary quality (Borge et al., 2017), and co-exposure to other pollutants (e.g., phthalate, bisphenol A, and heavy metals) or other DBP species (e.g., haloacetonitriles and halobenzoquinones) that might be even more toxic (Ahmed et al., 2005; Braun et al., 2017a, 2017b; Fu et al., 2017; Hyland et al., 2019; Moser et al., 2007; Valeri et al., 2017). Third, although the NBNA test is a validated tool for behavior assessment, the majority of infants in our present study (n = 409, 93.3%) had a normal NBNA score ranging from 37 to 40, which hampers the estimation of risk for abnormal NBNA. A combination of other neurobehavior tests, such as Dubowitz neurologic examination and general movements assessment (Crowle et al., 2019; Romeo et al., 2012), would provide a more comprehensive assessment of the newborns' neurodevelopment. Moreover, the neonatal period may be limited to evaluate subtle behavioral effects that may only be evident during infancy or childhood. Since *in utero* exposures may cause "organizational" effects in the brain, future neurobehavioral assessments throughout childhood would be needed in this cohort to confirm the potential long-term effects of prenatal DBP exposure on the offspring (Braun et al., 2017a, 2017b; Mustieles and Fernandez, 2020). Fourth, there was no significant difference in most demographic characteristics between the overall study population (n = 1760) and participants included in our current analysis (n = 438), except for maternal age and education level, which were slightly lower in the current subsample. Although these two covariates were accounted for in all the regression models, the influence of potential selection bias cannot be fully ruled out either. Fifth, because of multiple comparisons, the possibility that some of our findings are due to chance cannot be fully excluded. However, we are reassured by the consistency in results in various sensitivity analyses. Our results are also consistent with prior toxicological studies showing that maternal exposure to DBPs can impair fetal neurodevelopment (Ahmed et al., 2005; Singh, 2006). Finally, a large proportion of our participants had a low socioeconomic status, which may limit the generalizability of our findings.

5. Conclusion

Based on the XGDBP cohort study, we found that higher concentrations of blood BDCM and urinary TCAA during specific pregnancy trimesters were associated with lower NBNA scores, suggesting that BDCM and TCAA may impair fetal neurodevelopment differently throughout pregnancy. Our results highlight and strengthen previous evidence showing an association between DBP exposure and infant neurodevelopmental outcomes. However, more research is warranted to confirm our novel findings and to explore the potential underlying mechanisms.

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CRediT authorship contribution statement

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

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.2021.106838.

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