Research

Prenatal Exposure to Phthalates and Newborn Telomere Length: A Birth Cohort Study in Wuhan, China

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BACKGROUND: Telomere length (TL) is a marker of biological aging and is inversely related to aging-related diseases. The setting of TL at birth may have important implications for lifelong telomere dynamics; however, its determinants remain poorly understood.

OBJECTIVES: The purpose of our study was to explore the relationships between prenatal exposure to phthalates and umbilical cord blood TL.

METHODS: A total of 762 mother–newborn pairs were recruited from a birth cohort study performed between November 2013 and March 2015 in Wuhan, China. Relative cord blood TL was measured using quantitative real-time polymerase chain reaction. Six phthalate metabolites were measured in urine samples acquired from pregnant women during the three trimesters. Multiple informant models were applied to estimate the associations between prenatal exposure to phthalates and cord blood TL and to evaluate potential windows of vulnerability.

RESULTS: Exposure to mono-ethyl phthalate (MEP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-butyl phthalate (MBP), and di(2-ethylhexyl) phthalate (ΣDEHP) during the first trimester were inversely related to cord blood TL. In addition, we observed a female-specific association between maternal exposure to MEP during the first trimester and cord blood TL ($p_{\text{sex-int}} = 0.03$). The associations between maternal exposure to MECPP, MEHHP, MEOHP, and ΣDEHP during the first trimester and cord blood TL were consistent between males and females (all $p_{\text{sex-int}} > 0.10$).

CONCLUSION: This prospective study demonstrated that prenatal exposure to some phthalate metabolites were associated with shorter cord blood TL. Our results, if confirmed in other populations, may provide more evidence of adverse health outcomes of phthalate exposure and support the hypothesis that the intrauterine environment may be one of the major determinants for newborn TL. https://doi.org/10.1289/EHP4492

Introduction

Phthalates are widely used in plasticizers or solvents in consumer products such as cosmetics, toys, plastics, food packing, and building materials (Koch and Calafat 2009; Schettler 2006). Because phthalates are noncovalently bound to the products, they are easily released into the external environment and exposure may occur in humans through ingestion, inhalation, and dermal absorption (Schettler 2006; Wittassek et al. 2011). Food intake is the main route of high-molecular-weight phthalates (high-MWPs), whereas personal care products are the major source of low-molecular-weight phthalates (low-MWPs) (Rudel et al. 2011; Wormuth et al. 2006). Once absorbed, phthalates are quickly metabolized and excreted in the urine, where they can be measured. Phthalate metabolites have been consistently detected in urine from the general population and from pregnant women worldwide (Benjamin et al. 2017; Johns et al. 2015).

Due to the ubiquitous presence of phthalate and potential health consequences after phthalate exposure, there has been increasing concern, especially in susceptible populations such as pregnant women and fetuses. Phthalate metabolites can cross the placenta in humans and have been detected in cord blood (Latini et al. 2003; Mose et al. 2007). A growing body of literature has reported that prenatal phthalate exposures were related to adverse perinatal outcomes such as preeclampsia, preterm birth, pregnancy loss, and fetal retarded growth (Cantonwine et al. 2016; Casas et al. 2016; Ferguson et al. 2014c; Mu et al. 2015). Although phthalates have known endocrine-disrupting properties (Diamanti-Kandarakis et al. 2009; Halden 2010), there is also evidence from human studies that phthalate metabolites are related to increased biomarkers of oxidative stress (e.g., 8-isoprostane and 8-hydroxydeoxyguanosine) and inflammation [e.g., tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), IL-10, and IL-1β] in pregnant women (Ferguson et al. 2012, 2014a, 2015; Holland et al. 2016). Oxidative stress and chronic inflammation are considered potential pathways by which exposure to phthalates may influence adverse health effects (Ferguson et al. 2017; Holland et al. 2016).

Telomeres consist of noncoding repetitive sequences of DNA (TTAGGG) and nucleoproteins that together form a "cap" at the end of chromosomes and protect the integrity of the genomic content (Blackburn 1991). Telomere length (TL) shortens with each cell division and reflects biological aging (Benetos et al. 2001). Both high oxidative stress and inflammation have been linked to TL shortening. Telomeres with guanine-rich sequences are more sensitive to oxidative insult (Houben et al. 2008; Kawanishi and Oikawa 2004). Elevated inflammatory activity could accelerate leukocyte telomere shortening by promoting cell turnover (Jurk et al. 2014) as well as by inducing reactive oxygen species that damage telomeric DNA via oxidative stress (Jaiswal et al. 2000). Shorter TL has been related to aging-related diseases such as cardiovascular disease, type 2 diabetes, cancer, and all-cause mortality (Haycock et al. 2014; Mons et al. 2017; Willeit et al. 2010; Zhao et al. 2013).

Although studies on TL have been mainly conducted in adults, TL in early life is being increasingly considered as critical

to an individual's long-term health and disease risk (Fairlie et al. 2016; Heidinger et al. 2012; Moreno-Palomo et al. 2014). TL at birth represents an individual's initial setting of TL, which means that TL in adulthood is determined by newborn TL and subsequent attrition (Benetos et al. 2013; Hjelmborg et al. 2015; Sabharwal et al. 2018). Thus, factors that influence initial or newborn TL may be the potential determinants of lifetime health. Several studies have been performed to explore the determinants of newborn TL, such as maternal prepregnancy body mass index (BMI) (Martens et al. 2016), maternal psychosocial stress (Marchetto et al. 2016), maternal smoking (Mirzakhani et al. 2017), maternal exposure to polycyclic aromatic hydrocarbons (PAHs) (Perera et al. 2018), maternal particulate matter exposure (Martens et al. 2017), maternal residential traffic exposure (Bijnens et al. 2015), maternal heavy metal exposure (Wai et al. 2018), and maternal exposure to perfluoroalkyl and polyfluoroalkyl substances (Liu et al. 2018). However, studies regarding the effect of prenatal phthalate exposure on newborn TL are lacking. To date, only one cross-sectional study reported positive associations between urinary phthalates and TL in adults (Scinicariello et al. 2016).

Given that *in utero* life is considered to be a critical period of vulnerability in the early programing of subsequent health (Barker 1990), uncovering the associations of prenatal exposure to phthalate metabolites with newborn TL may provide new insights into the pathways of phthalate-related disorders. Therefore, we explored the associations of prenatal exposure to phthalate metabolites with newborn TL in a birth cohort study.

Methods

Study Population

The birth cohort study was conducted at the Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital) between November 2013 and March 2015. Briefly, 762 pregnant women were enrolled in the study during their first prenatal visit in Wuhan city, Hubei province, China. We recruited the participants using the following inclusion criteria: *a*) resident of Wuhan city, *b*) <16 weeks of pregnancy with a singleton gestation at recruitment, and *c*) planning to take prenatal care and delivery in the study hospital. In the present study, we excluded 16 participants due to unavailability of cord blood or ineligible DNA quality. The final analysis included 746 mother–newborn pairs. Of the eligible pregnant women, the number of women with urine samples was 746, 746, and 743 for the first, second, and third trimesters, respectively.

The study protocol was approved by the ethics committees of Tongji Medical College, Huazhong University of Science and Technology, and the Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital). All women provided written informed consent at enrollment.

Cord Blood Collection and TL Measurements

Umbilical cord blood was drawn immediately at delivery. Blood samples were centrifuged and stored at −80°C until DNA extraction. DNA was extracted from the leukocytes of umbilical cord blood using the Wizard® Genomic DNA Purification (Promega Corporation). To ensure good quality DNA samples, DNA concentration and purity were determined using a NanoDrop Spectrophotometer (ND-1000; Thermo Fisher Scientific), and those with the ratio of A260/280 ranging from 1.8 to 2.0 were considered eligible. Relative cord blood TL was determined based on the ratio of the telomere (T) repeat copy number to the single-copy gene (S) copy number (T/S ratio) for each indivi-

dual using the quantitative real-time polymerase chain reaction (qPCR) method, as described previously (Cawthon 2009; Qu et al. 2015). For the telomeres, the forward and reverse primers were 5′-ACACTAAGGTTTGGGTTTGGGTTTGGGTTTGGGTTAG-TGT-3′ and 5′-TGTTAGGTATCCCTATCCCTATCCCTAT-CCCTATCCCTAACA-3′ (Cawthon 2009). For the reference gene [human beta-globin (hbg)], the forward and reverse primers were 5′-GTGCACCTGACTCCTGAGGAGA-3′ and 5′-CCTTGATACCAACCTGCCCAG-3′ (Qu et al. 2015). We randomly selected 50 DNA samples from our study population and pooled them as the reference DNA, which was used to obtain a standard curve, ranging from 104 to 0.4 ng/μL ($R^2 > 0.99$). Each PCR was conducted using a 1.0-μL DNA sample (10 ng/μL) in a final volume of 10 μL per reaction. The telomere reaction mixture contained KAPA SYBR® FAST qPCR Kit Master MIX 1× (KAPA Biosystems; 5 μL/reaction), forward (0.27 μL/reaction–270 nM) and reverse (0.90 μL/reaction–900 nM) primers, and RNase-free water (2.83 μL/reaction). The single-copy gene reaction mixture contained KAPA SYBR® FAST qPCR Kit Master MIX 1× (KAPA Biosystems; 5 μL/reaction), forward (0.2 μL/reaction–200 nM) and reverse (0.2 μL/reaction–200 nM) primer, and RNase-free water (3.6 μL/reaction). The PCR thermal cycling conditions were set up as follows: 2 min at 50°C and 3 min at 95°C for activation of the DNA polymerase, followed by 40 cycles consisted of 3 s at 95°C for denaturation and 30 s at 60°C for annealing/extension. All samples were run in triplicate in 384-well plates using the ViiA™ 7 Dx Real-Time PCR System (Applied Biosystems). The intra-run and inter-run coefficients of variation for the TL measurements were 3.0% and 4.1%, respectively.

Urine Sample Collection and Phthalate Metabolite Measurements

We collected spot urine samples of the pregnant women at 13.0 ± 1.1, 23.6 ± 3.2, and 36.0 ± 3.3 weeks of gestation. The gestational ages of urine collection roughly reflect the first, second, and third trimesters. All urine samples were collected in polypropylene tubes and frozen at −20°C for further analysis.

We analyzed six phthalate metabolites in urine samples, including mono-ethyl phthalate (MEP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethylhexyl) phthalate (MEHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono-butyl phthalate (MBP). In addition to measuring the individual phthalate metabolites, the total concentration of di(2-ethylhexyl) phthalate (ΣDEHP) was estimated using the sum of the molar concentrations of MECPP, MEHP, MEHHP, and MEOHP. We analyzed phthalate metabolites in urine samples using solid-phase extraction coupled with ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS). The details of the analytical procedure have been previously described (Zhu et al. 2016, 2018). The limits of detection (LODs) were 0.01 ng/mL for MECPP, 0.05 ng/mL for MEOHP and MEHHP, and 0.1 ng/mL for MEP, MBP, and MEHP. Urinary phthalate metabolite concentrations <LOD were determined as the LOD divided by the square root of 2.

To adjust for variations in urine dilution, we corrected urinary phthalate concentrations by urinary specific gravity (SG) based on the following equation: $P_{SG} = P[(1.012 - 1)/(SG - 1)]$, where P_{SG} is the SG-corrected phthalate concentration, P is the observed phthalate concentration, the value 1.012 is the median SG in this study population, and SG is the specific gravity of the individual urine samples. SG was measured using a refractometer (Atago PAL-10S; Atago) while preparing urine samples for phthalate analysis. The SG-corrected phthalate concentrations were used for statistical analysis.

Covariates

Information on sociodemographic and lifestyle characteristics was obtained through standard questionnaires administrated by trained nurses at the first prenatal care visit and included maternal age, educational level, and passive smoking during pregnancy. Passive smoking during pregnancy was defined as exposure to secondhand smoke from family members in the household or colleagues at the workplace during pregnancy (Vardavas et al. 2016). Information on mothers' reproductive history, hypertensive disorders of pregnancy, gestational diabetes, and infants' sex and birth date was retrieved from medical records. Gestational age (weeks) was determined based on the last menstrual period. We defined gestational age <37 weeks as preterm birth. Prepregnancy weight was self-reported during the first prenatal care visit and height was measured using a stadiometer. The prepregnancy BMI was determined by dividing self-reported prepregnancy weight (in kilograms) by height squared (in meters squared).

Statistical Analysis

Continuous data were expressed as the mean ± standard deviation (SD) for normal distributions, geometric mean (interquartile range) for skewed distributions, or n (%) for categorical data. Urinary phthalate levels and cord blood TL were natural log-transformed to improve the normality of the distributions. Correlations between individual phthalate metabolites and SG were estimated using Pearson correlation coefficients or Partial Pearson correlation coefficients that adjusted for trimester. Reproducibility of urinary phthalate concentrations across the different three trimesters was determined by computing the intraclass correlation coefficients (ICCs) according to random intercept linear mixed models. The ICC was defined as the ratio of the between-person variance to the sum of within- and between-person variances.

Multiple informant models were applied to explore the associations between repeated prenatal urinary phthalate concentrations and newborn TL (Sánchez et al. 2011). The model treated individual phthalate concentrations in different trimesters (or windows) as informants and jointly estimated the difference in newborn TL for each doubling of urinary phthalate concentrations in each trimester, using a nonstandard version of generalized estimating equations. In this model, each exposure window did not adjust for urinary phthalate concentrations in other windows, but adjusted for the same covariates. The multiple informant model also provided a way to test differences in associations between urinary phthalate concentrations and newborn TL across the three trimesters. The null hypothesis for the test was that the phthalate coefficients were equal across the three trimesters.

To capture potential nonlinear relationships, we also used multiple informant models to assess the associations between quartiles of prenatal urinary phthalate concentrations and cord blood TL, with the lowest quartile as the reference. Quartiles of urinary phthalate concentrations were categorized based on trimester-specific cut points. Tests for linear trend across quartiles were carried out by assigning the median value of each quartile as a continuous variable. To enhance the interpretation of regression models consisting of ln-transformed exposure and/or outcome variables, we presented all regression coefficients and 95% confidence intervals (CIs) as percent change and 95% CI in cord blood TL for a doubling or quartiles of urinary phthalate concentrations. Multivariate models were adjusted for maternal age (continuous), prepregnancy BMI (continuous), educational level (junior high school or below, high school, college or above),

parity (primiparous, multiparous), passive smoking during pregnancy (yes, no), and infant sex (male, female).

Because previous investigations have suggested a sex-specific relationship between prenatal exposure to phthalates and fetal development, we explored whether infant sex modified the association between prenatal exposure to phthalates and newborn TL. Stratum-specific p-values for interaction between each phthalate metabolite and infant sex were estimated separately for each trimester using the Wald test (Kaufman and MacLehose 2013), with a $p < 0.1$ considered significant. We also conducted a series of sensitivity analyses with additional adjustment for gestational age at urine collection, excluding mothers with hypertensive disorders of pregnancy and gestational diabetes, and excluding preterm infants. Moreover, we fitted separate linear regression models to explore the relationships between prenatal exposure to phthalates and cord blood TL.

All statistical analyses were carried out using SAS (version 9.4; SAS Institute Inc.). A two-sided $p < 0.05$ was considered statistically significant.

Results

The characteristics of the 746 mother–newborn pairs are presented in Table 1. The mean prepregnancy BMI and maternal age of mothers were $20.8 \pm 2.8 \, \text{kg/m}^2$ and 28.6 ± 3.3 y, respectively. Among the 746 mothers, 589 (79.0%) were well educated, 244 (32.7%) were passively exposed to cigarette smoking, and 644 (86.3%) were primiparous. Approximately 19 (2.5%) and 53 (7.1%) of mothers were diagnosed with hypertensive disorders of pregnancy and gestational diabetes, respectively. Of the newborns, 383 (51.3%) were males. The rate of preterm birth was 2.4%. The characteristics of mothers carrying male infants were similar to those carrying female infants.

The detection rate, distributions, and variability (i.e., the ICCs) of SG-corrected urinary phthalate metabolites in each trimester are shown in Table 2. The detection rate of phthalate metabolites ranged from 87.0% to 99.9%. MBP had the highest median concentration in each trimester, followed by MEP, MECPP, MEHHP, MEOHP, and MEHP. The ICCs for urinary phthalate concentrations during the three trimesters ranged from 0.19 to 0.36, with the lowest ICC for MEHHP and the highest for MEP.

The detection rate and distributions of SG-corrected urinary phthalate metabolites during each trimester stratified by infant sex are shown in Table S1. The Pearson correlation coefficients between SG-corrected urinary phthalate metabolites ranged from 0.08 to 0.91 for the first trimester, 0.08 to 0.92 for the second trimester, and 0.05 to 0.96 for the third trimester, with the highest Pearson correlation coefficient between MEHHP and MEOHP in each trimester (see Tables S2–S4). The partial Pearson correlation coefficients of SG-corrected urinary phthalate metabolites adjusted for trimester ranged from 0.07 to 0.93 (see Table S5).

Table 3 displays the relationships of prenatal exposure to phthalate metabolites with cord blood TL. In the multivariate-adjusted models, each doubling of maternal urinary MECPP, MEHHP, and MEOHP during the first trimester were associated with 2.38% (95% CI: −4.22%, −0.51%), 2.53% (95% CI: −4.38%, −0.64%), and 2.90% (95% CI: −4.76%, −1.01%) shorter cord blood TL, respectively, with consistent inverse associations for the second and third trimesters. In addition, each doubling of maternal urinary ΣDEHP during the first trimester was associated with a 3.25% (95% CI: −5.26%, −1.20%) decrease in cord blood TL. The pattern was similar for the second trimester, whereas a positive association was observed for the third trimester.

Table 1. Characteristics of mother–newborn pairs, Wuhan, China, 2013–2015 ($n = 746$).

Characteristic	Total ($n = 746$)	Mothers carrying male infants ($n = 383$)	Mothers carrying female infants ($n = 363$)	p-Value
Maternal age (y)	28.6 ± 3.3	28.7 ± 3.5	28.5 ± 3.2	0.24
Prepregnancy BMI (kg/m^2)	20.8 ± 2.8	21.0 ± 2.9	20.8 ± 2.7	0.27
Educational level [n (%)]				0.77
Junior high school or below	42 (5.6)	23 (6.0)	19 (5.2)	
High school	115 (15.4)	56 (14.6)	59 (16.3)	
College or above	589 (79.0)	304 (79.4)	285 (78.5)	
Passive smoking [n (%)]				0.56
Yes	244 (32.7)	129 (33.7)	115 (31.7)	
No	502 (67.3)	254 (66.3)	248 (68.3)	
Gestational diabetes [n (%)]				0.82
Yes	53 (7.1)	28 (7.3)	25 (6.9)	
No	693 (92.9)	355 (92.7)	338 (93.1)	
Hypertensive disorders of pregnancy [n (%)]				0.30
Yes	19 (2.5)	12 (3.1)	7 (1.9)	
No	727 (97.5)	371 (96.9)	356 (98.1)	
Parity [n (%)]				0.10
Primiparous	644 (86.3)	323 (84.3)	321 (88.4)	
Multiparous	102 (13.7)	60 (15.7)	42 (11.6)	
Preterm birth (gestational age <37 weeks) [n (%)]				0.91
Yes	18 (2.4)	9 (2.3)	9 (2.5)	
No	728 (97.6)	374 (97.7)	354 (97.5)	
Cord blood telomere length (T/S ratio)	0.75 (0.56–0.95)	0.75 (0.55–0.97)	0.74 (0.57–0.93)	0.98

Note: Continuous variables are presented as mean ± SD (normally distributed) or geometric mean with 25–75th percentile (not normally distributed); categorical variables are expressed as n (%). Data were complete for all variables.

We also explored the associations between quartiles of prenatal exposure to phthalate metabolites and cord blood TL (see Table S6). Compared with maternal urinary MEP, MECPP, MEHHP, and MEOHP during the first trimester in the lowest quartile, those in the highest quartile were associated with 11.12% (95% CI: −17.95%, −3.73%), 11.64% (95% CI: −18.42%, −4.30%), 9.30% (95% CI: −16.26%, −1.74%), and 11.78% (95% CI: −18.56%, −4.43%) shorter cord blood TL, with similar patterns of associations for the second and third trimesters. Moreover, mothers in the highest quartile of urinary MBP and ΣDEHP during the first trimester had 8.43% (95% CI: −15.46%, −0.83%) and 11.98% (95% CI: −18.75%, −4.64%) shorter cord blood TL than in the lowest quartile, respectively. The inverse association of ΣDEHP was consistent for the second trimester, whereas positive associations of MBP and ΣDEHP were observed for the third trimester. Maternal urinary MEHP was not significantly associated with cord blood TL, regardless of trimester (Table 3; see also Table S6).

Analysis stratified by infant sex is presented in Table 4. Maternal urinary MEP during the first trimester was inversely associated with cord blood TL in females, whereas the association was close to the null for males (percent change, −3.07%; 95% CI: −5.20%, −0.89% and percent change, 0.24%; 95% CI:

−1.70%, 2.22%, respectively, $p_{\text{sex-int}} = 0.03$). The pattern of MEP was similar for the second trimester, whereas the inverse association was stronger in males than females for the third trimester; however, differences between males and females were not significant (all $p_{\text{sex-int}} > 0.10$). The inverse associations between maternal urinary MECPP, MEOHP, MEHHP, and ΣDEHP during the first trimester and cord blood TL were consistent between males and females (all $p_{\text{sex-int}} > 0.10$).

In the sensitivity analyses, the inverse relationships between maternal exposure to phthalate metabolites during the first trimester and cord blood TL were not materially changed with additional adjustment for gestational age at urine collection, or excluding mothers with hypertensive disorders of pregnancy and gestational diabetes ($n = 68$), or excluding preterm infants ($n = 18$) (see Table S7). In separate linear regression models, the relationships between prenatal phthalate exposure and cord blood TL were similar to those in the main analyses (see Table S8).

Discussion

In this study, we observed that exposure to MEP, MECPP, MEOHP, MEHHP, MBP, and ΣDEHP during the first trimester were inversely related to cord blood TL. The stratified analysis

Table 2. Distributions and intraclass correlation coefficients of maternal urinary phthalate metabolites according to trimester, Wuhan, China, 2013–2015.

	\>LOD (%)			GM			25th			50th			75th			
Phthalate metabolites (ng/mL)	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	ICC
MEP	97.8	98.9	98.9	10.12	9.10	10.18	5.04	4.13	4.72	9.72	8.07	9.80	20.28	20.41	22.54	0.36
MECPP	99.5	99.9	99.7	9.52	8.53	9.86	5.68	5.00	6.29	9.24	8.30	9.83	15.95	13.48	15.56	0.24
MEHHP	99.6	99.9	99.9	6.53	5.14	6.12	3.64	2.66	3.62	6.18	4.94	6.14	11.43	8.67	10.01	0.19
MEOHP	99.6	99.9	99.9	4.81	4.13	5.03	2.68	2.17	3.06	4.80	4.25	4.99	8.23	6.87	8.09	0.24
MBP	98.1	98.3	98.5	64.86	54.56	86.91	34.17	25.76	41.11	65.44	58.50	95.58	142.7	133.2	207.4	0.22
MEHP	89.2	88.0	87.0	2.35	1.88	1.85	1.08	0.89	0.81	2.81	2.18	2.24	5.68	4.85	4.98	0.32
ΣDEHP (nmol/L)	—	—	—	86.33	71.57	85.24	49.37	39.39	50.97	80.52	68.50	81.82	140.0	113.8	130.3	0.21

Note: The ICC was derived by dividing the between-person variance by the sum of the between- and within-person variances. Values range from 0 (no reproducibility of the same measurement within a subject) to 1 (perfect reproducibility). Phthalate metabolite concentrations are shown after substituting the >LOD values by LOD divided by the square root of 2. —, not applicable; DEHP, di(2-ethylhexyl) phthalate; GM, geometric mean; ICC, intraclass correlation coefficient; LOD, limit of detection; MBP, mono-butyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, mono-ethyl phthalate; ΣDEHP, molecular sum of MECPP, MEHP, MEHHP, and MEOHP (nmol/L).

Table 3. Associations between prenatal exposure to phthalate metabolites and cord blood telomere length, Wuhan, China, 2013–2015.

Phthalate metabolites	1st trimester ($n = 746$) Percent change (95% CI)	p-Value	2nd trimester ($n = 746$) Percent change (95% CI)	p-Value	3rd trimester ($n = 743$) Percent change (95% CI)	p-Value	p_{int}[a]
MEP	−1.09 (−2.53, 0.37)	0.14	−0.48 (−2.01, 1.09)	0.55	−0.92 (−2.41, 0.60)	0.23	0.74
MECPP	−2.38 (−4.22, −0.51)	0.01	−0.72 (−2.73, 1.33)	0.49	−0.87 (−2.96, 1.27)	0.42	0.31
MEHHP	−2.53 (−4.38, −0.64)	0.009	−1.25 (−3.18, 0.72)	0.21	−0.29 (−2.50, 1.97)	0.80	0.29
MEOHP	−2.90 (−4.76, −1.01)	0.003	−1.12 (−3.04, 0.83)	0.26	−0.51 (−2.65, 1.67)	0.64	0.16
MBP	−1.13 (−2.52, 0.28)	0.12	0.57 (−0.79, 1.95)	0.41	1.19 (−0.22, 2.62)	0.10	0.04
MEHP	−1.18 (−2.44, 0.11)	0.07	−0.30 (−1.60, 1.02)	0.65	0.88 (−0.35, 2.14)	0.16	0.02
ΣDEHP	−3.25 (−5.26, −1.20)	0.002	−0.72 (−2.73, 1.34)	0.49	0.63 (−1.70, 3.01)	0.60	0.02

Note: All models were adjusted for maternal age, prepregnancy BMI, parity, educational level, passive smoking during pregnancy, and infant sex. BMI, body mass index; CI, confidence interval; DEHP, di(2-ethylhexyl) phthalate; MBP, mono-butyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, mono-ethyl phthalate; p_{int}, p-value for interaction; ΣDEHP, molecular sum of MECPP, MEHP, MEHHP, and MEOHP (nmol/L).
[a]Score test of homogeneity of regression coefficients.

suggested that maternal urinary MEP during the first trimester was associated with shorter cord blood TL in female infants, whereas the association was close to the null for male infants. The inverse associations between maternal urinary MECPP, MEOHP, MEHHP, and ΣDEHP during the first trimester and cord blood TL were consistent between male and female infants.

Phthalate metabolites were detectable in maternal urine samples in our study, owing to the ubiquitous presence of phthalates. The concentrations of some phthalate metabolites (e.g., MEHHP, MEHP, and MEOHP) in our study were comparable with those in other studies of Chinese pregnant women (Gao et al. 2017; Zhang et al. 2018; Zhu et al. 2018). However, most concentrations of urinary phthalate metabolites (MEHHP, MECPP, MEHP, and MEOHP) among pregnant women from the United States (Soomro et al. 2018), Mexico (Téllez-Rojo et al. 2013), Spain (Casas et al. 2016), France (Philippat et al. 2012), and Greece

(Myridakis et al. 2015) were higher than those reported in the present study. Compared with pregnant women from Canada (Arbuckle et al. 2014) and Denmark (Tefre de Renzy-Martin et al. 2014), similar concentrations of urinary MECPP, MEHP, MEOHP, and MEHHP and lower concentrations of MEP were shown in our study. The differences in phthalate exposure levels in different regions may result from variations in lifestyle behaviors, use of consumer products, and living environments. In our study, we observed that ICCs for urinary phthalate concentrations ranged from 0.19 to 0.36, which indicated a high variability across the whole pregnancy. ICCs for MEOHP and MEHP throughout pregnancy in our study were higher than those reported among studies from the United States (Ferguson et al. 2014b) and Mexico (Watkins et al. 2017a). Compared with previous studies (Ferguson et al. 2014b; Watkins et al. 2017b; Zhang et al. 2018), lower ICCs for most urinary phthalate metabolites (MEP, MECPP, MEHHP, and MBP) were shown in

Table 4. Associations between prenatal exposure to phthalate metabolites and cord blood telomere length, stratified by infant sex, Wuhan, China, 2013–2015.

Phthalate metabolites	1st trimester ($n = 746$) Percent change (95% CI)	p-Value	2nd trimester ($n = 746$) Percent change (95% CI)	p-Value	3rd trimester ($n = 743$) Percent change (95% CI)	p-Value
MEP						
Male	0.24 (−1.70, 2.22)	0.81	−0.19 (−2.48, 2.16)	0.88	−1.37 (−3.42, 0.72)	0.20
Female	−3.07 (−5.20, −0.89)	0.006	−0.87 (−2.90, 1.21)	0.41	−0.24 (−2.41, 1.97)	0.83
$p_{sex-int}$	0.03		0.67		0.46	
MECPP						
Male	−2.05 (−4.41, 0.37)	0.10	−0.69 (−3.44, 2.13)	0.63	−1.09 (−3.91, 1.82)	0.46
Female	−3.11 (−6.08, −0.05)	0.05	−0.88 (−3.81, 2.14)	0.56	−0.27 (−3.41, 2.96)	0.87
$p_{sex-int}$	0.59		0.93		0.71	
MEHHP						
Male	−2.10 (−4.62, 0.49)	0.11	−0.74 (−3.45, 2.05)	0.60	−0.31 (−3.25, 2.73)	0.84
Female	−3.17 (−5.91, −0.36)	0.03	−1.81 (−4.54, 1.00)	0.21	0.02 (−3.35, 3.50)	0.99
$p_{sex-int}$	0.58		0.59		0.89	
MEOHP						
Male	−2.67 (−5.23, −0.04)	0.05	−0.89 (−3.53, 1.82)	0.52	−0.69 (−3.47, 2.18)	0.63
Female	−3.23 (−5.93, −0.44)	0.02	−1.40 (−4.18, 1.47)	0.34	0.11 (−3.28, 3.62)	0.95
$p_{sex-int}$	0.77		0.80		0.72	
MBP						
Male	−0.55 (−2.40, 1.34)	0.57	1.21 (−0.84, 3.30)	0.25	0.79 (−1.29, 2.90)	0.46
Female	−1.86 (−3.99, 0.31)	0.09	0.06 (−1.72, 1.87)	0.95	1.61 (−0.29, 3.56)	0.10
$p_{sex-int}$	0.37		0.41		0.57	
MEHP						
Male	−1.40 (−3.16, 0.39)	0.12	−0.88 (−2.68, 0.95)	0.34	1.12 (−0.70, 2.95)	0.23
Female	−0.84 (−2.67, 1.03)	0.38	0.48 (−1.39, 2.38)	0.62	0.67 (−1.01, 2.37)	0.44
$p_{sex-int}$	0.67		0.31		0.73	
ΣDEHP						
Male	−3.35 (−6.15, −0.48)	0.02	−0.86 (−3.64, 2.00)	0.55	0.93 (−2.18, 4.14)	0.56
Female	−3.17 (−6.05, −0.19)	0.04	−0.58 (−3.50, 2.43)	0.70	0.31 (−3.21, 3.94)	0.87
$p_{sex-int}$	0.93		0.89		0.80	

Note: All models were adjusted for maternal age, prepregnancy BMI, parity, educational level, and passive smoking during pregnancy. BMI, body mass index; CI, confidence interval; DEHP, di(2-ethylhexyl) phthalate; MBP, mono-butyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono (2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, mono-ethyl phthalate; $p_{sex-int}$, p-value for interaction between urinary phthalates and infant sex; ΣDEHP, molecular sum of MECPP, MEHP, MEHHP, and MEOHP (nmol/L).

the present study. The different ICCs were possibly due to differences in the consumption of personal care products, living environments, and dietary habits in different regions.

A growing body of literature has shown associations of exposure to environmental hazards with TL in adults, including metals [cadmium (Zota et al. 2015), lead (Wu et al. 2012), and arsenic (Li et al. 2012)], air pollution [black carbon (McCracken et al. 2010) and particulate matter (Hou et al. 2012; Pieters et al. 2016)], persistent organic pollutants (POPs) (Mitro et al. 2016), polychlorinated biphenyls (PCBs) (Callahan et al. 2017), and benzene (Bassig et al. 2014). However, evidence on the variations of newborn TL in relation to early life environmental exposures is limited. A birth cohort study of 641 mother–newborn pairs from Belgium suggested that prenatal particulate matter $\leq 2.5~\mu m$ in aerodynamic diameter ($PM_{2.5}$) exposure was associated with shorter newborn TL (Martens et al. 2017). Martens et al. (2016) also reported that prepregnancy BMI was associated with shorter newborn TL. Our study revealed a similar, but not statistically significant, association. The possible reason might be that the participants in the study by Martens et al. had a much higher average prepregnancy BMI than found in our study. In addition, Perera et al. (2018) found that prenatal exposure to PAHs from coal burning was inversely related to cord blood TL. Overall, our findings and those from previous studies suggest that newborn TL may be influenced by multiple environmental stressors with small individual effects. To date, the relationships between prenatal exposure to phthalates and newborn TL have not been reported. Only a cross-sectional study based on data from the National Health and Nutrition Examination Survey (NHANES) 1999–2002 ($n = 2,742$) had evaluated the relationships between urinary phthalate metabolites [MEP, MBP, MEHP, and mono-benzyl phthalate (MBzP)] and leukocyte TL in adults ≥ 20 y of age (Scinicariello et al. 2016). Contrary to our findings, Scinicariello et al. (2016) found that urinary MEHP was related to longer TL among all subjects and that urinary MBP and MBzP were related to longer TL only among people ≥ 60 y of age. Given that the telomere dynamics in early life were different from those in later life (Frenck et al. 1998; Turner et al. 2019), the difference in research subjects (newborn vs. adult) was expected to be the major contributor to the discrepancies between the two studies. In addition, differences in study design (longitudinal vs. cross-sectional) as well as exposure time period, exposure concentration, and exposure duration might be reasons for the inconsistent findings.

Although the potential mechanisms underlying the relationships between maternal exposure to phthalates and cord blood TL are yet to be elucidated, oxidative stress and chronic inflammation are two plausible hypotheses. Exposure to phthalates has been associated with increased oxidative stress among pregnant women (Ferguson et al. 2014a, 2015). Because of the high guanine content of the telomere sequence, telomeres are more vulnerable to damage induced by oxidative stress (Houben et al. 2008; Kawanishi and Oikawa 2004). Moreover, telomeric DNA is deficient in the repair of single-strand breaks, compared with genomic DNA; oxidative stress can induce single-strand breaks, resulting in increased telomere shortening (Houben et al. 2008; Kawanishi and Oikawa 2004). Exposure to phthalate metabolites during pregnancy could also affect newborn telomere biology through chronic inflammation. Evidence suggests that chronic inflammation is related to increasing amounts of leukocytes and their more rapid expenditure, which requires a higher rate of cell replication and subsequently results in more TL attrition.

Although the associations between prenatal exposure to phthalates and newborn TL did not differ materially by trimester for many of the metabolites in our study, first-trimester exposure to ΣDEHP was related to shorter newborn TL. Early

pregnancy is generally a critical period for environmental exposures, and the developing fetus is highly vulnerable to adverse factors related to adverse birth outcomes (Mook-Kanamori et al. 2010). Unexpectedly, we also found that exposure to some phthalate metabolites during the third trimester were associated with longer newborn TL, although the association was not statistically significant. We considered that the different patterns of the associations between phthalates and newborn TL across the three trimesters might be due to the different TL dynamics during the developmental stages of the embryo and fetus. Several human and animal studies have demonstrated that cells might use different mechanisms to regulate telomere maintenance at different stages of development (Liu et al. 2007; Schaetzlein et al. 2004). Furthermore, the positive associations might indicate the presence of a potential compensatory mechanism in response to phthalate exposure insults. Telomerase can synthesize telomere DNA sequences to compensate or reverse telomere erosion due to oxidative stress insults, thereby maintaining telomere length (Greider 1996; Hug and Lingner 2006; Shore and Bianchi 2009). Additional detailed studies are essential to confirm the critical time window and the potential mechanisms.

In the stratified analysis, we observed that the inverse associations between maternal urinary MECPP, MEOHP, MEHHP, and ΣDEHP during the first trimester and cord blood TL were similar between male and female infants. Meanwhile, maternal exposure to MEP during the first trimester was related to shorter newborn TL only in females. The possible explanations for the sex-specific results might be the action of insulin-like growth factor 1 (IGF-1). Exposure to phthalate was reported to be inversely associated with IGF-1 (Boas et al. 2010; Wu et al. 2017). Epidemiological studies reported that IGF-1 concentration was positively associated with TL (Kaplan et al. 2009; Movérare-Skrtic et al. 2009). In addition, previous studies reported that female newborns had higher concentrations of IGF-1 than males (Geary et al. 2003; Vatten et al. 2002), which might potentially result in sex-specific effects. Moreover, evidence has suggested that increased cortisol exposure is associated with shorter TL (Choi et al. 2008; Tomiyama et al. 2012). Our previous study indicated that prenatal exposure to phthalates was positively related to the level of glucocorticoids (measured by cortisol and cortisone) in female infants but was inversely related to glucocorticoid levels in male infants (Sun et al. 2018). This might partly explain the effects of phthalates on female TL.

Our study has some strengths. The effects of prenatal phthalate exposure on newborn TL were estimated in the largest prospective study to date. In addition, the prospective cohort design and availability of urine samples from each trimester allowed us to estimate associations between newborn TL and phthalate metabolites in maternal urine samples collected at multiple time points. Moreover, we used multiple informant models to estimate the associations between maternal phthalate exposure and newborn TL according to trimester. The statistical method may be more advantageous than the separate regression models for each exposure window (Sánchez et al. 2011).

Our study also has some limitations. First, although we adjusted for some potential confounders, we cannot fully eliminate the possible residual confounding by some unobserved confounding factors. For example, the differences in individual metabolism and excretion pattern may affect urinary phthalate metabolite concentration. Second, given that phthalates are rapidly metabolized and have a short half-life, a single spot urine sample available at each trimester may not fully reflect exposure profiles at each specific window over the duration of pregnancy. Although we repeatedly measured urinary phthalate concentrations at the three trimesters, exposure measurements were still

limited due to the low ICCs, which indicated the temporal variability of phthalate concentrations over pregnancy. Third, given the high intercorrelations among several phthalate metabolites, we did not perform multi-phthalate models controlling for other individual phthalates that might be mutually confounded. To reduce the confounding by correlated phthalates, we summed all phthalate metabolites with the same chemical into one variable (i.e., DEHP). Fourth, most of the participants in the present study were Han Chinese women, and generalizability to other ethnic groups is uncertain. Furthermore, the educational level for the participants (79.0% were college or above) in the present study, which may reflect better health behaviors or higher socioeconomic status and lead to low rates of adverse pregnancy outcomes (i.e., preterm birth), may limit the generalizability of our results to other populations.

Conclusions

Our findings offer the first preliminary evidence that maternal exposure to phthalates is related to shorter TL in newborns. Such an effect may have lifetime health implications, considering that newborn TL may be critical to an individual's telomere biology and a major determinant of TL in later life (Benetos et al. 2013; Hjelmborg et al. 2015; Sabharwal et al. 2018). Future prospective investigations are warranted to further explore the effects of phthalate-related telomere shortening at birth on offspring health outcomes later in life.

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