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In Utero Exposure to Endocrine-disrupting Chemicals and Telomere Length at Birth

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Abstract

Telomere length correlates with morbidity and mortality. While telomere length appears to be influenced by hormone levels, the potential impact of exposure to endocrine-disrupting chemicals (EDCs) has not been studied. We examined the association between maternal gestational concentrations of biomarkers of EDC exposure and telomere length at birth in the Harvard Epigenetic Birth Cohort. EDC (phenols and phthalates) biomarker concentrations were measured in maternal spot urine samples during the first trimester and telomere length in maternal and cord blood among 181 mother-newborn dyads. Maternal and newborn telomere length exhibited a positive correlation (Spearman ρ=0.20 (p-value< 0.01). Infant telomere length was associated with maternal biomarker concentrations of specific EDCs, and most of these associations were observed to be infant sex-specific. Prenatal exposure to triclosan, a non-paraben phenol with antimicrobial properties, was one of the most strongly associated with telomere length; telomere

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Competing Interests

The authors declare no competing interests.

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Human Subjects Approval

This study was approved by the Institutional Review Board of the Brigham and Women's Hospital, Boston, MA.

length was 20% (95% CI 5% – 33%) shorter among boys in the highest quartile of maternal biomarker concentrations compared to the lowest quartile. In contrast, we observed longer telomere length associated with increased gestational concentrations of mono-isobutyl phthalate, and among boys, with increased concentrations of mono-2-ethylhexyl phthalate. In this birth cohort, we observed associations between maternal gestational exposure to select EDC biomarkers and telomere length, most of which were sex-specific. These findings need to be confirmed in future studies.

Keywords

Telomeres; EDCs; Phenols; Phthalates; in utero

1. Introduction

Telomeres are genomic structures at the ends of eukaryotic chromosomes, which protect chromosomes against nucleolytic decay (Blackburn, 1991). They are composed of long hexameric (TTAGGG)n repeats complexed to a core set of six proteins, called shelterin complex (Palm and de Lange, 2008). The activity of the enzyme that maintains telomere length, telomerase, is generally very low in somatic cells. Consequently, telomeric repeats in somatic cells shorten by 30–100 base pairs (bps) with each cell division until the telomeres reach a critical length that signals cells to senescence and apoptosis occurs (Blackburn, 1991) (Dahse et al., 1997). Shelterin protects telomere ends by forming a compact structure between shelterin subunits and telomeric DNA (Bandaria et al., 2016).

The age-adjusted inter-individual variation in telomere length is substantial; rates of telomeric attrition are attributed to both genetic inheritance and environmental factors (Broer et al., 2013) (Cassidy et al., 2010) (Cassidy et al., 2010) (Hjelmborg et al., 2015) (Kurz et al., 2004) (Mirabello et al., 2009) (Nawrot et al., 2004) (Shiels et al., 2011) (von Zglinicki, 2000) (Zhang et al., 2013). Given its mutability and association with cellular senescence, telomere length has been described as a “molecular clock” that is reflective of the “exposome” experience throughout the life-course (Aragona et al., 2000). Telomere length may also be viewed as a marker reflective of cellular coping, which imparts resilience against environmentally-induced genomic trauma and subsequent adverse outcomes (Wong et al., 2014). Several environmental factors affect telomere length through dysregulation of the shelterin complex (Shoeb et al., 2019). Interestingly, telomere length correlates across various target tissues such as leukocytes, skeletal muscle, skin, and subcutaneous fat (Daniali et al., 2013).

When telomeres erode to a critically short length, beyond what is known as the Hayflick limit, an apoptotic cascade is usually initiated to prevent the proliferation of cells possessing aberrant genomic insults (Hayflick, 1985) (Olovnikov, 1996) (Shay and Wright, 2000). However, should the apoptotic process be evaded, degraded telomeres can expose reactive chromosomal ends that recruit DNA repair enzymes, which may result in translocations or chromosomal fusions; these structural abnormalities may initiate and promote adverse cellular events, such as neoplasia (Hayflick, 1985) (Olovnikov, 1996) (Shay and Wright,

2000). Indeed, telomere length has been established as a biomarker of numerous chronic diseases, including cancer and cardiovascular disease (Ma et al., 2011) (Wentzensen et al., 2011). However, a recent paradigm posits that the relation between telomere length and susceptibility to chronic disease is more nuanced than previously accepted (Aviv et al., 2003) (Daniali et al., 2013). Although shorter telomere length may protect tissue from becoming cancerous by priming the cells for apoptosis, shorter telomeres also increase the risk of cardiovascular disease and premature mortality in adult life. Conversely, longer telomeres may reduce susceptibility to cardiovascular disease, but extend cellular lifespan and permit the accrual of aberrant genomic events, which may increase cancer risk in later life. This duality of telomere length with respect to disease susceptibility is classically known as antagonistic pleiotropy (Aviv and Harley, 2001).

Twin studies have suggested an important genetic contribution to telomere length (Slagboom et al., 1994); however, the impact of the intrauterine conditions on telomere length have been little explored. The prenatal period from conception to birth is of particular interest since it is the phase of life marked by the most rapid physical growth and thus accelerated mitotic proliferation of cells. This may make the terminal fragments particularly vulnerable to adverse intrauterine conditions. Telomere dynamics, specifically inter-individual differences in telomere length, are thought to be largely established during the prenatal and perinatal period, and consequently track throughout the lifecourse (Benetos et al., 2013). The few studies that have explored telomeres in the human fetus have found the absolute within-person telomere length consistent across organs, tissues, and cell types (Kimura et al., 2010) (Okuda et al., 2002) (Youngren et al., 1998). A recent study by Factor-Litvak et al. of leukocyte telomere length among 490 newborn-mother-father triads observed considerable inter-individual variation in the telomere length of newborns; the degree of variation was comparable to that observed among the mothers and fathers, suggesting that variation between adults is in large parts attributable to *in utero* exposures and to genetic factors (Factor-Litvak et al., 2016). This study also reported longer telomeres in girls than in boys (Factor-Litvak et al., 2016), another study similarly suggesting sex differences in hematopoietic cell subsets at birth (Aubert et al., 2012). This difference may be attributable to the influence of hormone exposure on telomere length (Calado et al., 2009). However, not all studies have observed a difference in telomere length at birth by infant sex (Okuda et al., 2002). In spite of the evidence of telomere length heritability from twin and other studies, there has been limited investigation of the correlation between parental and offspring's telomere length. Greater insight into the contributors to telomere length variability during intrauterine life may enhance our understanding of the Developmental Origins of Health and Disease (DOHaD).

The role of hormones or endocrine active substances in telomere shortening is insufficiently understood. Age-adjusted telomere length is longer in women than in men (Benetos et al., 2001) (Jeanclos et al., 2000), consistent with the longer expected lifespan among women compared to men. Some have postulated that a slower rate of telomere attrition explains the telomere sex difference. This view was predicated on the fact that an estrogen-response element is present in the promoter of the catalytic subunit of telomerase; estrogen can potentially stimulate telomerase to attenuate the rate of telomere shortening in premenopausal women, possibly accounting for the sex difference (Bayne et al., 2007).

A recent study by Dalgard et al. suggested that the rate of telomere shortening is faster in premenopausal women than postmenopausal women (Dalgård et al., 2015), and slower in women than men. The authors concluded that the sex difference in telomere length is established early, during periods of growth and development (Dalgård et al., 2015). The findings by Factor-Litvak et al. would also suggest that sex differences are determined as early as at birth (Factor-Litvak et al., 2016).

Similar to endogenous hormones, endocrine disrupting chemicals (EDCs) may also bind and activate steroid receptors. EDCs are ubiquitously found in numerous consumer-based products (Braun et al., 2013). EDCs, such as phthalates and bisphenol A (BPA), have modulated endogenous testosterone and estradiol hormone levels in animal studies (Autian, 1973) (Hannas et al., 2011) (Howdeshell et al., 2007). These chemicals have received significant regulatory and media scrutiny because of their potential to adversely affect human development during gestation, and infancy (Braun et al., 2013). BPA is equipotent with estradiol in activating rapid signaling systems via non-nuclear receptors (Watson et al., 2007). Hence, EDCs may have similar effects as estrogen and protect the telomeres against premature shortening. Conversely, several phthalates and phenols may suppress steroidogenesis, and thereby reduce estrogen concentrations. Indeed, endogenous sex hormones, such as 17β-estradiol, are potent mitogens, which have been suggested to increase mitotic division and subsequently affect the rate of telomeric attrition (De Vivo et al., 2009).

Given the dearth of evidence in this area, we examined the impact of gestational exposure to select EDCs on telomere length at birth and the correlation between maternal and newborn's telomere length in a large prospective birth cohort.

2. Materials and methods

2.1. Study Population

The study population consisted of women who were concurrently enrolled in two large birth cohorts, the Harvard Epigenetic Birth Cohort (HEBC) and the Predictors of Preeclampsia Study (POPS), at the Brigham and Women's Hospital (BWH) in Boston, MA (Michels et al., 2011). The HEBC was initiated to study prenatal determinants of epigenetic markers in cord blood and placenta. The HEBC comprises 1,941 mother-child dyads, and data and biospecimens were collected from June 2007 to June 2009. Cord blood and placenta were collected within 30 minutes of delivery and immediately processed. After umbilical cord and placenta were detached from mother and child, cord blood was collected from the base of the cord and divided into an EDTA and an RNA later tube. All samples were collected and stored in a uniform manner. Maternal blood samples were routinely collected at delivery and made available for research purposes. Initiated in 2007, POPS is a prospective study of women beginning their prenatal care within clinics and private practices affiliated with the Brigham and Women's Hospital (N=1,608). Maternal urine samples were gathered at the first prenatal visit (<16 weeks gestation), and at 4 additional visits during the pregnancy. Additional information about this cohort has been published elsewhere (McElrath et al., 2012). The study population was restricted to 181 mother-child singleton dyads participating

in both the HEBC and POPS, where the mother contributed a first-trimester urine sample between 2007 and 2009, and cord blood was available.

2.2. Urine Sample Collection, Storage and Processing

Urine samples from the first prenatal visit (<16 weeks) were collected in polypropylene urine cups and frozen at −80°C. Subsequently, samples wer e defrosted at 4°C overnight. Each sample was vortex mixed well and specific gravity (SG) was measured at BWH using a handheld refractometer (Atago, Bellevue, WA) that was calibrated with deionized water before each measurement. Urine was aliquoted to 1.6 mL polypropylene tubes and refrozen at −80°C. For each participant, one tube was shipped on dry ice overnight to the Centers for Disease Control and Prevention (CDC) for analysis.

2.3. Quantification of Urinary Biomarkers of Phthalates and Phenols

Urinary concentrations of total (free plus conjugated) species of eight phenols and 11 phthalate metabolites (listed in Tables 2a and 2b) were quantified in 196 urine samples using on-line solid phase extraction-high performance liquid chromatography-isotope dilution-tandem mass spectrometry as described previously (Silva et al., 2008) (Ye et al., 2005). Quality control materials, prepared at the CDC with pooled human urine, were analyzed in each batch along with standards, blank, and study samples. The limits of detection (LOD) ranged from 0.2 to 2.3 ng/mL depending on the analyte. Specific gravity has been proposed as a valid alternative to adjust for dilution over urine creatinine because creatinine levels may be confounded by multiple aspects, such as muscularity, urine flow, and time of day (Adibi et al., 2008) (Hauser et al., 2004). Phenol body burden was estimated by the molar summation of three biomarker classifications: Phenols (all phenols), Parabens, and Non-Parabens. Phthalates body burden was estimated by the molar summation of four metabolites classifications: Phthalates (all phthalates metabolites), high molecular weight (HMW), low molecular weight (LMW), and di-2-ethylhexyl phthalate (DEHP) metabolites.

2.4. DNA Isolation

Maternal blood samples and cord blood samples were collected at birth. Buffy coat was extracted from whole blood and stored in cell lyses solution at −20°C until DNA extraction. Peripheral blood leukocyte DNA was extracted using the QIAmp DNA blood kits (QIAGEN, Venlo, Netherlands). DNA quantity and quality of the 190 cord blood samples and the 183 maternal blood samples was assessed using Nanodrop.

2.5. Real-Time Quantitative PCR for Relative Telomere Length

Average relative telomere length were assessed using Real-Time Quantitative PCR (qPCR) (Cawthon, 2002) at the Dana Farber/Harvard Cancer Center Genotyping and Genetics for Population Sciences. This assay determines the copy-number ratio between telomeric repeats and a single-copy (36B4) reference gene (T/S Ratio, −dCt). The T/S ratio is reflective of the average telomere length across all chromosomes in a population of cells and will be calculated for each participant by subtracting the average 36B4 threshold cycle (Ct) value from the average telomere Ct value. The T/S ratio value for all experimental samples was compared to the T/S ratio of a reference sample, consisting of a pooled genomic DNA

sample. The relative T/S ratio (−ddCt) was determined by subtracting the T/S ratio of the reference sample from the T/S ratio of each unknown sample, and then exponentiating ($2^{-\,-ddCt}$). Although this assay provides a relative measurement of telomere length, ratios of telomere repeat copy number to a single gene copy number highly correlate with absolute telomere lengths determined by Southern blot ($r = 0.68$; $P < 0.001$) (Cawthon, 2002).

A modified version of the qPCR telomere assay was performed in a 384-well format with a 7900HT PCR System (Life Technologies, Carlsbad, CA). Briefly, 5ng of buffy-coat derived genomic DNA was dried down in a 384-well plate and resuspended in 10μL of either the telomere or 36B4 reaction mixture for 2 hours at 4°C. The telomere reaction mixture consists of 1x Quantitect SYBR Green Master Mix (Qiagen, Venlo, Netherlands), 2.5mM of DTT, 270nM of Tel-1 primer-(GGTTTTTGAGGGTGAGGGTGAGGGTGAGGGTGAGGGT), and 900nM of Tel-2 primer-(TCCCGACTATCCCTATCCCTATCCCTATCCCTATCCCTA). The reaction proceeded for 1 cycle at 95°C for 5 min, followed by 40 cycle s at 95°C for 15 sec, and 54°C for 2 min. The 36B4 reaction consists of 1x Quantitect SYBR Green Master Mix, 300nM of 36B4U primer-(CAGCAAGTGGGAAGGTGTAATCC), and 500nM of 36B4D primer-(CCCATTCTATCATCAACGGGTACAA). The 36B4 reaction proceeded for 1 cycle at 95°C for 5 min, followed by 40 cycles at 95°C for 15 sec, and 58°C for 1 min 10 sec. All samples for both the telomere and 36B4 reactions were performed in triplicate on different plates. Each 384-well plate contained a 6-point standard curve from 0.625ng to 20ng to assess PCR efficiency. A slope of −3.40+/−0.15 for the standard curve of both the telomere and 36B4 reactions was considered acceptable. Quality control samples were interspersed throughout the plates in order to assess inter-plate and intra-plate variability of Ct values.

2.6. Statistical Analysis

Data analysis was restricted to singleton births for which we had quantified first trimester maternal EDC urinary biomarkers and offspring telomere length (n=181, mother-infant dyads). Models integrating maternal telomere length were subset to 174 dyads with EDC biomarker measurements, and both maternal and cord blood telomere length estimates. Due to the skewed distribution of relative T/S ratios, estimates were log-transformed in all parametric analyses. Concordantly, we estimated the Spearman correlation between maternal leukocyte and cord blood telomere length. First, we evaluated whether specific maternal or perinatal characteristics were associated with telomere length in cord blood. We regressed each characteristic on log-transformed cord blood telomere length, and reported the relative change in telomere length and associated 95% confidence interval (CI) between characteristic categories or per unit change. Likelihood ratio tests were used to appraise whether infant sex significantly (α-level=0.05) modified the association between each characteristic and cord blood telomere length. Specifically, we compared models for log-transformed cord blood telomere length as a function of individual maternal or perinatal characteristics and infant sex, to models further integrating a product term between that characteristic and infant sex. Likelihood ratio tests were similarly used to assess whether specific maternal or perinatal characteristics modified the association between maternal and cord blood telomere length. We compared models for log-transformed cord blood telomere length as a function log-transformed maternal telomere length, to models further

integrating a main effect for specific maternal or perinatal characteristics and a product term between that characteristic and maternal telomere length. Multivariable linear regression models were used to investigate the association between telomere length at birth and phenols and phthalates exposure estimated from concentrations of their biomarkers in first trimester urine. Similar to the telomere measurements, EDC biomarker concentrations were log-transformed to reduce the influence of outliers on regression coefficient estimates. Log-transformed cord blood telomere length was modeled as a function of each log-transformed EDC biomarker concentration and EDC burden estimate individually, adjusting for maternal age at birth (years; continuous), maternal pre-pregnancy BMI (kg/m^2; continuous), race/ethnicity (white vs. nonwhite), and smoking during pregnancy (yes vs. no). From these models we report the relative change in telomere length and associated 95% CI given a doubling of EDC metabolite concentration, adjusting for the above listed characteristics. Heterogeneity in the association between telomere length and EDC biomarker concentration by infant sex was assessed by adding a product term between EDC concentrations and infant sex to our multivariable models. A likelihood ratio test was used to evaluate whether the product term significantly improved model fit (α-level=0.05), and sex-specific associations between EDC biomarker concentration and telomere length were estimated based on these models. To accommodate more complicated dose-response relationships, we also estimated the relative change in telomere length between quartiles of EDC biomarker concentrations, adjusting for the same characteristics listed above. To evaluate trend across quartiles, the log of the median biomarker concentration within each quartile was included in multivariable models as a continuous variable. Associations between maternal EDC biomarker concentrations and cord blood telomere length could potentially reflect an influence of chronic exposure to specific compounds on maternal gamete telomere length that is inherited by the offspring. We therefore considered sensitivity analyses further adjusting for maternal telomere length. All analysis was conducted in R version 3.5.1.

3. Results

The mean age at delivery of the women included in this study was 33.0 years (S.D. 5.1), with a range of 19–43 years. Table 1 describes the characteristics of the subset of 181 participants included in this study. Tables 2a and 2b describe the EDC biomarkers quantified including LOD, proportion of women with detectable concentrations of EDC biomarkers, and specific gravity-adjusted geometric means. The Spearman correlation between maternal and newborn telomere length was 0.20 (p= 0.0083). Table 3 provides the association between maternal and perinatal characteristics and infant telomere length at birth assessed in cord blood. None of the characteristics assessed was associated with newborn's telomere length. Effect modification by infant sex was observed for conception by assisted reproductive technology (ART), with ART being associated with shorter telomeres compared to spontaneous conceptions in boys. In girls, maternal smoking during pregnancy was associated with longer telomeres, but only five of the 181 mothers smoked during pregnancy, providing instable estimates.

The relative change in cord blood telomere length given a doubling of maternal urinary concentrations of individual biomarkers and summations of specific EDC classes is provided in Table 4. Sex significantly (Wald test; α-level=0.05) modified the association between

several biomarkers and cord blood telomere length, including triclosan and three DEHP metabolites, mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), and mono-2-ethyl-5-carboxypentyl phthalate (MECPP). Among boys, a doubling of first-trimester maternal triclosan concentrations was associated with 3% (95% CI 1% −5%) shorter telomere length at birth, adjusting for maternal age, ethnicity, pre-pregnancy BMI, smoking during pregnancy, gestational age, folic acid use, and use of ART. In other words, male infant telomere length was 3% shorter among mothers with first trimester triclosan concentrations of e.g. 20 ng/mL compared to those with a concentration of 10 ng/mL, holding the adjustment variables constant. In contrast, a doubling of MEHP urinary concentration was associated with 3% (95% CI 0%−6%) longer telomere length in adjusted models that included a statistical interaction between biomarker concentrations and infant sex. Although the relation between MEOHP and MECPP concentrations, respectively, and telomere length trended in a similar direction among boys, the association did not reach statistical significance. Among girls, a doubling of the maternal gestational mono-n-butyl phthalate (MnBP) concentration was associated with 5% longer telomeres (95% CI 0% −10%), but there was no statistically significant effect modification by sex.

For ease of interpretation and to accommodate more complicated dose-response relations, we estimated the relative change in cord blood telomere length comparing each quartile of EDC biomarker concentration to the lowest quartile (Table 5), adjusting for the same covariates as in Table 4. Analogous to our prior models, we evaluated potential effect modification of the relation between quartiles of biomarker concentrations and telomere length by infant sex (likelihood ratio test; α-level=0.05). Sex similarly modified the association between quartiles of triclosan concentrations and telomere length. Compared to boys in the lowest quartile of maternal triclosan concentrations, boys in the highest quartile had 20% (95% CI 5% - 33%) shorter telomeres. Infant sex also modified the association between quartiles of LMW phthalates and telomere length. Girls for whom maternal LMW phthalates was in the second and fourth (highest) quartiles had longer telomeres than girls in the lowest quartile. For both girls and boys, quartile of maternal mono-isobutyl phthalate (MiBP) urinary concentration was associated with telomere length (likelihood ratio test, p=0.02). MiBP concentrations in the highest quartile were associated with 15% (95% CI 2% - 29%) longer telomeres among offspring relative to those in the lowest quartile.

Adjustment for maternal telomere length did not appreciably alter the results. Maternal telomere length was not found to be associated with any of the EDC biomarkers studied (data not shown).

4. Discussion

In this study nested in the Harvard Epigenetic Birth Cohort, we found gestational exposure to select EDCs was associated with the newborn’s telomere length measured in cord blood. In most cases, these associations were sex-specific, with boys more likely affected. Similarly, telomere length in boys was more affected by childhood adversities in a study of Romanian orphans (Drury et al., 2012). We also found modest but significant association between maternal telomere length and newborn’s telomere length; however, adjustment

for maternal telomere length did not markedly attenuate the association between EDC biomarkers and infant telomere length.

The correlation between parental and offspring telomere length has recently garnered attention. Early studies in Sweden and Pennsylvania, USA, suggested a stronger correlation with paternal than maternal telomere length (Njajou et al., 2007) (Nordfjäll et al., 2005) (Nordfjäll et al., 2010). However, a study in Belgium (Nawrot et al. 2004) and a more recent meta-analysis (Broer et al., 2013) of four different populations found a stronger correlation for maternal-offspring telomere length. A subsequent meta-analysis on the available evidence in 2014 found no important difference between maternal and paternal inheritance of telomere length; the study reported a 0.38 maternal-offspring correlation and a 0.36 paternal-offspring correlation (Eisenberg, 2014). Recently, Factor Litvak and colleagues found newborn telomere length stronger associated with mother's than with father's telomere length (Factor-Litvak et al., 2016). While we did not have paternal values available, we did observe a significant correlation of 0.2 with maternal telomere length. These correlations may be related to genetic inheritance or reflect shared environmental exposures. The heterogeneity in the estimated correlation between offspring and parental telomere length between previous studies may in part be due to differences in parental age studied, if the association between parental and offspring telomere length varies with parental age. In our study, maternal age did not modify the association between infant and maternal telomere length, nor was maternal age associated with infant telomere length. Of note, in most studies, offspring's telomere length was not measured at birth, but in childhood or adulthood. Our study therefore fills an important gap in evidence on cord blood telomere length and its correlation with maternal telomere length. It will be interesting to examine the longitudinal structure of this correlation: while the percentile ranking of telomere length in most individuals tracks throughout the lifecourse (Benetos et al., 2013), the two first decades of life have been highlighted as prime phase for faster telomere attrition since they represent a period of heightened susceptibility because of growth and proliferation (Aubert et al., 2012) (Sidorov et al., 2009).

Several studies have related older paternal age at conception with longer telomere in the offspring (Arbeev et al., 2011) (De Meyer et al., 2007) (Kimura et al., 2008) (Njajou et al., 2007) (Unryn et al., 2005), with approximately 15 to 20 base pairs longer telomeres in the offspring for each additional year of paternal age at conception (Aviv and Susser, 2013), suggesting an important role of sperm telomere length in shaping the child's lifelong health. Indeed, Aston and colleagues reported that while leukocytes telomeres in men become shorter with age, sperm telomeres become longer with age, potentially explaining the observed benefit of older paternal age for the newborn's telomere length at birth (Aston et al., 2012). Evidence from the 1946 British Birth Cohort supports a joint effect of parental ages on offspring's telomere length, however, no association was observed for maternal age independent of father's age (Wulaningsih et al., 2018). Conversely, longer leukocyte telomere length was found among infants with a later maternal age at birth of last child (Fagan et al., 2017). In our study, maternal age was not associated with infant telomere length.

Few studies had addressed factors during early life that may affect telomere length. Exposure to a number of gestational exposures including maternal smoking (Ip et al., 2017) (Mirzakhani et al., 2017) (Salihu et al., 2015), high maternal pre-pregnancy BMI (Martens et al., 2016), low birth weight (Lee et al., 2017) (Wojcicki et al., 2016), gestational age (Gielen et al., 2014) (Vasu et al., 2017), low maternal serum folate (Entringer et al., 2015) and low umbilical red blood cell folate (Louis-Jacques et al., 2016), male sex (Okuda et al., 2002) (Wojcicki et al., 2016) were associated with shorter telomere length in the newborn. Only one prior study examined the sex-specificity of these associations, and found differences by maternal smoking and maternal BMI (Bosquet Enlow et al., 2018). We also observed effect modification by sex of the child by maternal smoking but the scarcity of maternal smokers in our cohort does not permit robust conclusions. To our knowledge, the impact of ART conception on telomere length has not been previously studied. Our observation of shorter telomeres among boys conceived by ART compared to spontaneous conceptions needs to be confirmed in other birth cohorts; whether gamete handling during ART might affect telomeres has not been examined.

The effect of gestational exposure to phenols (or their precursors) and phthalates on telomere length at birth has not been previously studied. Exposure to the EDCs polybrominated diphenyl ethers, polychlorinated biphenyls, and per- and polyfluoroalkyl substances, however, has been examined but no important association with telomere length at birth were identified (Zota et al., 2018). The apparent role of sex hormone levels in telomere length makes EDCs likely candidates to influence these markers of cellular aging, in particular during susceptible windows when cellular pluripotency declines. We observed consistent associations with concentrations of triclosan in boys, as well as associations with concentrations of MiBP, and with MEHP in boys.

Triclosan is a ubiquitous non-paraben phenol with antimicrobial properties. Triclosan was detected in the urine of 75% of the U.S. population, presumably from exposure via use of consumer goods and personal care products, including soap, body washes, toothpaste, mouthwash, hand sanitizers, and cosmetics (Weatherly and Gosse, 2017). The U.S. Food and Drug Administration banned triclosan from use in over-the-counter antiseptic wash products in 2016 (U.S. Food & Drug Administration, 2016). Triclosan is absorbed via skin and oral mucosa with peak concentrations occurring between 12 and 18 hours after exposure (Moss et al., 2000) in human tissues and fluids. Exposure to triclosan has been associated with compromised immune function (Clayton et al., 2011), reduced fecundity (Vélez et al., 2015), risk of miscarriage (Wang et al., 2015), and reduced birth weight and birth length (Etzel et al., 2017) (Philippat et al., 2014). Triclosan has been found to display both estrogenic and androgenic activity by competing for and binding to the respective receptors (Gee et al., 2008). We found a 20% shorter telomere length among boys in the highest quartile of maternal gestational triclosan urinary concentration compared to boys in the lowest concentration quartile in adjusted models. If this association is confirmed in other studies, it may be mediated by triclosan’s androgenic activity.

Diisobutyl phthalate is used as plasticizer, solvent, and additive, e.g. in PET bottles. Concentrations of its metabolite, MiBP, have been increasing in the urine of the U.S. population (Centers for Disease Control and Prevention, 2019). We observed an increase in

cord blood telomere length with higher maternal urinary concentrations of MiBP, possibly reflecting hormone receptor activity.

MnBP, the major metabolite of dibutyl phthalate (DBP), a commonly used plasticizer, is prevalent in human biospecimens (Colón et al., 2000) (Zhu et al., 2006). DBP is weakly estrogenic, both DBP and MnBP are antiandrogenic, and show thyroid hormone receptor antagonist activity (Shen et al., 2009). Interestingly, we found longer telomeres in the cord blood of girls with higher maternal gestational MnBP concentrations, however, sex-specific differences were not statistically significant.

MEHP is an active metabolite of DEHP, which is a plasticizer found in many household items such as shower curtains, rainwear, toys, PVC floor tiles. The main exposure to DEHP is dietary, affecting foods during processing and packaging. DEHP induces endocrine disruption in males through its androgen and testosterone antagonistic activity (Araki et al., 2017) (Chen et al., 2017). While DEHP has been associated with lower reproductive function in men (Axelsson et al., 2015), we found positive associations between maternal MEHP with telomere length in boys. While androgen deficiency in adulthood did not affect telomere length in one study (Cheung et al., 2017), the potential interaction of intrauterine androgen and testosterone antagonism and telomere length remains to be explored.

To our knowledge, this is the first study exploring the relation between gestational exposure to select EDCs and telomere length. Limitations of our study include the availability of only one spot urine sample for the assessment of EDCs exposure, which will introduce non-differential misclassification due to random within-person variability of EDC biomarker concentrations. Because several EDCs biomarkers were evaluated, numerous statistical tests were performed, but we did not adjust for multiple comparisons due to the likelihood of random misclassification. Nevertheless, the prospective nature of our study, the considerable sample size, and assessment of a number of relevant covariates lend support to the robustness of its findings. We did not have sufficient statistical power to evaluate effect modification by infrequent maternal characteristics, such as maternal smoking.

5. Conclusions

In conclusion, in this prospective birth cohort we observed inverse associations between male newborn telomere shortening with maternal prenatal exposure to triclosan. Conversely, exposure to several phthalates were positively associated with telomere length. Our sample size was limited, hence our study is hypothesis generating and findings need to be confirmed in other birth cohorts.

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Highlights

- Telomere length is associated with longevity and various diseases
- Telomere length may already be affected by the intrauterine environment
- Intrauterine exposure to endocrine-disrupting chemicals affected telomere length
- Sex-specific differences were noted
- Prenatal exposure to triclosan was associated with 20% shorter telomeres in boys

Table 1.

Characteristics of Study Participants, n=181

Maternal age (years), Mean (SD)	32.81 (5.08)
Infant gender	
Female, N (%)	95 (52.49)
Male, N (%)	86 (47.51)
Maternal race/ethnicity	
White non-Hispanic, N (%)	126 (69.61)
Hispanic or Latino, N (%)	27 (14.92)
Asian/Pacific-Islander, N (%)	5 (2.76)
Black/African-American, N (%)	23 (12.71)
Pre-pregnancy body mass index*, Mean (SD)	25.37 (5.76)
Weight gain during pregnancy (kg), Mean (SD)	15.18 (6.24)
Assisted reproductive technology, N (%)	
No	162 (89.50)
Yes	19 (10.50)
Perinatal folic acid intake (pre- /post-conception), N (%)	
Yes/Yes	122 (67.40)
No/Yes	54 (29.83)
No/No	5 (2.76)
Smoking during pregnancy, N (%)	
No	176 (97.24)
Yes	5 (2.76)
Length of gestation (weeks), Mean (SD)	38.96 (1.26)
Birth weight (grams), Mean (SD)	3463.71 (459.31)
Birth length (cm), Mean (SD)	49.44 (2.37)

Table 2a.

Descriptive statistics for urine concentrations of phenols during the first trimester, n=181, Harvard Epigenetic Birth Cohort

Phenol biomarker	Abbrev.	Paraben Yes/No	LOD (ng/mL)	GM (ng/mL)
2,4-dichlorophenol	2,4-DCP	No	0.2	0.60
2,5-dichlorophenol	2,5-DCP	No	0.2	4.04
Benzophenone-3	BP-3	No	0.4	94.47
Bisphenol A	BPA	No	0.4	1.37
Butyl Paraben	BuPB	Yes	0.2	1.79
Methyl Paraben	MePB	Yes	1.0	182.24
Propyl Paraben	PrPB	Yes	0.2	43.20
Triclosan	TCS	No	2.3	16.05

Concentrations <LOD were assigned a value equal to one-half the LOD. Abbreviations: GM, geometric mean; LOD, limit of detection

Table 2b.

Descriptive statistics for urine concentrations of phthalates during the first trimester, n=181, Harvard Epigenetic Birth Cohort

Phthalate biomarker	Abbrev.	High/ Low MW	Parent Compound	LOD (ng/mL)	GM (ng/mL)
Mono-isobutyl phthalate	MiBP	Low	Diisobutyl *phthalate* (DiBP)	0.6	5.78
Mono-n-butyl phthalate	MnBP	Low	Dibutyl *phthalate* (DnBP)	0.6	13.14
Monoethyl phthalate	MEP	Low	Diethyl *phthalate* (DEP)	0.8	84.58
Mono-2-ethyl-5-carboxypentyl phthalate	MECPP	High	Di-2-ethylhexyl phthalate (DEHP)	0.6	42.71
Mono-2-ethyl-5-hydroxyhexyl phthalate	MEHHP	High	DEHP	0.7	30.85
Mono-2-ethylhexyl phthalate	MEHP	High	DEHP	1.2	4.43
Mono-2-ethyl-5-oxohexyl phthalate	MEOHP	High	DEHP	0.7	18.85
Mono-3-carboxypropyl phthalate	MCPP	High	Dioctyl *phthalate* (DOP)	0.2	1.44
Monocarboxyoctyl phthalate	MCOP	High	Diisononyl *phthalate* (DiNP)	0.7	6.86
Monocarboxynonyl phthalate	MCNP	High	Diisodecyl *phthalate* (DiDP)	0.6	1.99
Monobenzyl phthalate	MBzP	High	Benzylbutyl *phthalate* (BzBP)	0.3	5.43

Concentrations <LOD were assigned a value equal to one-half the LOD. Abbreviations: GM, geometric mean; LOD, limit of detection; MW, molecular weight

Table 3.

Association between maternal and perinatal characteristics and relative infant telomere length (95% CI) at birth assessed in cord blood

Characteristic	N	Overall[A]	Girls[B] (95% CI)	Boys[B] (95% CI)	P-value for interaction[C]
Maternal age (per year)	181	1.00 (1.00, 1.01)	1.00 (0.99, 1.02)	1.00 (0.99, 1.01)	0.75
Sex					
Female (Ref)	95	--	--	--	--
Male	86	1.01 (0.94, 1.09)	--	--	--
Race					
White (Ref)	126	--	--	--	0.99
Non-white	55	1.05 (0.97, 1.14)	1.05 (0.94, 1.18)	1.05 (0.94, 1.19)	
Pre-pregnancy BMI					
Normal/underweight (Ref)	102				0.27
Overweight/Obese	79	0.97 (0.90, 1.05)	1.01 (0.91, 1.12)	0.93 (0.83, 1.03)	
Weight gain during pregnancy (per 1 kg)	175	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.01 (1.00, 1.02)	0.50
Assisted Reproductive technology					
No (Ref)	162	--	--	--	0.00
Yes	19	0.92 (0.81, 1.04)	1.11 (0.94, 1.31)	0.74 * (0.62, 0.88)	
Perinatal folic acid intake (pre- /post-conception)					
Yes/Yes (Ref)	122	--	--	--	0.66
No/Yes	54	1.03 (0.95, 1.12)	1.00 (0.89, 1.13)	1.06 (0.94, 1.19)	
No/No	5	1.05 (0.83, 1.32)	1.33 (0.80, 2.23)	0.99 (0.76, 1.29)	
Smoking during pregnancy					
No (Ref)	176	--	--	--	0.01
Yes	5	1.03 (0.82, 1.30)	1.46 * (1.02, 2.09)	0.82 (0.61, 1.10)	
Length of gestation (in weeks)	181	0.98 (0.96, 1.01)	0.99 (0.95, 1.04)	0.97 (0.93, 1.02)	0.49
Birth weight (per 100 grams)	181	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	0.83
Birth length (per 10 cm)	174	0.99 (0.84, 1.16)	0.84 (0.66, 1.08)	1.11 (0.89, 1.38)	0.10

[A] Reporting relative change (95%CI) in cord blood telomere length associated with each maternal or perinatal characteristic

[B] Same as above model, but incorporating a product term between maternal/perinatal characteristic and infant sex, assuming effect measure modification by infant sex

[C] P-value for likelihood ratio test comparing model with to model without product term between characteristic and infant sex

* Indicates statistical significance at the 0.05 level

Table 4.

Relative change (95%CI) in cord blood telomere length associated with a doubling of gestational maternal concentration of EDC biomarkers among 181 infants in the HEBC

EDC biomarker	Overall[A]	Girls[B]	Boys[B]	P for interaction by sex[C]
Phenols	1.01 (0.99, 1.03)	0.99 (0.95, 1.02)	1.03 (0.99, 1.06)	0.10
Phenols - non parabens	1.01 (0.99, 1.02)	1.00 (0.98, 1.02)	1.01 (0.99, 1.04)	0.45
2,4-DCP	1.00 (0.98, 1.03)	1.01 (0.98, 1.05)	0.99 (0.95, 1.02)	0.23
2,5-DCP	1.01 (1.00, 1.03)	1.01 (0.99, 1.04)	1.01 (0.99, 1.04)	0.94
BP-3	1.01 (1.00, 1.02)	1.00 (0.98, 1.02)	1.02 (1.00, 1.04)	0.21
BPA	0.98 (0.95, 1.02)	1.00 (0.95, 1.04)	0.97 (0.92, 1.02)	0.39
Phenols - parabens	1.01 (0.98, 1.03)	0.99 (0.96, 1.02)	1.02 (0.99, 1.05)	0.23
BuPB	0.99 (0.98, 1.00)	0.99 (0.97, 1.00)	1.00 (0.98, 1.02)	0.30
MePB	1.01 (0.99, 1.03)	1.00 (0.97, 1.03)	1.02 (0.99, 1.05)	0.30
PrPB	1.00 (0.99, 1.02)	0.99 (0.97, 1.02)	1.01 (0.99, 1.04)	0.25
TCS	1.00 (0.98, 1.01)	1.01 (1.00, 1.03)	0.97*(0.95, 0.99)	0.00
Phthalates	1.00 (0.97, 1.03)	0.99 (0.96, 1.03)	1.02 (0.98, 1.06)	0.36
LMW phthalates	1.00 (0.98, 1.03)	1.00 (0.97, 1.03)	1.00 (0.96, 1.03)	0.78
MiBP	1.03 (1.00, 1.06)	1.04 (0.99, 1.08)	1.03 (0.98, 1.07)	0.74
MnBP	1.03 (1.00, 1.06)	1.05*(1.00, 1.10)	1.01 (0.97, 1.05)	0.20
MEP	1.00 (0.98, 1.02)	1.00 (0.98, 1.03)	1.00 (0.97, 1.03)	0.77
HMW phthalates	1.01 (0.99, 1.04)	0.99 (0.95, 1.03)	1.03 (1.00, 1.07)	0.09
DEHP	1.01 (0.98, 1.03)	0.98 (0.95, 1.01)	1.03 (1.00, 1.07)	0.03
MECPP	1.01 (0.98, 1.03)	0.98 (0.94, 1.01)	1.03 (1.00, 1.07)	0.02
MEHHP	1.01 (0.99, 1.03)	0.99 (0.96, 1.02)	1.03 (1.00, 1.06)	0.06
MEHP	1.01 (0.99, 1.03)	0.99 (0.96, 1.01)	1.03*(1.00, 1.06)	0.02
MEOHP	1.01 (0.99, 1.03)	0.98 (0.95, 1.02)	1.03 (1.00, 1.06)	0.04
MCPP	1.01 (0.98, 1.03)	1.01 (0.98, 1.05)	1.00 (0.97, 1.03)	0.61
MCOP	1.01 (0.98, 1.03)	1.01 (0.98, 1.05)	1.00 (0.97, 1.04)	0.77
MCNP	1.00 (0.97, 1.02)	1.03 (0.98, 1.07)	0.98 (0.94, 1.01)	0.07
MBzP	1.02 (0.99, 1.04)	1.03 (1.00, 1.06)	1.01 (0.98, 1.04)	0.26

[A] Reporting relative change (95%CI) in cord blood telomere length associated with a doubling of intrauterine exposure to specified EDC biomarker, adjusting for maternal age (years), ethnicity (white/non-white), pre-pregnancy BMI (kg/m^2), smoking during pregnancy (yes/no), gestational age (weeks), folic acid intake (pre-/post-conception; yes/yes, no/yes, no/no), use of assisted reproductive technology (yes/no), and infant sex (male/female)

[B] Same as above model, but incorporating a product term between EDC biomarker concentration and infant sex, assuming effect measure modification by infant sex

[C] P-value for likelihood ratio test comparing model with to model without product term between EDC biomarker concentration and infant sex

* Indicates statistical significance at the 0.05 level

Table 5.

Relative change (95%CI) in cord blood telomere length between quartiles of gestational maternal concentrations of EDC biomarkers among 181 infants in the HEBC

EDC biomarker		LRT[A]	Overall[B]	Girls[C]	Boys[C]	P for interaction by sex[D]
Phenols	Q2	0.63	0.95 (0.85, 1.06)	0.92 (0.79, 1.06)	0.98 (0.84, 1.16)	0.45
	Q3		0.95 (0.85, 1.06)	0.89 (0.76, 1.04)	1.02 (0.87, 1.19)	
	Q4		1.00 (0.90, 1.12)	0.93 (0.80, 1.08)	1.09 (0.92, 1.29)	
	Trend(p-value)		0.96	0.36	0.29	
Phenols - not parabens	Q2	0.55	0.97 (0.87, 1.08)	1.07 (0.91, 1.25)	0.88 (0.76, 1.03)	0.16
	Q3		0.99 (0.89, 1.11)	1.00 (0.86, 1.17)	0.98 (0.83, 1.15)	
	Q4		1.04 (0.93, 1.17)	1.03 (0.88, 1.19)	1.07 (0.91, 1.26)	
	Trend(p-value)		0.32	0.88	0.2	
2,4-DCP	Q2	0.62	0.95 (0.85, 1.07)	0.97 (0.83, 1.14)	0.94 (0.80, 1.11)	0.33
	Q3		0.93 (0.83, 1.05)	1.02 (0.87, 1.20)	0.85 (0.72, 1.00)	
	Q4		0.98 (0.88, 1.10)	1.03 (0.87, 1.22)	0.94 (0.81, 1.10)	
	Trend(p-value)		0.77	0.51	0.31	
2,5-DCP	Q2	0.59	0.95 (0.85, 1.06)	1.00 (0.87, 1.16)	0.89 (0.75, 1.05)	0.61
	Q3		1.03 (0.91, 1.16)	1.06 (0.91, 1.24)	0.99 (0.84, 1.17)	
	Q4		1.01 (0.89, 1.14)	1.01 (0.86, 1.18)	1.01 (0.85, 1.19)	
	Trend(p-value)		0.72	0.97	0.61	
BP-3	Q2	0.49	1.04 (0.93, 1.17)	1.20* (1.02, 1.41)	0.92 (0.79, 1.07)	0.01
	Q3		1.05 (0.93, 1.18)	1.08 (0.93, 1.26)	0.99 (0.84, 1.17)	
	Q4		1.09 (0.97, 1.23)	1.05 (0.89, 1.24)	1.14 (0.97, 1.33)	
	Trend(p-value)		0.16	0.94	0.04	
BPA	Q2	0.16	1.00 (0.90, 1.12)	1.03 (0.88, 1.20)	0.97 (0.82, 1.14)	0.90
	Q3		0.98 (0.88, 1.10)	1.02 (0.88, 1.18)	0.94 (0.79, 1.11)	
	Q4		0.90 (0.80, 1.01)	0.92 (0.78, 1.08)	0.87 (0.74, 1.03)	
	Trend(p-value)		0.07	0.35	0.08	
Phenols - parabens	Q2	0.96	1.00 (0.89, 1.11)	1.02 (0.87, 1.18)	1.00 (0.85, 1.18)	0.35
	Q3		1.02 (0.92, 1.14)	0.95 (0.82, 1.10)	1.11 (0.94, 1.31)	
	Q4		1.01 (0.91, 1.13)	0.98 (0.85, 1.13)	1.07 (0.90, 1.28)	
	Trend(p-value)		0.71	0.61	0.23	
BuPB	Q2	0.36	0.97 (0.87, 1.08)	1.03 (0.90, 1.19)	0.90 (0.75, 1.07)	0.14
	Q3		0.96 (0.86, 1.07)	0.93 (0.80, 1.08)	0.98 (0.83, 1.17)	
	Q4		0.90 (0.81, 1.02)	0.86 (0.74, 1.01)	0.93 (0.78, 1.11)	
	Trend(p-value)		0.11	0.04	0.87	
MePB	Q2	0.94	1.01 (0.90, 1.13)	1.01 (0.87, 1.19)	1.04 (0.88, 1.24)	0.52
	Q3		1.01 (0.91, 1.13)	0.96 (0.83, 1.10)	1.11 (0.92, 1.32)	
	Q4		1.03 (0.92, 1.16)	0.99 (0.85, 1.15)	1.11 (0.92, 1.34)	

EDC biomarker		LRT[A]	Overall[B]	Girls[C]	Boys[C]	P for interaction by sex[D]
	Trend(p-value)		0.58	0.73	0.18	
PrPB	Q2	0.95	1.00 (0.89, 1.11)	1.03 (0.89, 1.21)	0.97 (0.83, 1.14)	0.32
	Q3		0.98 (0.88, 1.10)	1.01 (0.87, 1.18)	0.95 (0.80, 1.13)	
	Q4		1.01 (0.91, 1.13)	0.97 (0.84, 1.11)	1.09 (0.91, 1.30)	
	Trend(p-value)		0.9	0.67	0.47	
TCS	Q2	0.59	0.99 (0.88, 1.11)	1.01 (0.87, 1.18)	0.93 (0.79, 1.10)	0.01
	Q3		0.93 (0.83, 1.05)	1.00 (0.86, 1.17)	0.84 * (0.71, 0.99)	
	Q4		0.98 (0.88, 1.10)	1.13 (0.98, 1.30)	0.80 * (0.67, 0.95)	
	Trend(p-value)		0.74	0.07	0.01	
Phthalates	Q2	0.99	1.02 (0.91, 1.14)	1.03 (0.88, 1.19)	1.01 (0.85, 1.20)	0.41
	Q3		1.01 (0.90, 1.13)	1.05 (0.90, 1.24)	0.98 (0.83, 1.15)	
	Q4		1.02 (0.90, 1.16)	0.98 (0.83, 1.15)	1.08 (0.90, 1.30)	
	Trend(p-value)		0.82	0.68	0.4	
LMW phthalates	Q2	0.31	1.05 (0.94, 1.18)	1.25 * (1.07, 1.45)	0.84 (0.72, 1.00)	0.00
	Q3		0.97 (0.87, 1.08)	1.03 (0.87, 1.22)	0.92 (0.80, 1.06)	
	Q4		1.07 (0.95, 1.21)	1.18 * (1.01, 1.37)	0.97 (0.82, 1.15)	
	Trend(p-value)		0.48	0.27	0.85	
MiBP	Q2	0.02	1.10 (0.99, 1.23)	1.11 (0.94, 1.31)	1.10 (0.95, 1.27)	0.96
	Q3		1.00 (0.90, 1.13)	1.02 (0.87, 1.19)	1.00 (0.85, 1.18)	
	Q4		1.15 * (1.02, 1.29)	1.18 (1.00, 1.39)	1.11 (0.95, 1.31)	
	Trend(p-value)		0.07	0.11	0.32	
MnBP	Q2	0.55	0.99 (0.88, 1.10)	1.01 (0.87, 1.18)	0.97 (0.82, 1.14)	0.9
	Q3		1.02 (0.91, 1.13)	1.05 (0.90, 1.23)	0.98 (0.84, 1.15)	
	Q4		1.07 (0.95, 1.21)	1.11 (0.94, 1.31)	1.03 (0.87, 1.22)	
	Trend(p-value)		0.28	0.18	0.79	
MEP	Q2	0.25	1.07 (0.96, 1.19)	1.18 * (1.02, 1.37)	0.93 (0.79, 1.10)	0.17
	Q3		0.96 (0.86, 1.07)	0.99 (0.84, 1.17)	0.92 (0.79, 1.07)	
	Q4		1.04 (0.93, 1.17)	1.09 (0.95, 1.27)	0.99 (0.83, 1.18)	
	Trend(p-value)		0.83	0.61	0.78	
HMW phthalates	Q2	0.37	1.10 (0.98, 1.23)	1.21 * (1.04, 1.42)	1.00 (0.84, 1.18)	0.02
	Q3		1.08 (0.97, 1.21)	1.03 (0.89, 1.18)	1.16 (0.98, 1.38)	
	Q4		1.08 (0.96, 1.21)	1.05 (0.90, 1.23)	1.10 (0.93, 1.30)	
	Trend(p-value)		0.31	0.98	0.14	
DEHP	Q2	0.79	1.03 (0.92, 1.16)	1.01 (0.87, 1.18)	1.05 (0.88, 1.24)	0.06
	Q3		1.00 (0.89, 1.12)	1.03 (0.88, 1.20)	0.97 (0.82, 1.15)	
	Q4		1.04 (0.93, 1.17)	0.93 (0.79, 1.09)	1.16 (0.98, 1.37)	
	Trend(p-value)		0.57	0.31	0.07	
MECPP	Q2	0.81	1.04 (0.93, 1.16)	1.03 (0.89, 1.20)	1.06 (0.89, 1.25)	0.12

EDC biomarker		LRT[A]	Overall[B]	Girls[C]	Boys[C]	P for interaction by sex[D]
	Q3		1.02 (0.91, 1.13)	1.02 (0.88, 1.17)	1.03 (0.86, 1.22)	
	Q4		1.05 (0.94, 1.18)	0.93 (0.80, 1.09)	1.17 (0.99, 1.38)	
	Trend(p-value)		0.49	0.33	0.05	
MEHHP	Q2	0.78	1.06 (0.94, 1.18)	1.04 (0.90, 1.22)	1.08 (0.91, 1.28)	0.18
	Q3		1.04 (0.92, 1.16)	1.05 (0.90, 1.23)	1.03 (0.86, 1.22)	
	Q4		1.05 (0.94, 1.18)	0.96 (0.82, 1.12)	1.16 (0.97, 1.37)	
	Trend(p-value)		0.57	0.5	0.13	
MEHP	Q2	0.49	0.93 (0.82, 1.04)	0.90 (0.76, 1.05)	0.95 (0.81, 1.12)	0.45
	Q3		0.98 (0.88, 1.10)	0.94 (0.81, 1.09)	1.02 (0.87, 1.21)	
	Q4		0.99 (0.88, 1.11)	0.90 (0.77, 1.07)	1.08 (0.92, 1.26)	
	Trend(p-value)		0.68	0.42	0.18	
MEOHP	Q2	0.67	1.05 (0.93, 1.17)	1.05 (0.90, 1.22)	1.05 (0.89, 1.24)	0.08
	Q3		1.00 (0.89, 1.12)	1.05 (0.90, 1.23)	0.96 (0.81, 1.13)	
	Q4		1.05 (0.94, 1.18)	0.97 (0.83, 1.13)	1.15 (0.97, 1.36)	
	Trend(p-value)		0.51	0.52	0.11	
MCPP	Q2	0.17	1.13 * (1.01, 1.26)	1.16 (0.99, 1.36)	1.11 (0.94, 1.30)	0.9
	Q3		1.07 (0.96, 1.20)	1.12 (0.95, 1.32)	1.03 (0.87, 1.21)	
	Q4		1.07 (0.96, 1.20)	1.09 (0.92, 1.29)	1.05 (0.90, 1.23)	
	Trend(p-value)		0.49	0.57	0.68	
MCOP	Q2	0.47	1.06 (0.94, 1.19)	1.11 (0.95, 1.30)	0.99 (0.84, 1.18)	0.73
	Q3		0.99 (0.89, 1.11)	1.00 (0.86, 1.17)	0.99 (0.84, 1.16)	
	Q4		1.06 (0.95, 1.18)	1.07 (0.92, 1.24)	1.05 (0.90, 1.23)	
	Trend(p-value)		0.48	0.75	0.5	
MCNP	Q2	0.44	0.92 (0.83, 1.03)	0.85 * (0.72, 0.99)	1.01 (0.87, 1.17)	0.18
	Q3		0.99 (0.88, 1.10)	0.99 (0.85, 1.15)	0.98 (0.83, 1.15)	
	Q4		0.98 (0.88, 1.10)	0.99 (0.85, 1.16)	0.96 (0.82, 1.13)	
	Trend(p-value)		0.97	0.53	0.54	
MBzP	Q2	0.21	0.95 (0.85, 1.07)	1.09 (0.93, 1.28)	0.83 * (0.71, 0.97)	0.06
	Q3		1.00 (0.89, 1.12)	1.10 (0.94, 1.29)	0.92 (0.79, 1.08)	
	Q4		1.07 (0.95, 1.20)	1.13 (0.96, 1.33)	1.05 (0.90, 1.23)	
	Trend(p-value)		0.17	0.21	0.44	

[A] Modeling the relative change in cord telomere length comparing each quartile of EDC biomarker concentration to the lowest quartile, adjusting for maternal age (years), ethnicity (white/non-white), pre-pregnancy BMI (kg/m^2), smoking during pregnancy (yes/no), gestational age (weeks), folic acid intake (pre-/post-conception; yes/yes, no/yes, no/no), use of assisted reproductive technology (yes/no), and infant sex (male/female). Reporting the likelihood ratio test (p-value) comparing the model with quartiles of EDC concentrations to one without

[B] Same as above model, reporting the adjusted relative change (95% CI) in cord telomere length comparing each quartile of EDC biomarker concentration to the lowest quartile. To evaluate trend across categories, we modeled the median log-transformed concentration within each quartile as a linear measure in our adjusted models.

[C] Same as above model, but incorporating a product terms between EDC biomarker quartile and infant sex. To evaluate difference in trend across categories by infant sex, we incorporated an product term between median log-transformed concentration within each quartile and infant sex in our adjusted models.

[D] Likelihood ratio test (p-value) comparing our model without product terms between EDC biomarker quartile and infant sex to our model with these terms

* Indicates statistical significance at the 0.05 level