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Maternal telomere length and oxidative stress in pregnancy: cross-sectional analysis with an exploratory examination of systemic inflammation

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Abstract

Background Telomere length (TL) is a marker of cellular aging associated with risk for age-related diseases and is known to be influenced by various factors, including oxidative stress and inflammation, in the contexts of stress and aging. The physiological demands of pregnancy may impact maternal TL, though research in this area is sparse. We tested oxidative stress and explored inflammation as predictors of maternal TL in a sample of women with normative pregnancies.

Methods Participants ($N = 88$, aged 18 to 46 years, 25% non-Hispanic Black, 65% non-Hispanic White) were recruited during their 2nd or 3rd trimester. TL was measured using saliva via qPCR as absolute TL. Oxidative stress was derived from principal component analysis of selected metabolites measured via urinary metabolomics. Inflammation was quantified as total IL-6 in serum. Hypotheses were tested with stepwise generalized linear models.

Results Longer TL was predicted by higher oxidative stress ($b = 0.20 \pm 0.08$; $P = .019$), controlling for maternal age, gestational age, race/ethnicity, maternal BMI, and income-to-needs ratio. In our exploratory analysis, longer TL was also predicted by higher IL-6 ($b = 0.76 \pm 0.20$; $P = .0003$) controlling for covariates. There was no significant interaction between oxidative stress and inflammation predicting TL.

Conclusion Our findings suggest that in normative pregnancies, both oxidative stress and inflammation are independently associated with longer telomere length. Given that these associations are inconsistent with the role of oxidative stress and inflammation on telomere biology in non-pregnant samples, future work should aim to replicate these findings in both normal and high-risk pregnancies, explore mechanisms underlying these associations using longitudinal designs, and examine how these relationships influence maternal and fetal health.

Keywords Telomere length, Oxidative stress, Inflammation, Pregnancy, Biological aging

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Background

The physiological demands of pregnancy necessitate significant adaptations in various body systems, including the cardiovascular, metabolic, and immune systems. These adaptations can unmask preexisting subclinical conditions or create new physiological strains that may have lasting effects on maternal health [1, 2]. Cellular aging measures, such as telomere length (TL), may assist in identifying women at risk for future disease due to the demands of pregnancy [3, 4]. Shorter TL is associated with risk for age-related diseases and, in the context of stress and aging, is influenced by various factors thought to be exacerbated during pregnancy including oxidative stress and inflammation [5, 6]. Research on TL and the interplay between oxidative stress and inflammation during pregnancy may provide an important window into understanding how pregnancy-induced physiological changes impact long-term maternal health.

The physiological demands of pregnancy may directly impact maternal TL, though extant research in this area is sparse and mixed [4, 7]. Among studies examining maternal TL during pregnancy, several found no within-person differences in TL from early to late pregnancy [8–10]; one study found an increase in TL across pregnancy, particularly for women under age 35 [11]. Cross-sectionally, the relationship between TL and parity among women is mixed, though theory suggests reproduction should exert a cost on the cellular systems responsible for maintaining TL, leading to shorter telomeres with parity [7, 12]. It is not known whether parity-related TL shortening would occur during pregnancy, postpartum, or across the lifespan as an increased rate of cellular aging.

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and antioxidants, may increase during pregnancy due to heightened metabolic activity [13]. ROS can damage cellular components, including DNA, leading to telomere shortening [14]. Elevated systemic oxidative stress levels during pregnancy may reflect the balance between ROS generated by maternal adaptations to the placenta and the maternal antioxidant capacity [15, 16]. Quantification of oxidative stress during pregnancy may vary based on gestational age, specific metabolites analyzed, and the presence of pregnancy-associated conditions such as preeclampsia [16–18]. For instance, Ferguson et al. [17] found that while 8-isoprostane, a marker of lipid peroxidation, remained relatively constant, 8-hydroxydeoxyguanosine (8-OHdG), a marker of oxidative DNA damage, steadily increased throughout pregnancy.

The relationship between TL and oxidative stress is further complicated by the role of inflammation. In non-pregnant populations, inflammation can increase ROS production and interfere with antioxidant defenses and chronically elevated systemic inflammation can lead to persistent oxidative stress and accelerated telomere shortening [14]. During pregnancy, inflammation is necessary for healthy fetal development and parturition, and thus must be balanced to tolerate the developing fetus while maintaining maternal protective functions [19]. Where maternal and fetal tissues meet, inflammatory profiles shift across different stages of pregnancy [20]. At the maternal-fetal interface, early pregnancy is characterized by a pro-inflammatory state necessary for implantation, whereas mid to late pregnancy is associated with an anti-inflammatory state to support fetal growth [21, 22]. Systemically, levels of maternal inflammation may change across pregnancy, with some research findings mirroring what is observed at the maternal-fetal interface (i.e., switch from a pro- to anti-inflammatory state across pregnancy) [23] and other research finding a general increase in systemic inflammation as pregnancy progresses [16]. In addition to the influence of timing of measurement with respect to gestation, differences in findings may depend on the specific markers of inflammation measured (e.g., neutrophil-lymphocyte ratio, interleukins, or C-reactive protein), or the specific tissue sampled [17, 23, 24].

The interplay between oxidative stress, inflammation, and TL during pregnancy may provide insights into long-term health risks for mothers. For example, chronic conditions such as hypertension and diabetes, which are influenced by oxidative stress and inflammation, may be linked to telomere dynamics during pregnancy [25, 26]. In this study, we examined oxidative stress and inflammation as predictors of maternal TL in a cohort of women recruited during their 2nd or 3rd trimester of pregnancy. We hypothesized that increased oxidative stress during pregnancy would be predictive of shorter TL, reflecting the physiological strain of pregnancy. Further, we explored the relationship between inflammation and TL during pregnancy, and hypothesized that oxidative stress and inflammation, being interrelated processes, might have interactive effects on maternal TL, with the combination of high oxidative stress and high inflammation predicting the shortest TL.

Materials and methods

Study design and sample recruitment

Our analytic sample was drawn from the ongoing Brain and Early Experiences (BEE) study, a prospective longitudinal study on the health and development of a racially and ethnically diverse cohort of pregnant women and their infants. For complete information on the BEE recruitment protocols and data collection procedures, see Mills-Koonce et al. [27] Briefly, women in their 2nd or 3rd trimester of pregnancy were recruited using advertisements throughout central North Carolina, USA from August 2018 through October 2020. Eligibility

criteria included: (1) singleton pregnancy, (2) primarily English-speaking at home and (3) living within a 45-minute radius of the study location. Women meeting the eligibility criteria were further screened into one of four groups to reduce confounding between socioeconomic status (SES) and racial identification: low-SES and non-Black racial identification, high-SES and non-Black racial identification, low-SES and Black racial identification, and high SES and Black racial identification.

After recruitment, participating women were invited for a prenatal laboratory visit to the Biobehavioral Laboratory at the University of North Carolina (UNC) at Chapel Hill School of Nursing for collection of biological specimens and psychosocial data. The University of North Carolina at Chapel Hill Institutional Review Board (#17-1914) approved the study, and informed consent was obtained from all participants. Of 233 participants who completed the prenatal visit, 113 provided saliva collection and consent for TL analysis, and 88 samples had sufficient DNA surviving quality control measures for TL analysis. These 88 participants comprise our final TL analytic sample. Summary statistics for both the full BEE prenatal cohort and our analytic sample are provided in Table 1.

Telomere length measurement via qPCR

TL was assessed using quantitative polymerase chain reaction (qPCR) on DNA extracted from saliva collected via passive drool using QIAamp DNA Mini Kit (Qiagen). The full Telomere Research Network guidelines for reporting are included in Supplemental File S1. Briefly, using a Rotor-Gene Q thermocycler connected to an uninterruptible power supply, two runs per qPCR assay were conducted – one quantifying telomere content (T) and one quantifying genome copy number (S) using the single copy gene *IFNBI* [28–30]. Standards for telomeric DNA contained known concentrations of 84 bp double-stranded oligomers with 16 copies of telomeric repeat (TTAGGG). Standards for genome copy number contained known concentrations of 83 bp double-stranded oligomers with a sequence corresponding to the *IFNB1* genomic region flanked by *IFNB1* primers. Comparison of telomeric content (T) to genome copy number (S) allowed for quantification of sample TL in an absolute unit of kilobase pairs.

Table 1 Descriptive statistics for full BEE study cohort and TL analytic sample

Variable, mean (SD)	Full Cohort (*N* = 233)	TL Analytic Sample (*N* = 88)	*p*-val
Age (years)	30.7 (5.43)	31.4 (5.3)	0.10
Gestational Age (days)	203 (27)	203 (27)	0.81
Pre-pregnancy BMI	27.7 (7.3)	27.5 (6.6)	0.77
Income to Needs Ratio	3.66 (3.5)	4.01 (2.8)	0.030
Primary Race/Ethnicity			
Black	82 (35%)	22 (25%)	0.09
White	128 (55%)	57 (65%)	0.14
Other	23 (9.9%)	9 (10%)	0.99

Inflammatory measurement via ELISA

For our exploratory analysis of inflammation, a subsample ($N = 122$) of women from the full BEE study completed the prenatal laboratory visit prior to the COVID-19 pandemic and had blood samples available for inflammatory measurement. Of these 122 women, 44 had both TL data and inflammatory data. Blood was collected via venipuncture in 2 mL EDTA tubes by a trained phlebotomist. Samples were immediately stored on ice before being centrifuged for 10 min at 2000 x g at 4 °C. 1 mL of serum was aliquoted into vials and stored at -80 °C. IL-6 concentration was determined using an electrochemiluminescence platform and quantified with the MESO QuickPlex SQ120 (Meso Scale Discovery, Gaithersburg, MD). Based on initial correlations with TL and the established relationship between IL-6 and adverse pregnancy outcomes [31], IL-6 was selected for downstream analysis from a 6-plex inflammatory panel assay (see Supplemental File S2). The intra-assay CV for IL-6 was 4.93% and the lower limit of detection was 0.06 pg/mL.

Oxidative stress measurement via NMR

Non-fasting prenatal urine samples were collected from all participants during their prenatal visit and transferred to The Pennsylvania State University for metabolomic profiling via nuclear magnetic resonance (NMR) spectroscopy. For each sample, 500 µl urine was mixed with 14 µl KF (5 M) and vortexed for 10 s followed by centrifugation at 12000 g for 20 min at 4 °C. 450 µl of supernatant was transferred into 5 mm 4" long SampleJet NMR tubes containing 8.3 µl EDTA-d12 (0.12 M). 45 µl PBS (1.5 M), pH 7.4, prepared in 100% D2O with 0.005% TSP (trimethyl silylpropanoic acid, w/v, NMR internal standard) was added into NMR tubes and mixed. NMR spectra were recorded using a Bruker's 600 MHz Instrument equipped with an AVANCE NEO console, a helium-cooled z-gradient triple resonance (1 H,13 C,15 N) inverse cryoprobe (all channel preamps are cooled) and a SampleJet autosampler. The one-dimensional [1]H spectra were acquired using Bruker's standard water suppression, 1D NOESY with presaturation and spoil gradients (noesygppr1d) pulse sequence with 96 scans and 64k data points over a spectral width of 9615 Hz. Acquisition time was 3.4 s and relaxation delay was 12 s. The experiments were performed in an automated fashion using Bruker's ICONNMR software at 298 K.

Data were processed employing TopSpin 4.1.4 (Bruker BioSpin Inc) software. multiple 1 H-NMR spectra were

overlaid using Chenomx NMR Suite Professional software package version 10.0 (Chenomx Inc., Edmonton, AB) and consistent peaks across samples were identified. Each identified peak was assigned to its respective metabolite (see Supplemental File S3 for details). All concentrations were normalized to creatinine abundance (μM of metabolite / mM of creatinine).

To construct the final oxidative stress variable, we selected a set of metabolites associated with oxidative stress. These metabolites were selected for their roles in oxidative pathways, redox reactions, and oxidative damage, as well as their involvement in mitochondrial dysfunction, protein oxidation, and DNA damage. The metabolites included were 1-Methylnicotinamide, 2-Aminoadipate, 3-Indoxylsulfate, Dimethylamine, Formate, Methylguanidine, Trimethylamine N-oxide (TMAO), N6-Acetyllysine, and Taurine [32–51]. To mitigate the influence of outliers and ensure more robust estimates, we applied winsorization, capping extreme values at the 5th and 95th percentiles (average of 8 values winsorized per metabolite, range: 7–13) [52, 53]. Metabolites were standardized to have a mean of zero and a standard deviation of one prior to use in a principal component analysis (PCA). To reduce the dimensionality of the data while retaining most of the variation, we derived the first principal component (PC1 = 93.5% of total variance captured) for use as our final "oxidative stress" variable (see Supplemental File 3 Table S2 for correlations between each metabolite and final composite oxidative stress variable).

Covariates

The following set of covariates known to interact with TL, oxidative stress, and inflammation were included in our analyses: maternal age in years, gestational age at time of sample collection, pre-pregnancy BMI, race/ethnicity, and income-to-needs ratio. Gestational age was measured in days; pre-pregnancy BMI was defined as the mother's self-reported pre-pregnancy weight over height (as kilograms/meters^2); race/ethnicity was self-reported and coded as either 'Black', 'White', or 'Other'; income-to-needs was defined as the ratio of family income to the federal poverty threshold. Pregnancy smoking status was initially included in the analysis, but the rate of smoking during pregnancy was so low (2 individuals total) that it was dropped from the analysis with no change in the estimates for other predictors or covariates.

Statistical analysis

Statistical analyses were performed with R version 4.1.2. Demographic differences between the full BEE prenatal cohort and the TL analytic sample were assessed via two-tailed Mann-Whitney U tests for continuous variables and two-way Chi-Square tests for dichotomous variables. Bivariate correlations among TL, oxidative stress, inflammation, and covariates were assessed using the 'cor' function in base R to calculate Pearson or Phi coefficients as appropriate. TL was normally distributed with one outlier at the right end of the distribution (see Supplemental File S4 for Q-Q plot and histogram of original TL values); this value was winsorized to the 95th percentile; analyses with winsorized and non-winsorized versions of TL were consistent and results with the winsorized outcome are reported here. Generalized linear models were fit with TL as the outcome using the 'glm' function.

To maximize statistical power and data utilization, and to ensure robust estimates, we constructed a fully imputed dataset using random forest imputation with the missForest package, employing default parameters [54]. Application of missForest for imputation of missing biological data gives less biased results than other imputation methods based on a range of accuracy metrics [55, 56]. We imputed 5 values (5.7%) for the oxidative stress variable, and 44 values (50%) for the inflammation variable. The out-of-bag (OOB) error estimate indicated a normalized root mean squared error (NRMSE) of 0.239, suggesting a reasonably accurate imputation. Data were analyzed both with and without imputation. Imputed and complete-case datasets produced similar results, and we report imputed results below (see Supplemental File S5 for comparison of results with and without imputation). Statistical significance was set at two-tailed $P<.05$. To address the issue of multiple comparisons and control the expected proportion of false positives among rejected hypotheses, we applied the Holm correction using the 'p.adjust' function in the 'stats' library with method = "holm" and report our adjusted p-values below for each of our final covariate adjusted models.

Results

Sample descriptives

Participants in our analytic sample were, on average, 30.7 ± 5.43 years old at the time of sample collection, with 25% self-identified Black, 65% self-identified White, and 10% self-identified as a race/ethnicity other than Black or White (4 women self-identifying as "Other" for race and "Hispanic or Latino" for ethnicity; 5 women self-identifying as "Other" for race and "Not Hispanic or Latino" for ethnicity). Due to sample size restrictions, we were unable to analyze these groups separately. Compared to the full BEE prenatal cohort, our sample had a slightly higher income-to-needs ratio (BEE prenatal cohort income-to-needs = 3.66 ± 3.5; TL analytic sample income-to-needs = 4.01 ± 2.8; $P=.030$). There were no differences by race/ethnicity, maternal age, gestational age at sample collection, or pre-pregnancy BMI (Table 1).

Relationships among TL and measures of external validity were directionally appropriate [57], though not

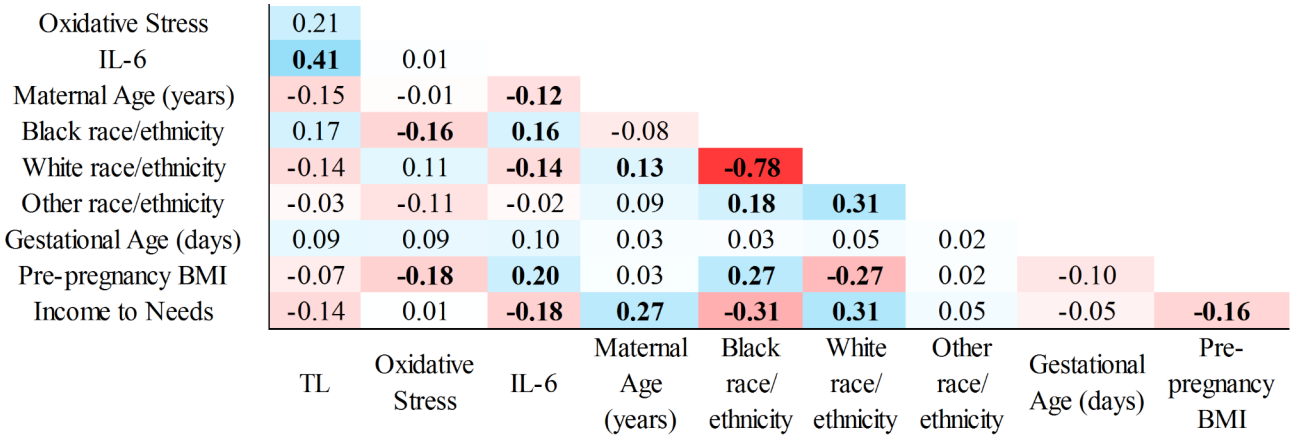

Fig. 1 Correlations among TL, predictors, and demographic variables; red = negative correlation, blue = positive correlation, darkness of color indicates strength. Correlations meeting $P < .05$ are bold. See Supplemental File S6 for full correlations and *p*-values

Table 2 Estimates and standard errors for oxidative stress predicting TL

Model	Oxidative Stress		
	b±SE	*p*-val	Model R^2
Model 1 (Oxidative Stress)	0.14 (0.07)	0.070	0.04
Model 2 (+ maternal age)	0.14 (0.07)	0.067	0.05
Model 3 (+ gestational age)	0.14 (0.07)	0.069	0.05
Model 4 (+ race/ethnicity)	0.17 (0.07)	0.022	0.11
Model 5 (+ maternal BMI)	0.18 (0.07)	0.022	0.11
Model 6 (+ income to needs)	0.18 (0.07)	0.022*	0.11

*Holm-adjusted *p*-value

Table 3 Estimates and standard errors for inflammation predicting TL

Model	Inflammation (IL-6)		
	b±SE	*p*-val	Model R^2
Model 1 (IL-6)	0.71 (0.16)	< 0.0001	0.19
Model 2 (+ maternal age)	0.73 (0.16)	< 0.0001	0.19
Model 3 (+ gestational age)	0.74 (0.17)	< 0.0001	0.19
Model 4 (+ race/ethnicity)	0.71 (0.17)	< 0.0001	0.21
Model 5 (+ maternal BMI)	0.72 (0.17)	< 0.0001	0.22
Model 6 (+ income to needs)	0.72 (0.17)	0.0001*	0.22

*Holm-adjusted *p*-value

statistically significant in our sample: shorter TL was associated with older maternal age, White and Other race/ethnicity, and higher pre-pregnancy BMI, and longer TL was associated with Black race/ethnicity (Fig. 1). TL was positively correlated with oxidative stress ($r = .21$, $P = .053$), and IL-6 ($r = .34$, $P < .001$). As previously reported for the BEE cohort [58], Black race/ethnicity was correlated with higher BMI ($r = .27$, $P < .001$) and White race/ethnicity was correlated with lower BMI ($r = -.27$, $P < .001$). Black race/ethnicity was also correlated with lower oxidative stress ($r = -.16$, $P = .021$) and higher IL-6 ($r = .16$, $P = .059$). Pre-pregnancy BMI was negatively correlated with oxidative stress ($r = -.18$, $P = .004$) and positively correlated with IL-6 ($r = .20$, $P < .001$).

Telomere length, oxidative stress, and inflammation

Adjusting for maternal age, gestational age, race/ethnicity, pre-pregnancy BMI, and income to needs, higher oxidative stress was associated with longer TL (b = 0.18 ± 0.07; Holm-adjusted $P = .022$) such that a one unit increase in oxidative stress predicted an additional 180 bps of TL (Table 2).

With the same covariate adjustments, higher inflammation measured as IL-6 was associated with longer TL (b = 0.72 ± 0.17; Holm-adjusted $P = .0001$); each additional unit increase in IL-6 predicted a 720 bps longer TL (Table 3).

Table 4 Estimates and standard errors for oxidative stress and inflammation predicting TL

Model $R^2 = 0.27$	b±SE	*p*-val
Oxidative Stress	0.18 (0.07)	0.022*
IL-6	0.68 (0.17)	0.0002*
Maternal Age (years)	0.01 (0.02)	0.72
Gestational Age (days)	-0.002 (0.004)	0.64
Race/Ethnicity (ref = non-Hispanic White)		
Non-Hispanic Black	0.54 (0.28)	0.052
Other	0.06 (0.38)	0.86
Maternal BMI	-0.01 (0.05)	0.77
Income to Needs Ratio	-0.01 (0.05)	0.86

*Holm-adjusted *p*-value

Controlling for inflammation, oxidative stress remained predictive of longer TL (b = 0.18 ± 0.07; Holm-adjusted $P = .022$) adjusting for all other covariates (Table 4). Similarly, controlling for oxidative stress, inflammation predicted longer TL (b = 0.68 ± 0.17; Holm-adjusted $P = .0002$). An interaction term between oxidative stress and inflammation was not significantly associated with TL (b = 0.14 ± 0.16; $P = .86$) adjusting for all other covariates.

Discussion

We investigated oxidative stress and inflammation as predictors of TL in a cohort of women with normative pregnancies. Our analysis revealed that higher oxidative stress, as measured by the first principal component derived from a set of oxidative stress-related metabolites, was significantly associated with longer TL. Similarly, higher IL-6, a marker of inflammation, was also associated with longer TL. These associations remained when controlling for each other and other covariates, suggesting independent effects of oxidative stress and inflammation on TL during healthy pregnancies.

The positive associations between oxidative stress and TL and inflammation and TL observed in our study contrasts with the commonly held view that increases in these factors typically lead to telomere shortening [14, 59, 60]. However, it is important to consider that during pregnancy, the physiological and biochemical environment is highly dynamic and regulated differently compared to the non-pregnant state [16, 21, 61]. For the non-pregnant individual, increased oxidative stress is related to telomere damage and shortening [6]. However, pregnancy induces adaptive responses that may upregulate telomere repair and elongation mechanisms, leading to longer telomeres despite elevated oxidative stress and inflammation [13]. Furthermore, the role of inflammation in pregnancy is complex and a gradual increase in circulating inflammatory mediators, such as IL-6, may be associated with a healthy pregnancy [62].

If increased oxidative stress and inflammation are indicative of a healthily progressing pregnancy, higher levels of both factors may be more likely in individuals with longer TL in our sample of non-high-risk healthy pregnancies, as longer TL is also associated with healthy aging. Oxidative stress and inflammation may reflect adaptive processes during pregnancy, where such cellular stressors trigger compensatory telomere maintenance mechanisms to support fetal development and maternal health. Alternatively, longer TL may be an indicator of overall cellular health, which could correlate with higher oxidative stress and inflammation in individuals experiencing healthy pregnancies. Further research is needed to better understand directionality among these factors, how mechanisms of TL regulation operate during pregnancy, and their implications for maternal and child health.

Our findings contribute to the growing body of literature on the determinants of TL during pregnancy and underscore the importance of understanding oxidative stress and inflammation as potential indicators of future maternal health outcomes. Pregnancy can act as a physiological stress test that reveals underlying susceptibilities to future age-related diseases [61, 63]. Understanding relationships among TL, oxidative stress, and inflammation during pregnancy may help predict the likelihood of developing diseases influenced by these factors later in life.

Our study has several strengths, including the use of advanced metabolomic profiling and comprehensive assessment of factors known to interact with the telomere system. The carefully controlled design of the study, including selection of a representative mix of low- and high- income women for each race/ethnicity category, enhances the robustness of our findings as both income and race/ethnicity are known to influence telomeres, oxidative stress, and inflammation. However, our study also has limitations. Saliva contains a variety of cell types, and the TL of cells in saliva will vary depending on the relative concentrations of these cell types. Because our study did not control for cell type composition in saliva, this represents a potential source of variability in our findings. Future studies incorporating cell composition adjustments or alternative tissue sources for TL measurement would provide more robust insights into these associations. Our sample size, while sufficient for the analyses conducted, may limit the generalizability of our findings. Further limiting the generalizability of our study, women pregnant with multiple fetuses, severe pregnancy complications, or birthing complications were excluded from recruitment and therefore our sample likely reflects mechanisms operating in a subset of normative, healthy pregnancies. Additionally, the cross-sectional nature of our analysis precludes causal inferences or conclusions about directionality among our variables. Future research should aim to replicate our findings in larger cohorts beginning with assessment prior to pregnancy. Longitudinal studies are needed to elucidate the causal pathways linking oxidative stress, inflammation, and TL during pregnancy and beyond into the postpartum period. Investigating the potential interactive effects of oxidative stress and inflammation on telomere dynamics across different stages of pregnancy and later into the life course could provide deeper insights into the mechanisms driving these associations.

In conclusion, our study provides evidence that higher oxidative stress and elevated inflammation are associated with longer telomere length in healthy pregnant women. These findings underscore the importance of considering the unique physiological and developmental contexts of individuals when studying the determinants of telomere length. Understanding the interactions among oxidative stress, inflammation, and telomere biology during pregnancy may have significant implications for maternal health, potentially informing strategies to optimize future health outcomes for both mother and child.

Abbreviations

TL Telomere length
aTL Absolute telomere length

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-025-07542-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

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Study proposal: LE, PGP, IS; Data analysis: LE; Telomere assays: QY, JK; Metabolomic assays: CC; Metabolomic profiling: ATA, QY, LEP; Manuscript drafting: LE, QY, ATA; Reading, editing, and final approval: LE, QY, ATA, CC, LEP, JK, CP, RMK, SJS, PGP, IS.

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Data availability
The dataset used during the current study is available on reasonable request directed to the Brain and Early Experiences study team and this manuscript's corresponding author.

Declarations

Ethics approval and consent to participate
The University of North Carolina at Chapel Hill Institutional Review Board (#17-1914) approved the study, and informed consent was obtained from all participants. This study was conducted in adherence to the principles outlined in the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Hauspurg A, Countouris ME, Catov JM. Hypertensive disorders of pregnancy and future maternal health: how can the evidence guide postpartum management?? Curr Hypertens Rep. 2019;21(12):96. https://doi.org/10.1007/s11906-019-0999-7
2. Hauspurg A, Ying W, Hubel CA, Michos ED, Ouyang P. Adverse pregnancy outcomes and future maternal cardiovascular disease. Clin Cardiol. 2018;41(2):239–46. https://doi.org/10.1002/clc.22887
3. Panelli DM, Wang X, Mayo J, et al. Association of pregnancy complications and postpartum maternal leukocyte telomeres in two diverse cohorts: a nested case-control study. BMC Pregnancy Childbirth. 2024;24(1):490. https://doi.org/10.1186/s12884-024-06688-5
4. Panelli DM, Bianco K. Cellular aging and telomere dynamics in pregnancy. Curr Opin Obstet Gynecol. 2022;34(2):57–61. https://doi.org/10.1097/GCO.0000000000000765
5. Etzel LC, Shalev I. Effects of psychological stress on telomeres as genome regulators. Stress: genetics, epigenetics and genomics. Elsevier. 2021;109–17. https://doi.org/10.1016/B978-0-12-813156-5.00009-1
6. Rossiello F, Jurk D, Passos JF. D'Adda Di Fagagna F. Telomere dysfunction in ageing and age-related Diseases. Nat Cell Biol. 2022;24(2):135–47. https://doi.org/10.1038/s41556-022-00842-x
7. Houminer-Klepar N, Bord S, Epel E, Baron-Epel O. Are pregnancy and parity associated with telomere length? A systematic review. BMC Pregnancy Childbirth. 2023;23(1):733. https://doi.org/10.1186/s12884-023-06011-8
8. Mitchell AM, Kowalsky JM, Epel ES, Lin J, Christian LM. Childhood adversity, social support, and telomere length among perinatal women. Psychoneuroendocrinology. 2018;87:43–52. https://doi.org/10.1016/j.psyneuen.2017.10.003
9. Panelli DM, Leonard SA, Wong RJ, et al. Leukocyte telomere dynamics across gestation in uncomplicated pregnancies and associations with stress. BMC Pregnancy Childbirth. 2022;22(1):381. https://doi.org/10.1186/s12884-022-04693-0
10. Zota AR, Geller RJ, Romano LE, et al. Association between persistent endocrine-disrupting chemicals (PBDEs, OH-PBDEs, PCBs, and PFASs) and biomarkers of inflammation and cellular aging during pregnancy and postpartum. Environ Int. 2018;115:9–20. https://doi.org/10.1016/j.envint.2018.02.044
11. Saberi S, Kalloger SE, Zhu MMT et al. Dynamics of leukocyte telomere length in pregnant women living with HIV, and HIV-negative pregnant women: A longitudinal observational study. Saretzki G, ed. PLOS ONE. 2019;14(3):e0212273. https://doi.org/10.1371/journal.pone.0212273
12. Pollack AZ, Rivers K, Ahrens KA. Parity associated with telomere length among US reproductive age women. Hum Reprod. 2018;33(4):736–44. https://doi.org/10.1093/humrep/dey024
13. Chiarello DI, Abad C, Rojas D, et al. Oxidative stress: normal pregnancy versus preeclampsia. Biochim Biophys Acta BBA - Mol Basis Dis. 2020;1866(2):165354. https://doi.org/10.1016/j.bbadis.2018.12.005
14. Barnes RP, Fouquerel E, Opresko PL. The impact of oxidative DNA damage and stress on telomere homeostasis. Mech Ageing Dev. 2019;177:37–45. https://doi.org/10.1016/j.mad.2018.03.013
15. Grzeszczak K, Łanocha-Arendarczyk N, Malinowski W, Ziętek P, Kosik-Bogacka D. Oxidative stress in pregnancy. Biomolecules. 2023;13(12):1768. https://doi.org/10.3390/biom13121768
16. Mannaerts D, Faes E, Cos P et al. Oxidative stress in healthy pregnancy and preeclampsia is linked to chronic inflammation, iron status and vascular function. Torrens C, ed. PLOS ONE. 2018;13(9):e0202919. https://doi.org/10.1371/journal.pone.0202919
17. Ferguson KK, Meeker JD, McElrath TF, Mukherjee B, Cantonwine DE. Repeated measures of inflammation and oxidative stress biomarkers in preeclamptic and normotensive pregnancies. Am J Obstet Gynecol. 2017;216(5):527..e1-527.e9.
18. Sharma JB, Sharma A, Bahadur A, Vimala N, Satyam A, Mittal S. Oxidative stress markers and antioxidant levels in normal pregnancy and pre-eclampsia. Int J Gynecol Obstet. 2006;94(1):23–7. https://doi.org/10.1016/j.ijgo.2006.03.025
19. Palm M, Axelsson O, Wernroth L, Larsson A, Basu S. Involvement of inflammation in normal pregnancy. Acta Obstet Gynecol Scand. 2013;92(5):601–5. https://doi.org/10.1111/aogs.12093
20. Sykes L, MacIntyre DA, Yap XJ, Teoh TG, Bennett PR. The Th1:Th2 dichotomy of pregnancy and preterm labour. Mediators Inflamm. 2012;2012:1–12. https://doi.org/10.1155/2012/967629
21. Mor G, Aldo P, Alvero AB. The unique immunological and microbial aspects of pregnancy. Nat Rev Immunol. 2017;17(8):469–82. https://doi.org/10.1038/nri.2017.64

22. PrabhuDas M, Bonney E, Caron K, et al. Immune mechanisms at the maternal-fetal interface: perspectives and challenges. Nat Immunol. 2015;16(4):328–34. https://doi.org/10.1038/ni.3131
23. Ferguson KK, McElrath TF, Chen Y, Mukherjee B, Meeker JD. Longitudinal profiling of inflammatory cytokines and C-reactive protein during uncomplicated and preterm pregnancy. Am J Reprod Immunol. 2014;72(3):326–36. https://doi.org/10.1111/aji.12265
24. Szarka A, Rigó J, Lázár L, Bekő G, Molvarec A. Circulating cytokines, chemokines and adhesion molecules in normal pregnancy and preeclampsia determined by multiplex suspension array. BMC Immunol. 2010;11(1):59. https://doi.org/10.1186/1471-2172-11-59
25. Fraser A, Nelson SM, Macdonald-Wallis C, et al. Associations of pregnancy complications with calculated CVD risk and cardiovascular risk factors in middle age: the Avon longitudinal study of parents and children. Circulation. 2012;125(11):1367–80. https://doi.org/10.1161/CIRCULATIONAHA.111.044784
26. Heida KY, Velthuis BK, Oudijk MA, et al. Cardiovascular disease risk in women with a history of spontaneous preterm delivery: A systematic review and meta-analysis. Eur J Prev Cardiol. 2016;23(3):253–63. https://doi.org/10.1177/2047487314566758
27. Mills-Koonce WR, Willoughby MT, Short SJ, Propper CB. The brain and early experience study: protocol for a prospective observational study. JMIR Res Protoc. 2022;11(6):e34854. https://doi.org/10.2196/34854
28. Hastings WJ, Eisenberg DTA, Shalev I. Uninterruptible power supply improves precision and external validity of telomere length measurement via qPCR. Exp Results. 2020;1:e52. https://doi.org/10.1017/exp.2020.58
29. O'Callaghan NJ, Fenech M. A quantitative PCR method for measuring absolute telomere length. Biol Proced Online. 2011;13:3. https://doi.org/10.1186/1480-9222-13-3
30. Wolf SE, Hastings WJ, Ye Q et al. Cross-tissue comparison of telomere length and quality metrics of DNA among individuals aged 8 to 70 years. Saretzki G, ed. PLOS ONE. 2024;19(2):e0290918. https://doi.org/10.1371/journal.pone.0290918
31. Geroges HM, Norwitz ER, Abrahams VM. Predictors of Inflammation-Mediated preterm birth. *Physiology*. Published online August 6, 2024:physiol.00022.2024. https://doi.org/10.1152/physiol.00022.2024
32. Alacam H, Dikmen ZG, Yaman H, et al. The role of asymmetric dimethyl arginine and oxidant/antioxidant system in preeclampsia. Fetal Pediatr Pathol. 2011;30(6):387–93. https://doi.org/10.3109/15513815.2011.618869
33. Barisione C, Ghigliotti G, Canepa M, Balbi M, Brunelli C, Ameri P. Indoxyl sulfate: a candidate target for the prevention and treatment of cardiovascular disease in chronic kidney disease. Curr Drug Targets. 2015;16(4):366–72. https://doi.org/10.2174/1389450116666141230114500
34. Biliotti E, Giampaoli O, Sciubba F, et al. Urinary metabolomics of HCV patients with severe liver fibrosis before and during the sustained virologic response achieved by direct acting antiviral treatment. Biomed Pharmacother. 2021;143:112217. https://doi.org/10.1016/j.biopha.2021.112217
35. Brunt VE, Gioscia-Ryan RA, Casso AG, et al. Trimethylamine-N-Oxide promotes Age-Related vascular oxidative stress and endothelial dysfunction in mice and healthy humans. Hypertension. 2020;76(1):101–12. https://doi.org/10.1161/HYPERTENSIONAHA.120.14759
36. Chang Qxian, Chen X, Ming-xin, Yang, et al. Trimethylamine N-Oxide increases soluble fms-like tyrosine Kinase-1 in human placenta via NADPH oxidase dependent ROS accumulation. Placenta. 2021;103:134–40. https://doi.org/10.1016/j.placenta.2020.10.021
37. Dai Y, Huo X, Cheng Z, Faas MM, Xu X. Early-life exposure to widespread environmental toxicants and maternal-fetal health risk: A focus on metabolomic biomarkers. Sci Total Environ. 2020;739:139626. https://doi.org/10.1016/j.scitotenv.2020.139626
38. Gil AM, Duarte D, Pinto J, Barros AS. Assessing exposome effects on pregnancy through urine metabolomics of a Portuguese (Estarreja) cohort. J Proteome Res. 2018;17(3):1278–89. https://doi.org/10.1021/acs.jproteome.7b00878
39. Huang Y, Sun L, Liu N, et al. Polo-like kinase 1 (Plk1) Up-regulates telomerase activity by affecting human telomerase reverse transcriptase (hTERT) stability. J Biol Chem. 2015;290(30):18865–73. https://doi.org/10.1074/jbc.M114.635375
40. Hung S, Kuo K, Wu C, Tarng D. Indoxyl sulfate: A novel cardiovascular risk factor in chronic kidney disease. J Am Heart Assoc. 2017;6(2):e005022. https://doi.org/10.1161/JAHA.116.005022
41. Huo X, Li J, Cao YF, et al. Trimethylamine N-Oxide metabolites in early pregnancy and risk of gestational diabetes: A nested Case-Control study. J Clin Endocrinol Metab. 2019;104(11):5529–39. https://doi.org/10.1210/jc.2019-00710
42. Jordan F, Nemeria N, Gerfen G. Human 2-Oxoglutarate dehydrogenase and 2-Oxoadipate dehydrogenase both generate Superoxide/H2O2 in a side reaction and each could contribute to oxidative stress in mitochondria. Neurochem Res. 2019;44(10):2325–35. https://doi.org/10.1007/s11064-019-02765-w
43. Lin H, Levison BS, Buffa JA, et al. Myeloperoxidase-mediated protein lysine oxidation generates 2-aminoadipic acid and lysine nitrile in vivo. Free Radic Biol Med. 2017;104:20–31. https://doi.org/10.1016/j.freeradbiomed.2017.01.006
44. Maitre L, Robinson O, Martinez D, et al. Urine metabolic signatures of multiple environmental pollutants in pregnant women: an exposome approach. Environ Sci Technol. 2018;52(22):13469–80. https://doi.org/10.1021/acs.est.8b02215
45. Olkowicz M, Czyzynska-Cichon I, Szupryczynska N, et al. Multi-omic signatures of atherogenic dyslipidaemia: pre-clinical target identification and validation in humans. J Transl Med. 2021;19(1):6. https://doi.org/10.1186/s12967-020-02663-8
46. Pietzke M, Meiser J, Vazquez A. Formate metabolism in health and disease. Mol Metab. 2020;33:23–37. https://doi.org/10.1016/j.molmet.2019.05.012
47. Piras C, Neri I, Pintus R, et al. First trimester metabolomics 1H-NMR study of the urinary profile predicts gestational diabetes mellitus development in obese women. J Matern Fetal Neonatal Med. 2024;35(25):8275–83. https://doi.org/10.1080/14767058.2021.1970133
48. Wang Y, Sharpless N, Chang S. p16INK4a protects against dysfunctional telomere–induced ATR-dependent DNA damage responses. J Clin Invest. 2013;123(10):4489–501. https://doi.org/10.1172/JCI69574
49. Wang M, Liang Q, Li H, et al. Normal pregnancy-induced amino acid metabolic stress in a longitudinal cohort of pregnant women: novel insights generated from UPLC-QTOFMS-based urine metabolomic study. Metabolomics. 2016;12(8):131. https://doi.org/10.1007/s11306-016-1067-9
50. Zgoda-Pols JR, Chowdhury S, Wirth M, Milburn MV, Alexander DC, Alton KB. Metabolomics analysis reveals elevation of 3-indoxyl sulfate in plasma and brain during chemically-induced acute kidney injury in mice: investigation of nicotinic acid receptor agonists. Toxicol Appl Pharmacol. 2011;255(1):48–56. https://doi.org/10.1016/j.taap.2011.05.015
51. Zhou M, Ford B, Lee D, et al. Metabolomic markers of phthalate exposure in plasma and urine of pregnant women. Front Public Health. 2018;6. https://doi.org/10.3389/fpubh.2018.00298
52. Han X, Liang L. MetabolomicsR: a streamlined workflow to analyze metabolomic data in R. Bioinforma Adv. 2022;2(1):vbac067. https://doi.org/10.1093/bioadv/vbac067
53. Ritchie SC, Surendran P, Karthikeyan S, et al. Quality control and removal of technical variation of NMR metabolic biomarker data in ~120,000 UK biobank participants. Sci Data. 2023;10(1):64. https://doi.org/10.1038/s41597-023-01949-y
54. Stekhoven DJ, Bühlmann P. MissForest—non-parametric missing value imputation for mixed-type data. Bioinformatics. 2012;28(1):112–8. https://doi.org/10.1093/bioinformatics/btr597
55. Shah AD, Bartlett JW, Carpenter J, Nicholas O, Hemingway H. Comparison of random forest and parametric imputation models for imputing missing data using MICE: A CALIBER study. Am J Epidemiol. 2014;179(6):764–74. https://doi.org/10.1093/aje/kwt312
56. Wei R, Wang J, Su M, et al. Missing value imputation approach for mass Spectrometry-based metabolomics data. Sci Rep. 2018;8(1):663. https://doi.org/10.1038/s41598-017-19120-0
57. Ye Q, Apsley AT, Etzel L, et al. Telomere length and chronological age across the human lifespan: A systematic review and meta-analysis of 414 study samples including 743,019 individuals. Ageing Res Rev. 2023;90:102031. https://doi.org/10.1016/j.arr.2023.102031
58. Williams CY, Wylie A, Ghobrial V, Coe CL, Short SJ. Racial differences in the associations between adiposity, placental growth hormone and inflammatory cytokines in pregnant women. Front Endocrinol. 2023;14:1100724. https://doi.org/10.3389/fendo.2023.1100724
59. Abbas G, Salman A, Rahman SU, et al. Aging mechanisms: linking oxidative stress, obesity and inflammation. Matrix Sci Med. 2017;1(1):30–3. https://doi.org/10.26480/msm.01.2017.30.33
60. Carrero JJ, Stenvinkel P, Fellström B, et al. Telomere attrition is associated with inflammation, low fetuin-A levels and high mortality in prevalent haemodialysis patients. J Intern Med. 2008;263(3):302–12. https://doi.org/10.1111/j.1365-2796.2007.01890.x

61. Giller A, Andrawus M, Gutman D, Atzmon G. Pregnancy as a model for aging. Ageing Res Rev. 2020;62:101093. https://doi.org/10.1016/j.arr.2020.101093
62. Vilotić A, Nacka-Aleksić M, Pirković A, Bojić-Trbojević Ž, Dekanski D, Jovanović Krivokuća M. IL-6 and IL-8: an overview of their roles in healthy and pathological pregnancies. Int J Mol Sci. 2022;23(23):14574. https://doi.org/10.3390/ijms232314574
63. Rich-Edwards JW, Fraser A, Lawlor DA, Catov JM. Pregnancy characteristics and women's future cardiovascular health: an underused opportunity to improve women's health?? Epidemiol Rev. 2014;36(1):57–70. https://doi.org/10.1093/epirev/mxt006

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