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Prenatal maternal stress prospectively relates to shorter child buccal cell telomere length

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ABSTRACT

Prenatal exposure to stress increases risk for suboptimal child and adult mental and physical health outcomes, hypothesized to occur via fetal exposure to maternal stress hormones that alter growth and development. One proposed pathway through which stress exposure in utero could affect the offspring is by accelerating cellular aging in the form of telomere attrition. We tested this hypothesis in a cohort of 111 mother-child dyads, where mothers were assessed over 6 or more years, beginning prior to conception, and later during pregnancy, postpartum, and when the children were 3–5 years old. Adjusting for child age and concurrent maternal stress, we found that higher maternal perceived stress in the 3rd trimesters of pregnancy was predictive of shorter child buccal telomere length (bTL) ($\beta = -0.24$, $p < .05$), while maternal preconception and postpartum maternal stress were not associated with bTL (all p's > 0.42). These findings suggest a vulnerable time period in pregnancy when maternal stress influences offspring telomere length, suggesting the early embedding of adult disease might occur through biological aging pathways.

1. Introduction

Prenatal exposure to maternal stress increases risk for suboptimal child and adult health outcomes such as cardiovascular and metabolic disease (Entringer et al., 2010; Ellman et al., 2008; Dunkel Schetter, 2010). This in utero or fetal programming of adult disease, first characterized by Barker (Barker DJP, 1998), is thought to occur through exposure of the fetus to a less than optimal in utero environment that alters growth and development. One proposed pathway through which exposure to stressors and resultant stress hormones could increase risk for suboptimal health outcomes is through accelerating cellular age via telomere attrition (Entringer et al., 2010; Shalev et al., 2013; Coimbra et al., 2017). Telomere length is a repetitive sequence of DNA at the chromosomal ends that can be lost during clonal expansion (Blackburn, 1991), a process occurring across tissues during fetal growth. Telomere length is a marker of biological aging (Aviv, 2011), with shortened telomere length predictive of increased risk for numerous health outcomes (Farzaneh-Far et al., 2008; Fitzpatrick et al., 2007) and earlier mortality (Bakaysa et al., 2007; Cawthon et al., 2003). Rapid growth of fetal cells can be accompanied by activated telomerase, an enzyme that rebuilds the telomere (Blackburn, 2000; Forsyth et al., 2002); however, stress may interfere with this process (Epel et al., 2009; Choi et al., 2008). In particular, cortisol has been shown to down-regulate the activity of telomerase (Choi et al., 2008), thereby offering a pathway through which stress hormone exposure may accelerate aging by shortening telomere length in the fetus, referred to as the fetal programming of telomere biology hypothesis (Entringer et al., 2018).

Stress, particularly during early life, and also chronic stress in adulthood, have been associated with shorter telomere length and accelerated telomere shortening (Shalev et al., 2013; Epel et al., 2004; Shalev et al., 2012; Rentscher et al., 2020). Fetal exposure to maternal stress has also been linked to offspring telomere length (Marchetto et al.,

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2016; Entringer et al., 2013; Send et al., 2017). Maternal recall of a major stressful life event occurring during the pregnancy was associated with shorter telomere length in offspring in adulthood, although the trimester in which the stressful event occurred was not identified (Entringer et al., 2011). Alternatively, several studies have reported newborn cord blood telomere length to be shorter in offspring whose mothers reported high stress during either the first trimester (Entringer et al., 2013) or the third trimester (Marchetto et al., 2016; Send et al., 2017) of pregnancy, but neither study examined multiple trimesters. To date research has been limited by considering only a single time point of prenatal stress. Likewise, investigators have derived telomere length estimates from cord blood of newborns, or adult offspring, but have not as yet observed this effect in the offspring during young childhood. Preconception stress might also have an impact on child health (Keenan et al., 2018), yet no research to date has examined the relationship of stress prior to conception and offspring telomere length. Theoretically, timing of stress exposure may be critically important to clarification of the fetal origins hypothesis.

The present study followed mothers who had previously given birth at least once in the year prior to conception of a subsequent child, then followed through the next pregnancy with assessments in second and third trimester, and at 1-month postpartum. In a follow-up study, child telomere length was measured from DNA extracted from buccal samples obtained at an in home visits occurring when the child was 3–5 years of age. We hypothesized that higher maternal stress would predict shorter child buccal telomere length (bTL). We further explored whether there were sensitive periods when maternal stress had a greater impact on telomere length – specifically, preconception, second trimester or third trimester of pregnancy, and postpartum/early life.

2. Methods

2.1. Procedures

Data were collected from participants in the Community Child Health Network, comprised of five sites (Washington, D.C., Baltimore, Maryland, Los Angeles County, California, Lake County, Illinois, and seven counties in North Carolina) that enrolled 2,510 Latina, White, and African-American women. Study design and sample characteristics are reported elsewhere (Ramey et al., 2015). Women were recruited to the CCHN study after the birth of a child and followed for two years. Mothers were interviewed during the inter-pregnancy interval or pre-conception up to 4 times, *M(SD)* = 3.44(2.7) months, 2nd trimester, *M (SD)* = 20.6(3.9) weeks, 3rd trimester, *M(SD)* = 33.1(3.3) weeks, and post-partum, *M(SD)* = 12.7(5) weeks. A subset of 242 women in three sites participating in the follow-up study had a subsequent pregnancy and participated in at least one interview during the pregnancy. Of those who could be located, 127 agreed to participate in a follow-up home visit with their offspring at 3 of the 5 original sites (eastern North Carolina, Washington, DC, and Lake County IL). Of these, 111 had children who provided buccal samples using a cheek swab from which telomere length was determined (see participant flowchart Fig. 1).[1] Mothers were instructed to avoid feeding their child prior to the visit, and children were asked to rinse their mouth with water prior to sample collection. Buccal cell samples were collected from the inside of each child's cheek by rotating a cytology brush (one for each cheek), and this swab was then placed in buccal cell lysis provided as part of the Gentra Puragene buccal cell extraction kit (Qiagen, Germantown, MD).

[1] The 111 women in the current sample were older (t(242) = -4.91, p < .001) and had higher incomes (t (241) = -2.93, p < .01) compared to the 131 women who had subsequent pregnancies but did not participate. There were no significant ethnic/racial or educational differences (p's > .29).

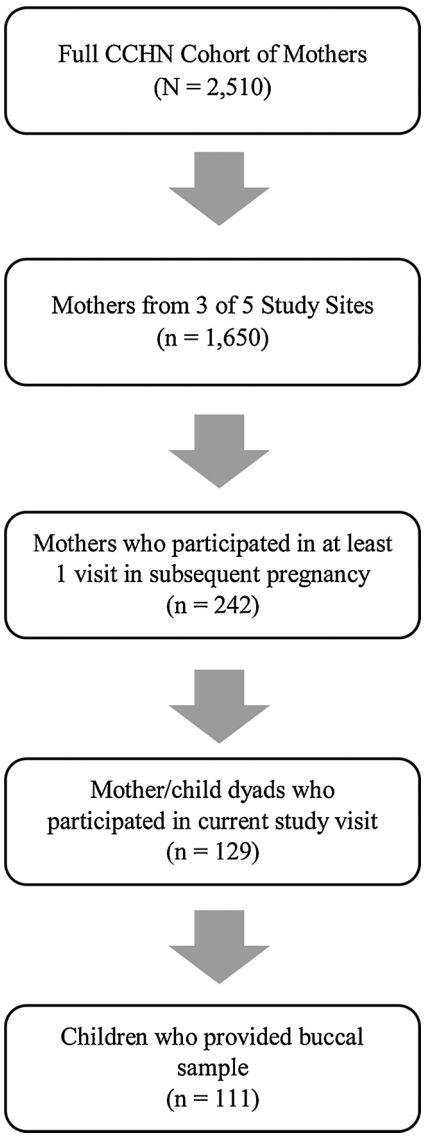

Fig. 1. Flow diagram for data collection at 3 Preconception study sites.

2.2. Measures

2.2.1. Perceived stress scale

Maternal stress was measured using the Perceived Stress Scale (PSS), a validated, reliable instrument of perception of stress over the past month (Cohen & Williamson, 1988). The 10-item questionnaire includes items assessing the general unpredictability and uncontrollability of stressors (e.g., *In the past month, how often have you found that you could not cope with all the things that you had to do?)* and mothers answered on a 5-point Likert scale ranging from *never* (0) to *almost always* (4). Mothers completed the PSS up to three times in the year prior to conception (α range .77–.83), during the 2nd trimester (α = .87), 3rd trimester (α = .86), and 1-month post-partum (α = .70). Higher scores indicate higher levels of perceived stress. Preconception stress using the PSS was assessed within 12 months of conception.

2.2.2. Buccal Telomere Length (bTL)

Children provided buccal cell samples when they were 3–5 years old. Genomic DNA was extracted from buccal cells using the Gentra Puragene buccal cell extraction kit (Qiagen, Germantown, MD). DNA quality was determined using NanoDrop full-spectrum spectrophotometer, and quantity verified using high sensitivity Invitrogen Quant-iT

dsDNA assay kit.

Telomere length values were estimated using a standard real-time quantitative polymerase chain reaction (qPCR) methodology as reported previously (Carroll et al., 2016). Values are expressed as the ratio of the estimated concentration generated by PCR of the telomere gene (T) divided by the hemoglobin single (S) copy gene = (T/S). Primer used were *Tel1b* [CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGTT], *Tel2b* [GGCTTGCCTTACCCTTACCCTTACCCTTACCCTTACCCT], *hgb1* [GCTTCTGACACAACTGTGTTCACTAGC], and

hgb2 [CACCAACTTCATCCACGTTCACC]. Samples were run in triplicate and then assessed for reliability, with acceptable intra-assay (range: 0.1–6 %; average = 1%) and inter-assay variability for both T and S plates (range: 0.9–4 %; average = 2%; ICC = .995). Assays were completed in two batches, with a subset of samples run in each batch (ICC = .988). Telomere estimates between batches were similar (R^2 = .96) with no significant differences in estimates. Batch was included as a covariate in all models.

2.3. Demographic and medical factors

Interviews and medical charts provided data on child and mother demographics, father age, birth outcomes, and maternal medical conditions. Treatment of covariates is described in detail the plan of analyses.

2.4. Statistical analyses

Sample descriptives and bivariate correlations were analysed using IBM SPSS Statistics version 25. Regression analyses were run using MPlus version 7 employing full information maximum likelihood to account for missing data. Multivariate outlier analyses, using DFFITS, DFBETAS, Cook's distance as criteria (Neter et al., 1989), were conducted to identify potential influential cases. Tolerance and variance inflation factors were checked to account for potential issues with multicollinearity. Tolerance values ranged from 0.41 to 0.65 and Variance Inflation Factors were all less than 2.5, suggesting minimal influence of multicollinearity (Fox, 1992). Outlier analyses revealed no influential cases; therefore, all participants were included in analyses. Child bTL values identified as outliers (± 3 SD from the Mean) were winsorized. Child bTL values were then z-transformed for analyses to improve comparability across studies, as has been recommended (Verhulst, 2020)

Preliminary analyses examined sample characterstics and bivariate correlations of child buccal telomere length with child demographic (child age, sex, race as African-American vs. other; ethnicity as Hispanic vs. other), mother demographic (years education, per capita income adjusted for cost of living in the site), father age, mother health (pre-pregnancy BMI, smoking during pregnancy, gestational diabetes) and pregnancy outcome variables (child birth weight, gestational length) to identify potential covariates given previous links to these factors and child telomere length (Liu et al., 2019; Needham et al., 2012; Tarik et al., 2019; Factor-Litvak et al., 2016; Xu et al., 2014; Ip et al., 2017; Akkad et al., 2006; Martens et al., 2016). Any variable significantly associated with child telomere length was included as a covariate in follow-up analyses. In addition, child age was included in all analyses given its established relationship with telomere length. PSS was measured multiple times before preconception. For these analyses, we used the PSS measure most proximal to timing of conception (range 0 months – 12 months) to represent "preconception maternal stress."

Main analyses tested whether maternal stresss in preconception, 2nd trimester, 3rd trimester, and post-partum predicted child telomere length at age 3–5 years in 4 separate multiple regression equations, controlling for child age, batch (1 or 2) when telomere samples were assayed, and pre-pregnancy BMI. All timepoints of maternal stress were then inputed into one model to examine which time point predicted child telomere length over and above the others. Finally, regression analyses were re-run, controlling for concurrent maternal stress to check if results remained consistent.

3. Results

Table 1 shows sample characteristics of the mother-child dyads in the current analyses. Nearly half (46.8 %) of children were of Hispanic ethnicity, while the remaining were non-Hispanic Caucasian (28.8 %), African-American (18.4 %), and mutiracial (9.2 %). Child bTL was not significantly associated with child race (African American vs. all others; p = 0.25) or ethnicity (Hispanic vs. all others; p = 0.95), child sex (p = 0.29), child BMI (p = .61), mother age (p = .90), father age

Table 1
Participant Demographics and Medical Factors.

Variable	*M*	*SD*	Range	Telomere Length, r or M(SD), p value
Mother Age at T1	27.10	5.26	18.19–39.32	r = -.01, p = .90
Father Age at T1	28.58	6.26	18.68–51.00	r = -.07, p = .55
Maternal Education (years)	12.76	3.39	6 - 21	r = .02, p = .81
Household Income at T1, Per capita	16,424.28	26,747.27	0 – 241, 80.04	r = -.03, p = .79
Pre-pregnancy Body Mass Index (BMI)	29.95	7.31	18.00 – 54.00	r = .26, p = .02
Perceived Stress				
Preconception	13.18	5.34	1 - 26	r = -.13, p = .24
2nd Trimester	14.30	5.88	0 - 29	r = -.21, p = .11
3rd Trimester	17.61	5.73	5 - 33	r = -.25, p = .03
Postpartum	17.04	6.13	4 - 39	r = -.13, p = .24
	Category	*N*	%	
Maternal Ethnicity				F = .37, p = .77
	Hispanic	54	48.6	1.71(.99)
	Non-Hispanic Caucasian	36	32.4	1.62 (.75)
	African American	19	17.1	1.48 (.65)
	Multiracial	2	1.8	1.80 (.85)
	M	*SD*	Range	
Child Age at SC1	3.84	0.41	3.35–5.48	r = -.22, p = .02
Child BMI	16.25	1.64	12–25	r = .05, p = .61
Gestational Length (weeks)	38.84	1.74	29.71–42.00	r = -.15, p = .13
Birth weight (g)	3,225.13	590. 19	1247 – 4750	r = -.12, p = .26
	Category	*N*	%	
Child Sex				t = -1.28, p = .20
	Female	61	55.0	1.64 (.64)
	Male	50	45.0	1.49 (.64)
Child Ethnicity				F = .46, p = .72
	Hispanic	52	46.8	1.57 (.63)
	Caucasian	32	28.8	1.66 (.65)
	African American	18	16.2	1.50 (.66)
	Multiracial	9	8.1	1.42 (.46)
Child Buccal Telomere Length	1.57	.63	.17 – 3.00	–

Note. Household income is yearly income adjusted for cost of living. Child buccal telomere length is non-transformed values.

(p = .55), mother education (p = .81), mother adjusted per capita income (p = 0.79), mother gesational diabetes (N = 7; p = .38), mother smoking history (N = 7, p = .55), gestational length (p = .13) or child birth weight (p = 0.26). Mother pre-pregnancy BMI was positively associated with child bTL (r = .26, p = .02). Child age was negatively associated with bTL (r = −0.22, p = .02). Children BMIs were normal, average household income was middle class, and 55 % were female.

PSS scores at preconception, second and third trimester and postpartum were significantly related over time at p < .01 (r values range .39–.47). In a first step, each PSS score was tested for an association with child bTL, adjusting for child age and batch of telomere assay (see Table 2). Results indicate that maternal stress in the 2nd trimester, and 3rd trimester each had a modest relationship to bTL, although only 3rd trimester stress met the p < .05 threshold for significance (b (SE) = −.04 (.02), β = −.25, p < .05; See Fig. 2). Maternal stress preconception and postpartum did not significantly relate to child telomere length (all p's > .12). Sensitivity analyses were performed to determine if the 3rd trimester was the most sensitive in predicting child telomere length with maternal stress from all other time points entered simultaneously, controlling for child age and batch (Table 2). Analyes revealed a similar effect size of maternal stress in the 3rd trimester on offspring bTL (b (SE) = -.04 (.02), β = -.24, p = .06), while all other time points were non-significant when included in the same regression model, with an overall R^2 = .19, p = .012. Additional adjustment for concurrent maternal stress did not modify these results (individual model third trimester, b (SE) = -.04 (.02), β = -.24, p = .033; simultaneous model third trimester, b (SE) = -.04 (.02), β = -.23, p = .078). Secondary analyses controlling for gestational length did not modify the results. In this simultaneous regression model the tolerance, VIF, and standard errors were within normal limits and do not suggest multicollinearity was a problem.

4. Discussion

The current study examined whether maternal stress reported in the past month at four different critical periods, preconception, second trimester, third trimester, and postpartum, was prospectively related to child buccal telomere length at 3–5 years old. The stress measure used (PSS) is a well validated standardized scale that assesses properties of stress such as uncontrollability, inability to cope, and other aspects reflecting chronic stress from any and all sources in life (Cohen et al., 1983). Analyses examined and controlled for many maternal, birth, and child factors. Additional analyses controlling for maternal stress at the time of the buccal collection and for length of gestation did not alter these results. Our findings indicate that the strength of the association is strongest for third trimester prenatal maternal stress, while a similar coefficient (moderate effect) for second trimester prenatal maternal stress was marginally significant. In the model where all time points were entered simultaneously, only third trimester maternal stress predicted bTL of the child.

Table 2
Results of linear regression analyses testing the direct effect of each time point of maternal stress on child buccal telomere length (z-transformed).

	Individual			Simultaneous		
	b (SE)	β	p	b (SE)	β	p
Covariates						
Child Age	−.042 (.02)	−.210	.027			
Batch	.196 (.24)	.077	.405			
Maternal Pre-Pregnancy BMI	.030 (.01)	.233	.031			
Predictors						
Preconception (< 12 months)	−.029 (.02)	−.156	.126	−.003 (.003)	−.127	.221
2nd Trimester	−.045 (.02)	−.258	.062	−.012 (.03)	−.070	.730
3rd Trimester	−.042 (.02)	−.254	.016	−.041 (.02)	−.243	.062
Postpartum	−.015 (.02)	−.091	.360	.003 (.02)	.017	.900

Note: Covariate regression effects from an empty model. Individual: Regression models were run separately for each predictor. Simultaneous: Regression model run with all predictors entered simultaneously.

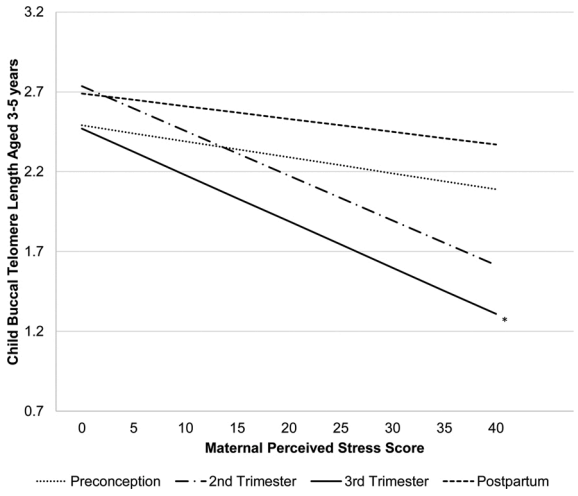

Fig. 2. Slope of the individual linear regression equation for perceived maternal stress predicting child buccal telomere length (T/S).
Note: Estimated slopes derived from regression models adjusting for child age, batch, and pre-pregnancy BMI, with perceived stress score predicting non-transformed child buccal telomere length. *p < .05.

Notably, we did not observe effects of maternal stress on offspring telomere length when the stress was measured within 12 months prior to conception, nor when stress was assessed in the postpartum period. These results are consistent with the fetal origins hypothesis arguing that maternal stress is most impactful on offspring health when it occurs in utero, and less impactful when there is not a shared biological milieu. Likewise, our findings are consistent with prior research indicating that maternal stress during pregnancy relates to newborn telomere length (Marchetto et al., 2016; Entringer et al., 2013; Send et al., 2017), and extend these into early childhood.

Maternal stress may impact fetal programming by altering cellular age, as indexed by buccal telomere length, with implications for risk of later health problems in offspring, including metabolic and cardiovascular disease (Haycock et al., 2014; Farzaneh-Far et al., 2010; Fitzpatrick et al., 2011; Chen et al., 2014). If stress experienced by the mother influences fetal development via programming the offspring's systems, the pathways through which this drives telomere loss are multiplicative. Stress hormones, including cortisol and catecholamines, both have plausible mechanistic roles. Prenatal stress has previously been associated with elevated maternal inflammation (Ross et al., 2019; Coussons-Read et al., 2012, 2007) and stress hormones (Davis and Sandman, 2010; Rakers et al., 2017). Indeed, recent findings have demonstrated a connection between a pro-inflammatory state in pregnancy with shorter newborn leukocyte telomere length (Lazarides et al., 2019), suggesting a mechanism through which maternal stress might alter child outcomes. Cortisol exposure in utero may contribute to decreased telomerase activity, which would reduce the capacity of rapidly reproducing stems cells from elongating telomere length in the fetus. In combination with this, catecholamines directly activate inflammatory pathways within immune cells (Cole et al., 2010), promoting cellular replication that can drive telomere loss. Catecholamines also stimulate cellular metabolic activity, a source of oxidative stress known to damage telomeric ends (Von Zglinicki, 2002), and potentially reduce telomere length if unrepaired before cell replication. The developing fetus has rapidly expanding cell populations and there may be times when cells are

particularly vulnerable to stress hormone exposure that induces telomere loss. Stress in late pregnancy could exert its effects on offspring telomere length via multiple biological pathways beyond the ones outlined above (Entringer et al., 2018; Rakers et al., 2017), and further research is warranted to better understand these dynamics.

Of note, a prior report examining cord blood and placental telomere length in newborns with maternal pre-pregnancy BMI in a large sample from Belgium (Martens et al., 2016) report a correlation of r=-.11, suggesting increasing BMI is associated with shorter newborn telomere length. In our smaller sample of multi-racial cohort residing in the United States of America, analyses show longer buccal telomere length in offspring ages 3–5 with higher maternal pre-pregnancy BMI. Our study differs in several ways, including a different population, with variability in diets, a greater distribution in BMI, and telomere length measured in young childhood rather than at birth. Our findings should be replicated in a larger sample of women designed to assess the impact of maternal BMI on offspring telomere length.

5. Limitations and future directions

The sample size varied by time point, and although we used statistical models that included all available data points, it remains possible that the strength of the effects observed would be altered if we had a complete dataset. Larger sample size would improve statistical power, which may result in effects such as second trimester stress and child bTL reaching statistical significance. Thus, the effect estimates generated for each time point when stress was assessed should be considered, irrespective of statistical significance. In addition, the timing of the assessment of preconception stress was on average six months prior to conception. Future research may consider the proximity of stress to conception as an important factor that might influence risk for shortened telomere length in the offspring. A more proximal assessment of stress in relation to conception such as within three months before conception may yield alternative findings. Child telomere length was captured using buccal samples, which has been shown to be highly correlated to circulating leukocyte telomere length (Gadalla et al., 2009); Nevertheless, bTL estimates may be less predictive of adult health risk than leukocyte telomere length values, and further work is warranted to determine the difference in risk prediction between these two sample sources. Additional limitations to the current analyses include an absence of biological indices of maternal stress (e.g., cortisol, catecholamines) that provide an additional way to examine the connection between stress and offspring telomere length, no measure of maternal telomere length during pregnancy which could relate to offspring telomere length, nor a measure of telomere length at birth to replicate prior reports on newborn telomere length. In addition, we did not replicate prior reports linking child sex and race with telomere length (Drury et al., 2015; Bosquet Enlow et al., 2019), although we were underpowered to properly test interactions. Despite these shortcomings, the study has several strengths. First, the prospective design allowed us to assess stress at four distinct times and. Unlike life events measures, the assessments were for a short recent time period (past month), providing for more accurate estimates of all stress exposures. Secondly, the timing of child assessments is novel and extends prior findings about telomere length at birth. Finally, the study sample is ethnically, racially, and socioeconomically diverse, giving better representation of these underrepresented groups.

6. Conclusion

In conclusion, we report that maternal stress in late pregnancy is prospectively associated with reduced child buccal telomere length at 3–5-years of age, independent of postpartum and concurrent maternal reported stress. These findings are consistent with the hypothesis of fetal programming of lifelong risk for disease and point to a mechanism by which fetal programming occurs, in this case potentially through shortened telomere length, a marker of biological aging.

Declaration of Competing Interest

The authors report no declarations of interest.

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