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Intergenerational transmission of childhood trauma? Testing cellular aging in mothers exposed to sexual abuse and their children

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ABSTRACT

Background: Exposure to maltreatment in childhood can lead to increased risk for poor health outcomes in adulthood. Child maltreatment and later poor health may be linked by premature biological aging. We tested whether childhood sexual abuse (CSA) was associated with telomere length (TL) in adult females. We further tested the hypothesis of intergenerational transmission of CSA-related effects by measuring TL in both CSA-exposed and non-exposed mothers and their children.

Methods: Participants were a subset of females and their children in a prospective-longitudinal cohort study of sexually abused females and a demographically comparable control group from the same Washington, D.C. area. TL was measured using qPCR in both leukocyte and buccal samples from females (N = 108, mean age 36.3 years) and buccal samples from their children (N = 124, mean age 10.5 years). Multilevel models were used to test associations between CSA-exposure and TL measured in leukocytes and buccal tissue in females and to test the intergenerational effect of maternal-CSA exposure on age-adjusted TL in their children.

Results: CSA-exposure was not associated with TL in adult females. Maternal TL and biological sex were significant predictors of child TL such that longer maternal TL predicted longer TL in children, and female children had longer TL than male children. However, maternal-CSA exposure did not predict TL in children.

Discussion: CSA-exposure was not associated with TL in this cohort of middle-aged females, nor was there evidence for an intergenerational effect of maternal-CSA exposure on child TL. This finding is in line with some previous results on CSA and adult TL. Previous significant results associating child maltreatment with shorter TL may be capturing a population of individuals exposed to either multiple types of maltreatment compared to controls with no childhood adversity, or maltreatment in childhood with concurrent TL measurements.

1. Introduction

Exposure to trauma during childhood can lead to increased risk for poor health outcomes in adulthood (Irish et al., 2010; Miller et al., 2011; Nusslock and Miller, 2016; Trickett et al., 2011). However, mechanisms conferring this risk at the biological level remain largely unknown. Telomere length (TL), a measure of cellular aging, has been suggested as a link between traumatic childhood experiences and the disproportionate disease burden impacting survivors (Shalev et al., 2013a).

TL has been established as a hallmark of aging (López-Otín et al., 2013) and thus, may serve as a useful indicator of accelerated aging due to trauma exposure (Ridout et al., 2018; Shalev, 2012). Experiencing trauma in childhood, for instance, has been linked to shorter TL cross-sectionally as well as to accelerated telomere shortening over time (Pepper et al., 2018; Ridout et al., 2018). Shalev et al. (2013b) demonstrated that children exposed to multiple kinds of violence between age 5 and 10 years showed significantly more telomere erosion (i.e., by age 10) than peers. Similarly, children exposed to institutional care (orphanages) had faster rates of telomere shortening in a dose-response

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manner relative to those not exposed to institutional care (Drury et al., 2012; Humphreys et al., 2016). Age-dependent shortening of telomeres, coupled with shortening observed due to stressor exposure, has given rise to the view of telomeres as cellular 'clocks' that can be used to distinguish biological age from chronological age (Shalev et al., 2013a[1]). TL, functioning as an indicator of cellular aging, may then represent a useful metric to quantify the impact psychological trauma has at the cellular level.

Research on the effects of child maltreatment often collapses various forms of maltreatment (e.g. physical/sexual abuse, neglect) into one category (e.g. 'toxic stressors' or 'adverse childhood experiences'). Given the frequent co-occurrence of multiple abuse types (Finkelhor et al., 2013; Vachon et al., 2015) and the difficulty in gathering large samples for abuse types with low population-level prevalence, treating all forms of child maltreatment as one category has been important in advancing our knowledge of the impact of early victimization. For instance, Tyrka et al. (2010) found that individuals reporting a history of child maltreatment had shorter telomeres than those without maltreatment history. Kananen et al. (2010) found that a greater number of childhood adversities associated with shorter TL in adulthood. Extant studies attempting to disentangle the unique impact of different forms of child maltreatment point to intriguing differences in the biological embedding of each maltreatment type. For example, a review of the literature highlights maltreatment-type-specific differences in brain structure and connectivity of maltreated individuals (Teicher et al., 2016). In females with pre-pubertal sexual abuse history, Heim et al. (2013) found evidence of thinning in portions of the somatosensory cortex associated with the clitoris and genital area. A recent meta-analysis on the impact of early adversity on TL demonstrates important differences in effect size depending on adversity type (e.g. abuse, neglect, all adversity) and timing (e.g. postnatal, pre-pubertal, adolescence) of exposure (Ridout et al., 2018).

Several studies testing the relationship between TL and child sexual abuse (CSA) found no association (Glass et al., 2010; Jodczyk et al., 2014; Mason et al., 2015; Vincent et al., 2017). Methodological differences (e.g. use of different questionnaires to assess abuse, level of sensitivity to abuse severity, length of time between abuse and TL assessment) between studies may contribute to divergent findings. Additionally, many of these studies relied on retrospective, unsubstantiated reports of CSA. Prospective work in cohorts with substantiated CSA supports a tendency for non-disclosure in a portion of adult survivors. Comparing self-report in adulthood to agency-notified and substantiated CSA in a prospectively followed birth cohort, Mills et al. (2016) found that 39.6 % of adults with agency-notified CSA did not recall the abuse when asked about it as young adults. Underreporting may contribute to contamination of control groups in retrospective studies of abuse, a problem that can contribute to variability in reported associations between adult health outcomes and CSA exposure (Shenk et al., 2016). Victims of CSA may also be more likely to experience other forms of maltreatment thus confounding attempts to disentangle the specific effects of CSA (Finkelhor et al., 2007; Mitchell et al., 2020). Collectively these issues highlight the need for further work with prospectively followed survivors of substantiated CSA, such as the current study, to uncover the biological embedding of trauma possibly unique to survivors of CSA.

Exposure to trauma in childhood may have effects that extend into the next generation representing an intergenerational transmission of trauma. This transmission is hypothesized to occur via environmental and biological mechanisms. Evidence suggests survivors of abuse suffer psychological and physiological consequences that can contribute to the recreation of high-risk environments wherein their children are more likely to be maltreated (Noll et al., 2009). Parenting difficulties such as poor monitoring, harsh discipline, and high parental stress are prominent in females who have experienced sexual abuse (DiLillo and Damashek, 2003) and may contribute to the recreation of high-risk environments. Moreover, research has identified mood disorders, alcohol/substance abuse and interpersonal violence as adulthood sequelae of CSA (Fergusson et al., 2008; McCloskey and Bailey, 2000), all of which have been shown to have a substantial impact on child development (Ammerman et al., 2009). There are also environmental and health conditions that are common in sexual abuse survivors (e.g. dropping out of high school, teen motherhood, and obesity [Trickett et al., 2011]) that can have major consequences for development of children. Additionally, there may be direct biological transmission of trauma. Recently, Bosquet Enlow et al. (2018) found that maternal CSA-exposure predicted shorter male newborn TL, and Esteves et al. (2020) found an interaction between maternal adverse childhood experiences and telomere attrition in newborns, providing possible evidence for an intergenerational transmission of trauma via accelerated cellular aging.

Biologically plausible modes of transmission for prenatal maternal trauma exposure on offspring TL include possible alterations to gametic TL prior to conception, the impact of maternal stress processes during pregnancy on fetal TL, or indirect influence on rates of telomere attrition postnatally (Dunkel Schetter, 2011; Epel, 2020). These alterations are thought to be driven by processes of dysregulated glucocorticoid signaling, excessive inflammation, and oxidative stress (Entringer et al., 2018; Nelson et al., 2018). Despite the multiple avenues by which children may be negatively impacted by parental CSA-exposure, studies examining intergenerational transmission of this trauma are surprisingly scarce.

Using data from the prospective-longitudinal Female Growth and Development Study of CSA-exposed females and matched controls, we sought to determine the specific impact of CSA on TL as a marker of biological aging. Assessments in this cohort (time 1–6) were carried out at key developmental points including childhood, adolescence, emerging adulthood (mean ages 11, 12, 13, 18, 20, 24 years), and most recently in adulthood (time 7, mean age 36.3 years). Time 7 added assessments of study members' children (N = 124, mean age 10.5 years). We first hypothesized that females exposed to CSA (median age at onset of abuse = 7.8 years) will have shorter mean TL in adulthood compared to females without CSA exposure. Second, we hypothesized that children of CSA-exposed females will have shorter mean TL compared to children of mothers without CSA exposure, providing evidence for group differences in TL across generations (i.e., intergenerational transmission of trauma).

2. Materials and methods

2.1. Study design and sample recruitment

The Female Growth and Development Study began in 1987 (T1, mean age 11 years) as a cross-sectionally designed study. Female subjects with substantiated sexual abuse were referred to the study by Child Protective Services (CPS) agencies in Washington, D.C. metropolitan area. Eligibility for participation included: (1) aged 6–16 years, (2) referral and agreement for participation within 6 months of disclosure of abuse, (3) substantiated sexual abuse perpetrated by a family member, and (4) agreement of participation by a non-abusing caregiver (typically biological mother). The median age for abuse onset was 7.8 years, median duration of abuse was 24 months, 70 % experienced penetration, and 60 % of the perpetrators were primary father figures. Control subjects were recruited from the same communities as the CSA-exposed participants through local advertisements. Eligibility for participation included: (1) no previous CPS referrals or contact, and (2) demographically comparable to a CSA-exposed participant. Control participants and CSA-exposed participants had comparable community features, zip codes, previous non-sexual trauma histories, socioeconomic status, number of parents in the family (1 vs. 2

[1] This reference should bee cited as Shalev et al., 2013b.

parent families), age, and racial/ethnic identities. After initial enrollment, 13 participants in the control group disclosed having a history of CSA. These females were coded as 'other'. Subsequently, information contained in the developmental histories, CPS caseworker reports, and parent/child interview notes were used to classify the 13 participants into the group (CSA vs. non-CSA) that best fit their individual case. Retaining or excluding these participants and their children did not change findings and thus they were included in all analyses.

Five follow-up assessments have been conducted since the start of the study (T2 – T6) with retention rates between 84–88 % at each time point (see Trickett et al., 2011 for a complete accounting of T1-T6). For T7, of the original cohort of 187 females, 16 dropped out prior to T7 assessment, 4 were deceased, and 2 were incarcerated leaving a total of 165 available for assessment. Of these remaining females, 132 were seen at T7 (retention rate of 80 %) with similar rates of retention across the two groups.

Of the 132 females retained in the study at T7, 108 (82 %) consented to and completed blood collection for DNA extraction and TL measurement. There were no group differences in age at study enrollment (T1), race/ethnicity, education at T7, or income at T7 between females consenting to TL measurement and those refusing, or between those consenting to TL measurement and the original study sample. Summary statistics for this sample are provided in Table 1.

As the original participants began to have children, these children have been recruited to participate in the study (Trickett et al., 2011). At T7, a total of 305 children were recorded from all of the original participating females. Due to their mother's lack of participation in T7, 152 children were not seen at T7. Of the children born to mothers participating in T7, 10 (split equally between the CSA and control females) were not seen due to family issues (e.g. CPS involvement, adoption out, residence in juvenile detention), 5 are deceased, and 13 refused sample collection for TL. A total of 125 children consented to and completed buccal swab collection for TL measurement. One child was excluded from analyses due to lack of maternal TL measurement, resulting in a final N = 124 children across 61 families (max = 5; median = 2; mode = 1 child per mother). There were no group differences in % CPS involvement or biological sex between children consenting to TL measurement and those refusing.

2.2. DNA extraction and telomere length analysis

At T7 blood and buccal samples were collected from females and buccal samples were collected from their children. For females, whole blood samples were collected in 10 mL EDTA blood tubes via an IV catheter into the antecubital vein, and immediately centrifuged for 10 min at 1500 *g* prior to collection of plasma. Due to ethical considerations associated with obtaining repeated blood samples from children, most studies have used saliva or buccal swabs instead of the peripheral blood cells. Although previous studies reported high correlations between somatic tissues (Daniali et al., 2013), for all intergenerational analyses, maternal buccal TL was included rather than blood TL to avoid cross-tissue confounding. DNA was extracted from buffy coat and buccal swabs using QIAamp DNA Mini Kit with no modification from factory guidelines (Qiagen, Germany). DNA purity was determined via 260/280 and 260/230 ratios using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific) and quantified using Quant-iT PicoGreen reagent (Thermo Fisher Scientific). However, no rigorous criteria for sample acceptance or rejection was applied at this stage. DNA was stored at -80 °C until TL analysis.

All TL assays were performed in one batch using a quantitative PCR protocol adapted from Cawthon (2002). Briefly, TL is expressed as a ratio of telomeric content (T) to a single-copy housekeeping gene (S). The single copy gene used in the assay is *36B4*. Separate PCR reactions using DNA from the same sample were conducted to quantify telomeric DNA content and *36B4* content on two independent plates. The cycling profile consists of denaturing at 95 °C for 15 s and annealing/extending at 60 °C for 1 min followed by fluorescence reading, 45 cycles. The final reaction mix for the telomeric DNA contains 1x SYBR Green Master Mix (Qiagen), 0.2U Uracil Glycosylase (Thermo Fisher Scientific), 0.1 u M forward primer, 0.1 u M reverse primer, and 3 ng DNA in a 20 u L reaction. The reaction mix for *36B4* contains 1x SYBR Green Master Mix, 0.2U Uracil Glycosylase, 0.3 u M forward primer, 0.5 u M reverse primer, and 3 ng DNA in a 20 u L reaction. The telomere primer sequences are: forward primer 5'CGGTTTGTTTGGGTTTGGGT-TTGGGTTTGGGTTTGGGTT3′; reverse primer 5'GGCTTGCCTTACCCTTACCCTTAC − CCTTACCCTTACCCT3′. The *36B4* primer sequences are: forward primer 5'CAGCAAGTGG-GAAGGTGTAATCC3′; reverse primer 5'CCCATTCTATCATCAACGGGTACAA3′. PCR amplifications used a robotic pipettor (QIAgility, Qiagen) to ensure maximum pipetting accuracy, and real-time qPCR was performed with a unique rotary design machine for sensitive and accurate optical performance (Qiagen's Rotor-Gene Q, Qiagen), which reduces well position effects. Samples derived from the same family (i.e. mother and children) were run on the same plate.

A serial dilution of five standards were used to identify a critical threshold of detection for extraction of Ct values. Average R^2 for the telomere and *36B4* standard curves were 0.9923 and 0.9924 respectively. The average PCR efficiency of reactions assessing telomeric content and genome copy number were 1.88 and 1.94 respectively. The T/S ratio was calculated using the formula $\frac{T}{S} = \frac{2^{Ct_{36B4}}}{2^{Ct_{Telo}}}$, where Ct is the cycle at which the sample crosses a critical threshold of detection for the *36B4* and telomere reactions respectively. The same threshold was used for all assays (*36B4* and telomere). Samples were run in triplicate and the mean Ct across replicates was used for calculating the T/S ratio. When the Ct of one replicate deviated from the mean Ct by more than 15 % it was considered an outlier and the mean Ct was recalculated using two replicates. This occurred for 51 T and 43 S estimations. In the case where Ct standard deviation for either T or S replicates was still greater than 0.25 after removal of a single outlier, or was greater than 0.25 without a clear outlier defined by the criteria above, the sample was reassessed for both telomeric content and genome copy number and subjected to the same quality control evaluation. A total of 9 samples were rerun a second time. One sample failing to reach quality control criteria after two assessments was removed from analyses. In this manner, the average intra-assay coefficient of variation (CV) for Ct values across replicates was less than 1%.

As a control for inter-assay variability, five control samples were run

Table 1
Summary statistics for the sample.

Variable, mean (SD)	Total	CSA-exposed	Control	p-values
Females	(N = 108)	(N = 50)	(N = 58)	–
Age (at DNA collection)	36.3(3.3)	36.8(3.4)	35.8(3.2)	0.11
Race/ethnicity				
Black	37 %	26 %	46.5 %	0.02*
Hispanic	4.6 %	6%	3.5 %	0.52
White	57.4 %	66 %	50 %	0.09
Waist-Height-Ratio (WHtR)	0.52(.15)	0.54(.13)	0.50(.16)	0.04*
Income ($1000/yr)	35(14.8)	34(11.6)	36(12.1)	0.97
Education	16.5(1.9)	16.2(1.9)	16.6(2.0)	0.64
Ever Smoke	51 %	61 %	42 %	0.07
Physical Abuse in Childhood	33 %	48 %	21 %	0.003**
Emotional Abuse in Childhood	37 %	46 %	31 %	0.11
Number of families	61	28	33	–
Children	(N = 124)	(N = 50)	(N = 74)	–
Age (at DNA collection)	10.5(5.2)	11.3(5.6)	10.0(4.8)	0.27
CPS involvement	12.8 %	13.7 %	12.2 %	0.80
Race/Ethnicity				
Black	42 %	26 %	52 %	0.004**
Hispanic	2.5 %	6%	0%	0.02*
White	32.5 %	48 %	22 %	0.002**
Sex Male(Female)	56(68)	22(28)	34(40)	0.99

on each plate. Control samples were selected such that each plate included control DNA extracted from blood of females, buccal of females, and buccal of children. For each plate, the Ct value of each control DNA was divided by the average Ct value for the same DNA across all runs to get a normalizing factor for that sample on a given plate. This was repeated for all controls on a given plate to get an average normalizing factor for that plate. In this manner, the average inter-assay CV was 0.81 % for telomere plates and 0.54 % for 36B4 plates.

To calculate the intra-class correlation coefficient (ICC) as an additional measure of within-plate repeatability among replicates of each sample (Eisenberg, 2016), we used a linear mixed model (PROC MIXED, SAS v.9.4) fitted with restricted maximum likelihood (REML) and unstructured covariance structure (TYPE = UN) of the raw Ct values separately for telomere and 36B4 plates. The within-plate repeatability was very high (Tel, ICC = 0.98; 36B4, ICC = 0.97). Between-plate repeatability was calculated by running 14 samples in duplicates across different plates. A linear mixed model was fit again using PROC MIXED with REML and unstructured covariance structure for Ct values as the outcome. Between-plate repeatability was also reasonably high (Tel, ICC = 0.71; 36B4, ICC = 0.78).

2.3. Other measures

Measures of socioeconomic status, smoking, and waist-to-height (WHtR) ratio were included as covariates due to known associations with TL (Needham et al., 2013). Income was assessed by self-report in increments of $1,000. For instance, a female coded as '15' for income reported a household yearly income between $14,000 - $14,999 per year and a female coded '25' for income reported between $24,000-$24,999 per year. Education was reported as years of schooling completed for 0–12 years (0 = no schooling, 12 = grade 12 without diploma). Females receiving their high school diploma or GED were scored 13 or 14, respectively, with some college, technical, associate, bachelor's, master's, professional, and doctoral degrees each coded as one additional advancement in education (scores of 16–21). Income and education were included as separate covariates. Individuals that smoked more than 100 cigarettes at any point in their lifetime were coded as '1' and those that had not were coded as '0' on the dichotomous variable "ever smoke." WHtR was measured concurrently with TL sampling and was calculated as the ratio of waist measurement in centimeters to height measurement in centimeters. WHtR is generally accepted as a more accurate measure of obesity and indicator of weight related disease risk than body mass index (Ashwell et al., 2014; Savva et al., 2013).

Measures of anxiety and depression were taken in both females (Brief Symptom Inventory – Anxiety [Spielberger, 1973], Beck Depression Inventory – Second Edition [Beck et al., 1996]) and children (State-Trait Anxiety Inventory for Children [Spielberger, 1973], Children's Depression Inventory – Second Edition [Kovacs, 1985]); higher scores indicate greater self-reported symptom severity. To investigate the possible unique influence of CSA, exposure to physical and emotional abuse in childhood was assessed in the females using a standardized Comprehensive Trauma Screen (CTI) (Barnes et al., 2009). Exposure to physical and emotional abuse were coded as separate variables as well as included with CSA-exposure as a comprehensive childhood abuse exposure measure (i.e., Total Abuse). To isolate the biological transmission of trauma in children's TL, several confounding factors were considered as covariates including: mother's age at first pregnancy and CPS involvement for the children (as a measure of direct trauma exposure).

2.4. Statistical analysis

Statistical analyses were performed with SAS V.9.4. Due to the small sample size and potential deviations from normal distribution of each variable, mean differences in continuous demographic variables between CSA-exposed and control groups of females and children (e.g. age, WHtR, years of education, income) were assessed using Wilcoxon rank-sum testing. Monte Carlo simulation of exact p-values for mean differences in demographic variables were assessed at a sampling depth of 100,000 (sample depths of 10,000 through 1000,000 were run with no resulting changes in significance of simulated exact p-values). Differences in categorical demographic variables (e.g. biological sex in children, race/ethnicity categories, smoking status, exposure to non-CSA abuse in childhood) were assessed using chi-square tests of homogeneity. No significant differences were found in demographic characteristics between individuals excluded for missingness and those included in analyses, and missing data on predictor variables were addressed simultaneously using multiple imputation and complete case analysis. We created 20 imputed datasets using IVEWare (Raghunathan et al., 2002), and combined imputed results with SAS MIANALYZE procedure. Data was analyzed both without imputation and with imputed missing data. Imputed and complete-case datasets produced similar results with no changes in direction or size of effects, and we report results with the imputed data.

To avoid confounding due to the strong correlation between maternal age and child age ($r = 0.46$; $p < .0001$), both child and maternal TL were age-adjusted for intergenerational models. TL variables for these analyses were created using standardized residuals derived from regressing log-transformed TL on age-in-months at time of collection. Log-transformations and age-adjustments of TL were conducted independently for females and children to account for generational differences. All intergenerational models were run with age-adjusted TL and then rerun as TL with age as a predictor yielding no differences in direction or significance, thus only age-adjusted TL models are reported here for analyses in children. To account for the nested data structures and violation of independence of observations multilevel linear modelling (MLM) was used to test both hypotheses.

For female-only models testing the impact of CSA, log-transformed TL measured in blood and buccal was regressed onto: an intercept only model (Model 1), a model conditioned on age and tissue type (Model 2), models conditioned on age, tissue type, and CSA-status (Model 3) and adjusted for other covariates (Model 4), models conditioned on age, tissue type, CSA-status, physical abuse, emotional abuse (Model 5) and adjusted for other covariates (Model 6), and models conditioned on age, tissue type, total abuse (Model 7) and adjusted for other covariates (Model 8). For intergenerational models log-transformed age-adjusted TL measured in children nested in mothers was regressed onto: an intercept only model (Model 1), a model conditioned on maternal TL (log-transformed age-adjusted buccal-TL) (Model 2), a model conditioned on maternal TL and child's sex (Model 3), a model conditioned on maternal TL, child's sex, and maternal CSA-status (Model 4), a model conditioned on maternal TL, child's sex, maternal exposure to CSA, physical abuse, and emotional abuse as separate variables (Model 5), a model conditioned on maternal TL, child's sex, and maternal exposure to total abuse as a combined variable (Model 6), and a model conditioned on maternal TL, child's sex, maternal exposure to abuse, and maternal smoking and income (Model 7). All models used an unstructured covariance structure (SAS v9.4 TYPE = UN), which does not assume an identical variance-covariance structure between tissues for each female or between children for every family in the dataset. Application of other plausible covariance structures decreased model fit. Measures of anxiety and depression in both females and children, CPS involvement for the children, and maternal age at first pregnancy were not associated with TL and inclusion of these covariates did not change the direction or associations in any model. These measures were therefore not included in analyses to avoid model-overfitting (Babyak, 2004; Hawkins, 2004); Statistical significance was set at two-tailed $p < 0.05$. Unless specified, all data are presented as mean ± standard error (SEM).

3. Results

3.1. Sample demographics

There were no significant differences detected in mean age at sample collection, smoking, endorsement of exposure to emotional abuse in childhood, years of education, or income between CSA-exposed and control females (Table 1). Consistent with previous analyses in this cohort, significant differences were found in WHtR between groups (Noll et al., 2007), with higher WHtR among CSA-exposed females (abuse = 0.54 ± .13; control = 0.50 ± .16). There were also differences along race/ethnicity (greater percentage of black females in the control group) and endorsement of exposure to physical abuse in childhood (CSA-exposed = 48 %; control = 21 %). In the children, no significant group differences were found in age at sample collection or sex (% female). There was a significant difference in minority status mirroring that of the mothers (Table 1).

3.2. Telomere length of females exposed to child sexual abuse versus controls

For mothers in this cohort with both buccal and leukocyte TL available (N = 72), the correlation between raw TL across the two tissues was strong (r = 0.69, p < .0001; Pearson's correlation) and consistent with previously reported cross-tissue TL correlations (Daniali et al., 2013; Friedrich et al., 2000). In an intercept-only model predicting TL as a repeated measure within individuals the ICC = 0.56, indicating 44 % of the total variance was accounted for by within person differences between tissues. In all models tested, tissue type was significantly predictive of TL (b = 0.27 ± .04; p < .0001) such that TL measurement in leukocytes was longer on average than measurement in buccal tissue.

Testing our first hypothesis in a within-person repeated measures MLM using both tissues, CSA status was not a significant predictor of TL in females (β = -0.02, p = .84). Some predictors typically associated with variation in TL (WHtR, education, race/ethnicity) were also not significantly associated with TL in this sample. Sensitivity analyses excluding Hispanic females did not alter findings. In fully adjusted models, income was significantly predictive of TL such that higher income predicted longer TL (Table 2). Separating out abuse subtypes (childhood sexual, physical, or emotional abuse) (Models 5 and 6) or including them as a combined measure of total abuse (Models 7 and 8) did not change our findings. All interaction models and inclusion of random slopes increased the AIC and BIC, indicating worse fitting models for the data. Linear regression analyses within each tissue (blood and buccal) separately yielded similar models as the full MLM with no change to final results.

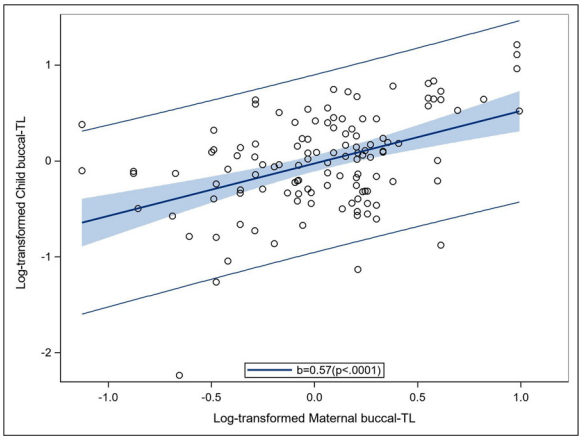

Fig. 1. Relationship between age-adjusted maternal and child buccal telomere length.

3.3. Testing associations between child telomere length and maternal factors

Given the strong cross-tissue correlation within mothers and the lack of blood samples in children, intergenerational models were tested using only buccal-TL to allow for testing of effects within the same tissue. In an intercept-only model the ICC = 0.48, indicating approximately 48 % of the total variance in age-adjusted child TL was accounted for by family-level factors and 52 % by individual-level factors. Age-adjusted maternal buccal-TL was significantly positively associated with age-adjusted child buccal-TL (β = 0.57 ± .1; p < .0001) (Fig. 1). Child's biological sex was significantly associated with age-adjusted child TL (Table 3) (β = -0.17 ± .08, p < .01). On average, males had shorter TL than females holding all other predictors constant.

We next tested our second hypothesis of intergenerational transmission of trauma using a random-intercept model (children nested in

Table 2
Predicting log-transformed telomere length in child sexual abuse exposed and non-exposed females.

			CSA-only		Separate Forms of Abuse		Total Childhood Abuse	
Predictor (β; ± SEM)	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Fixed Effects								
Intercept	−1.34(.04)	−2.22(.48)	−2.22(.48)	−1.94(.69)	−2.19(.48)	−2.00(.69)	−2.15(.47)	−1.94(.68)
Age	–	0.002(.001)	0.002(.001)	0.002(.001)	0.002(.001)	0.001(.001)	0.001(.001)	0.001(.001)
Tissue (blood)	–	0.28(.05)***	0.28(.05)***	0.27(.05)***	0.27(.04)***	0.27(.05)***	0.28(.04)***	0.27(.05)***
CSA-Status	–	–	−0.02(.09)	−0.03(.10)	−0.07(.09)	−0.07(.10)	–	–
Physical Abuse	–	–	–	–	0.19(.11)	0.15(.12)	–	–
Emotional Abuse	–	–	–	–	0.04(.11)	0.15(.13)	–	–
Total Abuse	–	–	–	–	–	–	0.06(.05)	0.08(.05)
WHtR	–	–	–	0.37(.33)	–	0.38(.11)	–	0.30(.32)
Ever Smoke	–	–	–	0.03(.11)	–	0.03(.11)	–	0.02(.11)
Education	–	–	–	−0.05(.03)	–	−0.04(.03)	–	−0.04(.03)
Income	–	–	–	0.01(.004)*	–	0.01(.004)*	–	0.01(.004)*
Race/ Ethnicity								
Black	–	–	–	0.04(.11)	–	0.09(.11)	–	0.11(.11)
Hispanic	–	–	–	−0.22(.23)	–	−0.28(.23)	–	−0.25(.23)
Random Effects								
Intercept	0.14(.03)	0.16(.03)	0.17(.03)	0.14(.03)	0.16(.03)	0.13(.03)	0.17(.03)	0.13(.03)
AIC/BIC	244/251	228/234	231/237	197/202	232/238	195/200	231/236	195/200

*p < 0.05; **p < 0.01; ***p < 0.001.

Table 3
Age-adjusted child telomere length predicted by maternal-level and child-level factors.

Predictor (β; ± SEM)	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Fixed Effects						
Intercept	−0.02(.06)	−0.04(.05)	−0.29(.13)	−0.33(.14)	−0.31(.15)	−0.29(.15)
Maternal-bTL	–	0.57(.12)***	0.57(.11)***	0.56(.12)***	0.54(.12)***	0.57(.12)***
Sex (Male)	–	–	−0.17(.08)*	−0.17(.08)*	−0.17(.08)*	−0.17(.08)*
Maternal CSA	–	–	–	−0.10(.10)	−0.16(.11)	–
Maternal Physical Abuse	–	–	–	–	−0.20(.13)	–
Maternal Emotional Abuse	–	–	–	–	0.05(.12)	–
Total Maternal Abuse	–	–	–	–	–	−0.004(.04)
Random Effects						
Intercept	0.13(.04)	0.08(.03)	0.06(.03)	0.06(.03)	0.07(.03)	0.07(.03)
AIC/BIC	182/189	161/166	160/164	162/166	164/169	164/169

*p < 0.05;**p < 0.01;***p < 0.001.

families) and stepwise inclusion of covariates. Maternal CSA-exposure was not significantly associated with child TL in any models tested (Table 3). Models including maternal sexual, physical, and emotional abuse exposure as independent variables or a total abuse exposure variable were a worse fit for the data than a model including only maternal TL and child's biological sex (Model 3). No interaction terms for CSA-exposure and other variables were significant. All interaction models and inclusion of random slopes increased the AIC and BIC, indicating worse fitting models for the data. Models excluding maternal bTL did not change the null association between child bTL and maternal exposure to CSA, other forms of abuse, or the total maternal childhood abuse variable.

4. Discussion

In the current study, we examined differences in biological aging, as measured by TL, between females exposed to CSA versus non-exposed control females. Further, we tested whether children of CSA-exposed females evince shorter (TL) compared with children of non-exposed mothers (i.e., the potential of intergenerational transmission of trauma). TL is highly heritable, and research supports a strong maternal influence on child TL at birth (Akkad et al., 2006). Though there is a high degree of variability in studies assessing maternal-offspring TL inheritance (Eisenberg, 2014), our findings on the maternal-offspring TL relationship are consistent with overall findings of a recent meta-analysis (Broer et al., 2013). Replicating previous research, maternal buccal TL was significantly and positively associated with child buccal TL, and females had longer TL than males. However, contrary to predicted hypotheses, we found no evidence for CSA-related group differences in TL of females nor of their children.

Though some evidence exists that individuals with a history of early adversity may have shorter TL in adulthood (Ridout et al., 2018), our findings are in line with previous work on the specific relationship between CSA and TL in middle-aged individuals (Glass et al., 2010; Jodczyk et al., 2014; Mason et al., 2015; Vincent et al., 2017). Studies that have found differences in TL between maltreated and non-maltreated adults have recruited individuals with moderate to severe retrospectively reported childhood maltreatment (Tyrka et al., 2010), or have condensed all forms of childhood adversity (e.g. severe chronic illness, familial mental health/alcohol dependency issues) into one measure of exposure (Kananen et al., 2010). Studies reporting no association between TL and maltreatment in adulthood have drawn from either birth cohorts (Jodczyk et al., 2014) or larger national cohorts (Glass et al., 2010; Mason et al., 2015). Participants in our study were recruited due to their substantiated CSA exposure in an attempt to avoid cross-group contamination. While such a prospective design has the potential to increase the ability to detect differences between maltreated individuals and controls, there may be additional important differences between our study and those previously reporting TL differences between groups. For instance, prospective recruitment implies immediate caregivers were knowledgeable about the abuse thus possibly more likely to take steps to end the abuse and seek help for their daughters, and preliminary evidence suggests this may moderate the relationship between certain forms of CSA and TL (Sosnowski et al., 2019). Retrospective reported abuse, in contrast, is more likely to have gone unaddressed during childhood, could have been more prolonged, and is less likely to be treated (Kendall-Tackett, 2004). Thus, retrospectively reported abuse may be more costly. There is also support for the idea that subjectively reported abuse may be differentially related to health outcomes than objectively determined abuse, possibly due to identification of differing groups of individuals depending on the reporting method (Baldwin et al., 2019). Retrospective reporting tends to be strongly related to subjective health outcomes (e.g. self-reported adult psychopathology [Danese and Widom, 2020]) with weaker and more variable associations to objective health outcomes (e.g. clinical measurements of physical health and cognitive ability) (Reuben et al., 2016). Conversely, objective measures of early adversity tend to have consistent associations with objectively measured poorer physical and mental health (Reuben et al., 2016). Though it is yet to be determined if this also holds true for measures of TL, retrospective vs. prospective study design remains an important distinction that likely influences the variability of associations between early adversity and TL.

This study aimed to investigate the specific impact of CSA exposure on TL in adulthood and the next generation. Exposure to other forms of adversity in childhood, including those with previously demonstrated impacts on TL (e.g. physical abuse, neglect, poverty, exposure to family and neighborhood violence, severe childhood illness) was not used as exclusionary criteria in recruitment of the original female participants for both the CSA-exposed and control groups. While our findings do not support a role of substantiated CSA-exposure or retrospectively reported physical and emotional abuse during childhood on TL during midlife, we are unable to speak specifically to the impact of adversity during childhood as a whole. It is plausible that exposures to childhood adversities outside of those captured in this study (e.g. extreme poverty, illness) could have impacted TL in the entire cohort thus obscuring differences due to abuse. Additionally, measures of severity of each abuse type were not included which may have impacted our ability to detect differences (Ridout et al., 2018).

The cohort of females studied has been prospectively followed since the early 1980's when their sexual abuse was substantiated, with retention rates between 84–88 % at each time point (Trickett et al., 2011). CSA-exposed and non-exposed females were closely matched demographically and from the same Washington, D.C. metropolitan area. The carefully executed nature of this decades-long study offered a unique opportunity to test differences due specifically to CSA-exposure between groups with respect to biological aging measured by TL.

That being said, we acknowledge limitations. An important issue with studies assessing the impact of maltreatment on TL is timing of

exposure vs. measurement. A recent meta-analysis on early adversity exposure and TL found that the magnitude of association between TL and exposure to early abuse/neglect decreases significantly with age; as individuals exposed to early trauma age, the magnitude of telomere shortening due to adversity decreases when compared to demographically similar controls (Ridout et al., 2018). In this cohort, the females were sexually abused between the ages of 6–16 years and telomere measurement occurred between twenty- and thirty-years post-abuse at a mean age of 36 years. It is possible that differences in TL between females due to CSA exposure in this sample have been washed out by decades of other accumulating influences on TL (e.g. smoking, psychological symptoms and treatments, etc.). Measurement of TL in the children also occurred several years after birth. This may limit our ability to extract the specific contribution of maternal-CSA exposure to children's TL as other environmental exposures within the children's lives may have altered their TL beyond what was inherited maternally. While we were able to control for differences in CPS involvement in the children, this is likely a poor estimate of adversity exposure in this subsequent generation and not necessarily sufficient to capture adversity factors that could influence TL.

We did not include measures of current stress exposure in mothers and children, thus it is plausible that we did not capture a vulnerability to stress that could be transmitted intergenerationally due to maternal CSA-exposure. Research supports the idea that early adverse experiences may confer a vulnerability to stress in later life leading to a differential impact of current stress (Kiecolt-Glaser et al., 2011); individuals exposed to CSA and their offspring may only display accelerated aging in the face of additional current stressors. It is also worth noting again that the CSA-exposed and non-exposed females in this cohort were exposed to other forms of child abuse and adversity, which may have led to shortening of TL for participants in both groups but no additional shortening due specifically to CSA-exposure. Power analyses indicated we were powered to detect small-medium effect sizes, but we may have been underpowered to detect smaller effects and it may be the case that CSA-specific effects on TL in adulthood and intergenerationally may be smaller than our power to detect. Larger samples in future prospective studies of substantiated abuse may be required to detect this effect.

In conclusion, although we found no evidence of the influence of CSA-exposure on TL as a measure of biological aging, it is possible that early trauma may be embedded within an individual as a vulnerability to stress and that this vulnerability could be transmitted intergenerationally. These null findings point to the need for within-person repeated measures, beginning in early life, of the biological embedding of early stress. Deepening our understanding of the possible intergenerational effects of early-life trauma may lead to more appropriate treatment for stress-related physical and mental health disorders.

Declaration of Competing Interest

The authors declare no conflict of interest

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