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Regular Article

Temperament and sex as moderating factors of the effects of exposure to maternal depression on telomere length in early childhood

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Abstract

Individual differences in sensitivity to context are posited to emerge early in development and to influence the effects of environmental exposures on a range of developmental outcomes. The goal of the current study was to examine the hypothesis that temperament characteristics and biological sex confer differential vulnerability to the effects of exposure to maternal depression on telomere length in early childhood. Telomere length has emerged as a potentially important biomarker of current and future health, with possible mechanistic involvement in the onset of various disease states. Participants comprised a community sample of children followed from infancy to age 3 years. Relative telomere length was assessed from DNA in saliva samples collected at infancy, 2 years, and 3 years. Maternal depressive symptoms and the child temperament traits of negative affectivity, surgency/extraversion, and regulation/effortful control were assessed via maternal report at each timepoint. Analyses revealed a 3-way interaction among surgency/extraversion, sex, and maternal depressive symptoms, such that higher surgency/extraversion was associated with shorter telomere length specifically among males exposed to elevated maternal depressive symptoms. These findings suggest that temperament and sex influence children's susceptibility to the effects of maternal depression on telomere dynamics in early life.

Keywords: Differential susceptibility; maternal depression; sex; telomere; temperament

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Introduction

The theory of differential susceptibility to context posits that individuals vary in their sensitivity to the influences of the social and physical environment on their health, with a minority subpopulation demonstrating exceptionally positive trajectories of health and development under supportive conditions and particularly poor trajectories under adverse conditions (Boyce, 2016). This differential susceptibility is hypothesized to arise in early life, driven by underlying neurobiological sensitivities to contextual influences (Boyce, 2016). Evidence for this theory has accumulated across multiple domains of exposures and developmental and health outcomes. Such findings have repeatedly shown that children who are highly reactive to their environment show exceptionally high or low rates of illness or psychological problems, depending on the quality of their social environment. More specifically, these children demonstrate the most optimal health and developmental outcomes under supportive and nurturing environmental conditions and the poorest outcomes under more stressful or adverse environments. Low reactive or average reactive children, on the other hand, demonstrate relatively little effect from positive or negative environmental exposures (Belsky & Pluess, 2013; Boyce, 2016). Thus, children's sensitivity to context is expected to moderate the influence of environmental exposures on developmental and health outcomes (Boyce, 2016).

The overall goal of the current study was to examine whether the effect of maternal depression on child telomere length in early life is moderated by child temperament and biological sex. Exposure to parental depression/psychopathology has been identified as a contextual stressor that differentially influences child outcomes, depending on their neurobiological responsivity (Boyce, 2016; Cummings et al., 2007; Shannon et al., 2007). Temperament and sex have been implicated as likely drivers of differences in individuals' sensitivity to context (Boyce, 2016). Telomeres—repeating nucleotide sequences of variable number that protect against chromosome deterioration and regulate cellular and tissue function (Blackburn & Gall, 1978)—was chosen as the outcome of interest given the potential role of telomeres in current and future health: Shorter telomere length has been found to be predictive of abnormalities in brain structure and functioning, the development of chronic physical diseases and

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mental health disorders throughout life, and earlier mortality (Geronimus et al., 2015; Hochstrasser et al., 2012; Rode et al., 2015). Notably, telomere erosion occurs most rapidly in the first years of life, and telomere biology may be particularly vulnerable to psychosocial exposures in early development (Bosquet Enlow et al., 2020; Coimbra et al., 2017; Frenck et al., 1998; Rufer et al., 1999; Sidorov et al., 2009; Zeichner et al., 1999). Further, telomere length at any given timepoint is determined by initial telomere length and subsequent attrition (Bosquet Enlow et al., 2018; Wadhwa et al., 2009). Consequently, telomere loss in early childhood may have particular impact on physical and mental health outcomes across the lifespan, highlighting the need to identify factors that influence telomere length dynamics in the first years of life.

Maternal depression has long been recognized as a major contextual stressor for children, beginning in utero and continuing into the postpartum period and throughout childhood (Goodman, 2007; Thompson & Henrich, 2023; Van den Bergh et al., 2017). Studies of maternal depression effects specifically on child telomere length dynamics are limited but suggestive. A few studies examining determinants of newborn telomere length have considered maternal depression in pregnancy, with evidence for both negative and positive associations, specifically evident among males (Bosquet Enlow et al., 2018, 2021). A study of 48 mother-infant dyads found that an increase in maternal depressive symptoms between infant ages 6 and 12 months was associated with shorter infant telomere length at age 18 months (Nelson et al., 2018). A study of childhood exposure to maternal depression from birth to age 5 years in a cohort of Latino children found that exposure to maternal clinical depression at 3 years of age was associated with shorter child telomere length at 4 and 5 years of age (Wojcicki et al., 2015). A study of 97 10-–14-year-old healthy, non-depressed daughters of mothers with and without a history of depression found that daughters of depressed mothers had shorter telomeres (Gotlib et al., 2015). Similarly, a study of 150 adolescents of depressed and non-depressed mothers found shorter telomere length among the former group (Nelson et al., 2021).

Variations in children's sensitivity to the effects of exposure to maternal depression have been attributed to genetic, epigenetic, and psychobiological processes (Thompson & Henrich, 2023). For example, data suggest that maternal depression has a more robust impact on children's affective and autonomic stress responsivity in children with specific genetic variants (Cao et al., 2018; Ludmer et al., 2015; Thompson & Henrich, 2023). Particularly relevant, a small study of 40 9-year-old boys found that those with greater genetic sensitivity scores related to dopamine and serotonin pathways had the shortest telomere lengths under adverse conditions (maternal depression, low income, low maternal education, unstable family structure, harsh parenting) and the longest telomere lengths in more advantaged environments (Mitchell et al., 2014). However, an examination of maternal depression and child telomere length in middle childhood in a much larger sample of boys and girls ($N = 2,879$) failed to observe an association, even after considering potential moderating effects of DRD2 (dopamine) genotypes (Thompson & Henrich, 2023). Other studies suggest that associations between maternal depression and child telomere length are found among children with increased physiological reactivity to stress (Gotlib et al., 2015; Nelson et al., 2018). In sum, the extant literature suggests an association, albeit inconsistent, between maternal depression and child telomere length across developmental stages, with some evidence for moderating effects of individual characteristics on this association. More research is needed to understand the specific factors that influence child susceptibility to maternal depression effects on telomere length dynamics, particularly in early development.

Temperament has been identified as a likely source of differential sensitivity to context (Boyce, 2016). Temperament traits present as behavioral manifestations of underlying physiological predispositions to sensitivity and reactivity to internal and external stimuli that interact with environmental contexts to contribute to developmental outcomes (Boyce, 2016). Temperament traits emerge in infancy, are relatively stable, and underlie expressions of stress reactivity, emotionality, and sociability (Gartstein & Rothbart, 2003; Stifter & Dollar, 2016). Researchers have identified three main temperament domains: negative affectivity, i.e., the tendency to express negative emotions (anger, fear, sadness); surgency/extraversion, i.e., level of approach behaviors, activity level, and impulsivity; and regulation/effortful control, i.e., the ability to control attention and behavior (Ahadi et al., 1993; Rothbart et al., 2000; Rothbart & Bates, 2007). Notably, temperament characteristics have been associated with differences in reactivity of physiological stress response systems implicated in telomere length dynamics, including the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (Bajgarova & Bajgar, 2020; Bosquet Enlow, Sideridis, et al., 2019; Calkins & Fox, 2002; Donzella et al., 2000; Gotlib et al., 2015; Huffman et al., 1998; Jones et al., 2018; Kroenke et al., 2011; Lee & Doan, 2020; Nelson et al., 2018; Perry et al., 2018; Tervahartiala et al., 2021). Moreover, there is evidence that caregiving and dyadic-relationship quality, which have been shown to be disrupted in the presence of maternal depression, can modify associations between child temperament and later developmental outcomes (Belsky et al., 1998; Belsky & Pluess, 2009; Bosquet Enlow, Petty, et al., 2019; Zhang et al., 2022). Thus, child temperament may be an important characteristic that influences children's sensitivity to the effects of maternal depression on telomere biology.

In a previous study using the cohort providing data for the current analyses, we found that temperament was associated with telomere length and telomere attrition rate across the first three years of life, without consideration of contextual variables (Bosquet Enlow et al., 2023). Specifically, analyses revealed that greater regulation/effortful control was associated with longer telomere length and that higher surgency/extraversion was associated with decreased rate of telomere attrition from infancy to age 3 years (Bosquet Enlow et al., 2023). Thus, the findings suggested a potential protective effect of these temperament characteristics on telomere erosion in the sample as a whole. Notably, this cohort is well resourced, and, consequently, the parents may have provided generally supportive conditions for their children's development. Children more temperamentally reactive to their environment may have been better able to benefit from any protective contextual influences on telomere dynamics. The current study extends these findings by examining how temperament characteristics are associated with telomere attrition under adverse environmental conditions, specifically exposure to maternal depression. Evidence that temperament traits confer differential susceptibility to both positive and negative environmental conditions on telomere length dynamics would enhance our understanding of the determinants of telomere length in early life. In the current study, we also consider the potential moderating effects of child sex on the associations of maternal depression and child temperament with child telomere length. Although we did not find sex-specific associations of temperament with telomere length in our prior study, other work suggests that males and females may be

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differentially susceptible to the effects of psychosocial exposures, including maternal depression, on telomere attrition, with males frequently showing greater vulnerability (Bosquet Enlow et al., 2018, 2021; Bosquet Enlow, Sideridis, et al., 2019; Zalli et al., 2014). Thus, child susceptibility to maternal depression effects on telomere biology may be influenced by child sex.

The primary objective of the current study was to examine whether temperament and biological sex impart differential susceptibility to the effects of exposure to maternal depression on telomere length during the first 3 years of life in a community sample of healthy children. Specifically, we tested whether the temperament traits of negative affectivity, surgency/extraversion, and regulation/effortful control moderated associations between exposure to elevated maternal depressive symptoms and measures of telomere length from infancy to age 3 years. We conceptualized higher levels of negative affectivity and surgency/extraversion as factors that confer greater sensitivity to the environment for several reasons, including evidence that both greater negative emotional reactivity, reflected in higher levels of negative affectivity, and greater positive emotional reactivity, reflected in higher levels of surgency/extraversion, have been associated with heightened sensitivity to the environment (Boyce, 2016); that studies have repeatedly shown that greater negative affectivity/emotionality increases a child's susceptibility to environmental influences (Boyce, 2016; Markovitch et al., 2023); and that activity level, a component of surgency/extraversion, particularly in combination with high negative emotionality, has been associated with greater environmental sensitivity (Markovitch et al., 2023). Higher levels of effortful control, on the other hand, may help regulate physiological, emotional, and behavioral stress reactivity, dampening negative environmental exposure effects on telomere biology (Calkins & Fox, 2002; Donzella et al., 2000; Huffman et al., 1998; Jones et al., 2018). Thus, we hypothesized that, in the context of exposure to elevated maternal depressive symptoms, higher levels of negative affectivity and surgency/extraversion and lower levels of regulation/effortful control would be associated with shorter telomere length relative to lower levels of negative affectivity and surgency/extraversion and higher levels of regulation/effortful control. We further hypothesized that higher levels of negative affectivity and surgency/extraversion and lower levels of regulation/effortful control would be associated with an increased rate of telomere attrition from infancy to age 3 years in the context of exposure to elevated maternal depressive symptoms. Finally, we examined whether any moderating effects were sex specific. We hypothesized that the joint effects of maternal depression exposure and temperament on telomere length and telomere attrition would be more pronounced among male children compared to female children, given that sex has been identified as a factor that influences individuals' sensitivity to context and that findings from numerous studies suggest that males are more vulnerable to the effects of a range of environmental exposures on a host of developmental outcomes, including maternal depression effects on telomere length in early life.

Method

Participants

Participants were recruited from a registry of local births comprising families who had indicated willingness to participate in developmental research. Families in the current analyses participated in a prospective study to examine the early development of emotion processing. Exclusion criteria included known prenatal or perinatal complications, maternal use of medications during pregnancy that may have significant impact on fetal brain development (i.e., anticonvulsants, antipsychotics, opioids), pre- or post-term birth (± 3 weeks from due date), developmental delay, uncorrected vision difficulties, and neurological disorder or trauma. After enrollment, families were no longer followed and their data were excluded from analyses if the child was diagnosed with an autism spectrum disorder or a genetic or other condition known to influence neurodevelopment. By design, families were enrolled in the parent study when the children were 5, 7, or 12 months old (T1), with a smaller subsample to be followed when the children were 2 years (T2) and 3 years (T3) of age. Supplemental funding obtained after the start of the parent project allowed for the collection of saliva samples at T1, T2, and/or T3 from families who were age eligible and interested in participating. To be included in the current analyses, participants needed to provide, at minimum, telomere length data, concurrent temperament data, and concurrent maternal depression data from at least one of these timepoints, which provided an analytic sample of $N = 600$.

Procedures

In-person study visits were administered at the T1 and T3 timepoints. Staff collected saliva samples for telomere length assaying during these visits. At T2, there were two options for saliva collection: Parents collected and returned the saliva sample via a mailer, or a research assistant collected the saliva sample during a home visit. Parents were instructed as to how to collect the sample during the T1 laboratory visit and provided links to online video instructions prior to the T2 collection. Sociodemographic data were obtained at T1 and child temperament and parental depressive symptom data at T1, T2, and T3 via online questionnaires completed by the child's primary caregiver, almost exclusively the child's mother (≥ 97%). Study procedures complied with APA ethical standards and were approved by the Institutional Review Board of Boston Children's Hospital. Parents provided written informed consent prior to the initiation of study activities. Participants were provided monetary compensation for their time.

Measures

Sociodemographics

At T1, the child's parent completed online questionnaires that inquired about the child's age, sex assigned at birth (hereafter "sex"), and race/ethnicity, maternal and paternal age and educational attainment, and annual household income. Child and parental age were considered as continuous variables. Child race was categorized as American Indian or Alaska Native, Asian, Black/African American, White, or more than one race. Child ethnicity was categorized as Hispanic/Latino or not Hispanic/Latino. Parental educational attainment was categorized as high school degree/GED or less, Associate's degree, Bachelor's degree, Master's degree, or graduate degree (M.D., Ph.D., J.D., or equivalent). Annual household income was scored into one of five categories, ranging from less than $35,000 per year to $100,000 per year or greater.

Maternal depressive symptoms

Maternal depressive symptoms were measured in infancy and at child ages 2 years and 3 years via the revised Beck Depression Inventory (BDI-IA; (Beck & Steer, 1993; Beck et al., 1988), a 21-item, highly reliable (internal consistency estimates from .73 to .92; Dozois et al., 1998) and valid self-report questionnaire that assesses

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the frequency and intensity of depressive symptoms over the prior two weeks. Individual items were scored on a 4-point scale (range 0–3) and summed, for a total possible range of 0–63. Cronbach's alpha scores in this sample were .75, .78, and .79 at infancy, 2 years, and 3 years, respectively. Higher scores indicate greater depressive symptoms, with scores of 0–9 suggesting no or minimal depression, 10–18 mild depression, 19–29 moderate depression, and 30–63 severe depression (Beck et al., 1988). Mothers were categorized as having either no/low (0–9) or elevated (≥ 10) depressive symptoms, and these groups were used in analyses to facilitate clinical interpretation of findings.

Temperament

At T1, parents completed the Infant Behavior Questionnaire-Revised (IBQ-R; Gartstein & Rothbart, 2003). At T2 and T3, parents completed the Early Childhood Behavior Questionnaire (ECBQ; Putnam et al., 2006), an age-upward extension of the IBQ-R. For both the IBQ-R and ECBQ, parents rated the frequency that their child engaged in specific day-to-day behaviors in the prior 1–2 weeks using a 7-point scale, with responses ranging from 1 (never) to 7 (always). Item scores were summed and averaged according to measure scoring rules to create subscale scores, with higher scores indicating greater levels of that temperament dimension. Cronbach alpha scores reported below were derived from the current sample.

The IBQ-R comprises 14 subscales, which factor analyses have previously shown contribute to composite measures for three domains of child temperament: negative affectivity ($\alpha = .80$), consisting of the subscales Sadness, Distress to Limitations, Fear, and Falling Reactivity/Rate of Recovery from Distress (reverse-scored); surgency/extraversion ($\alpha = .81$), consisting of the subscales Approach, Vocal Reactivity, High Intensity Pleasure, Smiling and Laughter, Activity Level, and Perceptual Sensitivity; and orienting/regulation ($\alpha = .70$), consisting of the subscales Low Intensity Pleasure, Cuddliness, Duration of Orienting, and Soothability (Gartstein & Rothbart, 2003).

The ECBQ, comprising 18 subscales, also provides three composite measures: negative affectivity (T2 $\alpha = .80$, T3 $\alpha = .77$), consisting of the subscales Discomfort, Fear, Sadness, Perceptual Sensitivity, Shyness, Soothability, Frustration, and Motor Activation; surgency/extraversion (T2 $\alpha = .70$, T3 $\alpha = .71$), consisting of the subscales Impulsivity, Activity Level/Energy, High Intensity Pleasure, Sociability, and Positive Anticipation; and effortful control (T2 $\alpha = .77$, T3 $\alpha = .80$), an age-upward extension of the IBQ-R orienting/regulation factor (Putnam et al., 2006), consisting of the subscales Inhibitory Control, Attentional Shifting, Attentional Focusing, Low Intensity Pleasure, and Cuddliness.

Telomere length

As previously described (Bosquet Enlow et al., 2020), telomere length was assessed from DNA extracted from saliva collected at T1, T2, and T3. Saliva samples were collected using the Oragene (DNA Genotek) kit and then stored at room temperature until DNA extraction. DNA was extracted from samples at the Psychiatric and Neurodevelopmental Genetics Unit (Massachusetts General Hospital) using the Oragene DNA extraction protocol. Relative telomere length was determined using a modified, high throughput (384-well format) version of the quantitative real-time polymerase chain reaction (PCR; Cawthon, 2002; Wang et al., 2008), performed at the De Vivo Laboratory (Harvard T.H. Chan School of Public Health). A recent meta-analysis determined that the PCR method is a valid technique for quantifying telomere length (Ridout et al., 2018). All laboratory personnel were blinded to participants' characteristics.

The average relative telomere length was calculated as the ratio of telomere repeat copy number to a single gene (36B4) copy number. Telomere length is reported as the exponentiated ratio of telomere repeat copy number to a single gene copy number corrected for a reference sample. Ratios of telomere repeat copy number to a single gene copy number highly correlate with absolute telomere lengths determined by Southern blot (Cawthon, 2002). The T/S ratio value for all samples at all timepoints was compared to that of a reference DNA quality control standard sample to normalize for experimental variations and allow comparison among sample sets. The T/S ratio has been shown to be linearly proportional to average telomere length. When an unknown sample is identical to the reference DNA in its T/S ratio, the T/S ratio value is 1. The T/S ratio of one individual relative to the T/S ratio of another should thus correspond to the relative telomere lengths of their DNA.

All of the samples were run at the same time within one batch across 15 plates. Because the assaying laboratory was provided no information about participant characteristics, placement of samples on plates was random regarding the independent variables; thus, any observed effects related to the study hypotheses would not be due to variation between plates. Five nanograms of genomic DNA were dried down in each 384-well plate and resuspended in 10 μL of either the telomere or 36B4 PCR reaction mixture and then stored at 4°C for up to 6h. The telomere reaction mixture consisted of 1x Thermo Fisher PowerUP SYBR Master Mix, 2.0 mM of DTT, 270 nM of Tel-1b primer, and 900 nM of Tel-2b primer. The reaction proceeded for one cycle hold at 50°C for 2 m and at 95°C for 2 m, followed by 35 cycles at 95°C for 15s and 54°C for 2 m. The 36B4 reaction consisted of 1x Thermo Fisher PowerUP SYBR Master Mix, 300 nM of 36B4U primer, and 500 nM of 36B4D primer. The 36B4 reaction proceeded for one cycle hold at 50°C for 2 m and at 95°C for 2 m, followed by 40 cycles at 95°C for 15s and 58°C for 70s. All samples for both the telomere and single-copy gene (36B4) reactions were performed in triplicate on different plates. Each 384-well plate also contained a 6-point standard curve from 0.625 ng to 20 ng using pooled saliva derived genomic DNA.

The standard curve assessed and compensated for inter-plate variations in PCR efficiency. The PCR efficiency was overall ~90%, and the linear correlation coefficient (R^2) values for both reactions were overall > 0.99. The T/S ratio (-dCt) for each sample was calculated by subtracting the average 36B4 Ct value from the average telomere Ct value. The relative T/S ratio (-ddCt) was determined by subtracting the T/S ratio value of the 5 ng standard curve point from the T/S ratio of each unknown sample. Quality control samples were interspersed throughout the test samples in order to assess inter-plate and intra-plate variability of threshold cycle (Ct) values. A combined inter- and intra-assay coefficient of variation (CV) calculated from the relative T/S ratio (-ddCt) of quality control samples was 10.43%. The quality cutoff used by the assaying laboratory is based on CVs of their internal quality controls and triplicate Ct CVs of individual samples. The internal quality control CV of 10.43% passed the laboratory's standard of 20%. For triplicate CVs of an individual sample, the laboratory utilizes a cutoff of 2%. If one of the triplicate CT values is greater than one standard deviation from the average, it is considered an outlier, and that value is omitted from further calculations. If omitting this value does not bring down the CV to below 2%, the data point is considered not reliable and fails. In this study, 96% of

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samples passed quality control standards, with 4% not passing quality control and thus not included in analyses.

Telomere PCR Primers:
Tel 1 GGTTTTTGAGGGTGAGGGTGAGGGTGAGGGTGAGGGT
Tel 2 TCCCGACTATCCCTATCCCTATCCCTATCCCTATCCCTA
36B4 (Single-copy gene) PCR Primers:
36B4u CAGCAAGTGGGAAGGTGTAATCC
36B4d CCCATTCTATCATCAACGGGTACAA

Covariates

Given prior evidence that age is consistently associated with telomere length and telomere attrition, age was considered as a covariate and/or moderator variable in analyses, as specified below. Age at saliva sample collection for deriving telomere length and age at completion of the questionnaire measures were very highly correlated within timepoint ($rs = .95 - .99$); thus, age at saliva sample collection was used for all analyses that included age as a variable. Previously published analyses indicated that the following variables were not associated with telomere length or telomere attrition in this cohort (see Bosquet Enlow et al., 2020 for details) and therefore were not considered as covariates in the current analyses: child race/ethnicity, maternal and paternal age, maternal and paternal education level, annual household income, child birthweight, presence of any serious illnesses or difficulties in child development since birth (T1) or since last assessment (T2, T3), and number of days saliva sample was in storage prior to DNA extraction. To address the study hypotheses, child sex was included as a moderator variable as indicated below.

Data analysis plan

We first performed descriptive analyses to demonstrate the sample characteristics. We used two-sample t-tests and Pearson's chi-squared tests to determine if participants with and without follow-up data differed on measures at infancy. We then analyzed associations among the maternal depression, child temperament, and child telomere length variables at infancy, 2 years, and 3 years.

To test our main hypothesis that child temperament and sex influence associations between maternal depressive symptoms and child telomere length, we used linear mixed models with relative telomere length as the dependent variable and child age (months), child sex (0 = male, 1 = female), exposure to elevated maternal depressive symptoms (0 = no, 1 = yes), and concurrent measures of child temperament (negative affectivity, surgency/extraversion, regulation/effortful control) as the independent variables. Random effects at the participant level included a random intercept and a random slope for age. We included in our model three 4-way interactions for age, sex, maternal depressive symptoms, and each temperament measure, in addition to all lower order 3-way and 2-way interactions, and main effects. These 4-way interactions assessed the joint effects of sex, maternal depressive symptoms, and each temperament domain on telomere attrition rate from infancy to age 3 years. That is, interactions with age test the hypothesis that *telomere attrition rate* varies depending on sex/maternal depressive symptoms/temperament. Terms not including age predict *telomere length irrespective of age*. We removed interaction terms that were not statistically significant (i.e., $p > .05$), starting with higher order terms, until we had a parsimonious model that remained hierarchically well-defined (i.e., we retained lower order terms regardless of significance if a higher order term was significant). We retained the age × surgency/extraversion term, as we previously showed this term to be associated with telomere length attrition in this cohort (Bosquet Enlow et al., 2023). We also retained main effect terms for the three temperament domain scores, allowing for consideration of the unique effects of each domain on telomere length; moreover, we previously showed in this cohort that higher regulation/effortful control was associated with longer telomere length across timepoints (Bosquet Enlow et al., 2023) and thus wanted to retain this term in the current model. Our reasoning for this approach, i.e., beginning with a fully specified model and then removing nonsignificant interaction terms, was to provide a direct test of our main hypotheses while minimizing unnecessary testing of simpler models, thereby reducing the overall number of analyses conducted. All tests were two-tailed, with alpha set at .05. Statistical analyses were performed with IBM SPSS Statistics (Version 28) and STATA (Version 16.1).

Results

Sample characteristics

Table 1 displays the sample sociodemographic characteristics. Children were predominantly non-Hispanic White (73.3%) and of middle to high socioeconomic status as reflected in parental education and annual household income. As previously described (Bosquet Enlow et al., 2020), available health indicators suggest that the sample was healthy overall and free from illness at the time of data collection. All children were born full term. Children were also of expected birthweight for gestational age ($M = 3508$g, $SD = 524$g, 98% > 2500g). As noted above, children were excluded from the study if there were any known developmental delays, neurological disorder or trauma, or maternal use of certain medications during pregnancy.

Descriptive analyses

Data during at least one timepoint were available for 600 participants, with 543 providing data at T1, 254 at T2, and 310 at T3; 220 provided data at one timepoint, 253 at two timepoints, and 127 at three timepoints, with 369 providing data during T1 and at least one follow-up timepoint. Participants missing data at T2 and/or T3 did not differ at T1 on child age at assessment, maternal depressive symptoms, temperament scores, or relative telomere length compared to those who had T2 and/or T3 data (all $ps > .05$, separate tests for participants missing T2 and participants missing T3 data).

Table 2 presents the descriptive data for the telomere, temperament, and maternal depressive symptom variables. Table 3 presents the bivariate correlations among the relative telomere length, temperament domain, and maternal depressive symptom scores at each timepoint. Relative telomere length scores were moderately correlated across timepoints, as were maternal depressive symptom scores. The scores for the same temperament domain were moderately correlated between T1 and later timepoints and strongly correlated between T2 and T3. Relative telomere length at T1 was modestly negatively correlated with surgency/extraversion at T1, whereas relative telomere length at T3 was modestly positively correlated with surgency/extraversion at T2. The positive correlation between relative telomere length at T3 and regulation/effortful control at T3 approached significance. Relative telomere length was not associated with maternal depressive symptoms at any timepoint in the bivariate correlational analyses.

In regard to sex differences, as previously reported, *t*-test analyses showed that females had longer relative telomere length

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Table 1. Sample characteristics (N = 600)

	M	*SD*	*n*	%
Child age, infant (T1) assessment (months)	8.51	3.04		
Child age, 2-year (T2) assessment (months)	24.84	1.47		
Child age, 3-year (T3) assessment (months)	37.74	2.07		
Child sex assigned at birth (male)			311	51.8
Child race				
White			476	79.3
Asian			21	3.5
Black/African American			8	1.3
American Indian or Alaska Native			1	0.2
More than one race			84	14.0
Did not report			10	1.7
Child ethnicity				
Not Hispanic or Latino			540	90.0
Hispanic or Latino			53	8.8
Did not report			7	1.2
Maternal age (years)	34.03	3.86		
Paternal age (years)	35.73	4.81		
Maternal education				
High school degree/GED or less			26	4.3
Associate's degree			5	0.8
Bachelor's degree			177	29.5
Master's degree			274	45.7
Graduate degree			116	19.3
Did not report			2	0.3
Paternal education				
High school degree/GED or less			49	8.2
Associate's degree			24	4.0
Bachelor's degree			180	30.0
Master's degree			189	31.5
Graduate degree			153	25.5
Did not report			5	0.8
Annual household income				
< $35,000			18	3.0
$35,000–$49,999			15	2.5
$50,000–$74,999			52	8.7
$75,000–$99,999			81	13.5
$100,000+			388	64.7
Did not report			46	7.7

than males at all timepoints and that males were rated as higher than females on surgency/extraversion at T3 (Bosquet Enlow et al., 2023). In chi-squared analyses, mothers of females tended to be more likely than mothers of males to endorse elevated depressive symptoms at T2 (19% vs. 10%, $p = .06$); there were no sex differences in maternal depressive symptoms at T1 or T3, $ps > .15$.

Table 2. Descriptive data for child relative telomere length, child temperament, and maternal depressive symptom variables

	M	*SD*	*Range*	*n*	%
Child relative telomere length					
T1 ($N = 543$)	1.27	0.21	0.24 – 1.96		
T2 ($N = 254$)	1.15	0.21	0.70 – 1.96		
T3 ($N = 310$)	1.12	0.18	0.70 – 1.84		
Child temperament domain scores					
T1 ($N = 543$)					
Negative affectivity	3.18	0.73	1.35 – 5.63		
Surgency/extraversion	4.72	0.71	2.44 – 6.64		
Regulation/effortful control	5.09	0.56	2.62 – 6.68		
T2 ($N = 254$)					
Negative affectivity	2.83	0.49	1.76 – 4.43		
Surgency/extraversion	4.93	0.55	3.62 – 6.54		
Regulation/effortful control	4.83	0.53	2.94 – 6.15		
T3 ($N = 310$)					
Negative affectivity	2.94	0.55	1.54 – 4.87		
Surgency/extraversion	4.96	0.54	3.38 – 6.64		
Regulation/effortful control	4.96	0.54	3.12 – 6.18		
Maternal depressive symptoms[a]					
T1 ($N = 543$)	5.63	4.20	0 – 27	75	13.8
T2 ($N = 254$)	5.00	3.97	0 – 18	36	14.2
T3 ($N = 310$)	5.31	4.43	0 – 32	43	13.9

Note. T1 = Time 1 (infancy); T2 = Time 2 (age 2 years); T3 = Time 3 (age 3 years). [a]*n* and % = number and percentage of sample, respectively, with elevated maternal depressive symptoms, i.e., Beck Depression Inventory (BDI) score ≥ 10.

Temperament and sex as moderators of the effect of exposure to maternal depressive symptoms on child telomere length

We fit our linear mixed model using 1,107 observations from 600 children, each of whom provided one to three relative telomere length scores. None of the four-way interaction terms (age × sex × maternal depressive symptoms × temperament domain) were significant; therefore, all were removed from the model. Thus, maternal depressive symptoms, child temperament, and child sex did not act jointly to influence telomere attrition rate across the first three years.

Maternal depressive symptoms × surgency/extraversion × sex emerged as the only significant 3-way interaction effect on relative telomere length irrespective of age. The relevant lower order 2-way interactions and the a priori forced 2-way interaction (age × surgency/extraversion) and the main effect terms were retained in the model, as noted above. The final model has the form:

$$\begin{aligned} \mathrm{E}[\mathrm{TL}_{ij}] = {} & \beta_0 + \beta_1 age_{ij} + \beta_2 F_j + \beta_3 SG_{ij} + \beta_4 NA_{ij} + \beta_5 EC_{ij} \\ & + \beta_6 MDS_{ij} + \beta_7 age * SG_{ij} + \beta_8 F * SG_{ij} + \beta_9 F * MDS_{ij} \\ & + \beta_{10} SG * MDS_{ij} + \beta_1 1F * SG * MDS_{ij} + u_j + u_{1j} age_{ij} + e_{ij} \end{aligned}$$

where TL is relative telomere length at time i (T1, T2, T3) for subject j, age is age in months, F is female sex, SG is surgency/extraversion, NA is negative affectivity, EC is regulation/effortful

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Table 3. Correlations among child relative telomere length, child temperament, and maternal depressive symptom scores

	TL_T1	TL_T2	TL_T3	NA_T1	S/E_T1	R/EC_T1	NA_T2	S/E_T2	R/EC_T2	NA_T3	S/E_T3	R/EC_T3	BDI_T1	BDI_T2
TL_T2	.39***													
TL_T3	.39***	.32***												
NA_T1	.00	.01	−.05											
S/E_T1	−.10*	.10	.07	.01										
R/EC_T1	.07	.08	.04	−.39***	.15***									
NA_T2	.03	.02	.00	.31***	.06	−.09								
S/E_T2	−.03	.00	.17*	−.06	.29***	.15*	.05							
R/EC_T2	.00	.04	.10	−.22***	.31***	.42***	−.22***	.22***						
NA_T3	−.05	−.06	−.03	.33***	.00	−.15*	.68***	.01	−.33***					
S/E_T3	.03	−.02	.02	−.01	.20**	.11+	.07	.60***	.16+	.05				
R/EC_T3	.05	.13	.09+	−.15**	.20**	.29***	−.16+	.13	.67***	−.30***	−.11+			
BDI_T1	−.01	−.02	−.05	.17***	−.02	−.07	.17**	−.05	−.16*	.13*	−.01	.00		
BDI_T2	−.07	−.05	.01	.17**	−.02	.00	.24***	−.01	−.11+	.20*	.06	−.05	.47***	
BDI_T3	−.03	−.01	.07	.27***	−.01	−.18**	.29***	.00	−.29***	.20***	.07	−.11+	.30***	.39***

Note. TL = relative telomere length; T1 = Time 1 (infancy); T2 = Time 2 (age 2 years); T3 = Time 3 (age 3 years); NA = negative affectivity; S/E = surgency/extraversion; R/EC = regulation/effortful control; BDI = Beck Depression Inventory categorized as 0 or 1, with 0 = < 10 total symptom score (suggesting no to minimal depressive symptoms) and 1 = ≥ 10 total symptom score (suggesting mild to severe depressive symptoms). $+p < .10$. $*p < .05$. $**p < .01$. $***p < .001$.

control, MDS is maternal depressive symptoms, u_j and $u_{1j}age_{ij}$ represent the random intercept and random slope for age, respectively, and e_{ij} is the residual error term. The fixed effect terms and coefficients are described in Table 4. A likelihood ratio test comparing our constrained model to a fully parameterized model (i.e., all interactions included) supports the goodness of fit of this more parsimonious model (chi-squared = 7.70, df = 20, $p = .993$).

Because the effect of surgency/extraversion varied by age, we needed to evaluate the effect at a specific age to be able to describe the effect for the categorical groups of no/low versus elevated maternal depressive symptoms and male versus female. Thus, we evaluated the effects of surgency/extraversion at the mean age across study assessments of 20 months. The analysis revealed that, among males with exposure to elevated maternal depressive symptoms, there was a negative association between surgency/extraversion and relative telomere length, $\beta_3 + \beta_{10} + 20 * \beta_7 = -0.081$, 95% CI [−0.150, −0.012], $p = .02$. Females exposed to elevated maternal depressive symptoms did not show this association, $\beta_3 + \beta_8 + \beta_{10} + \beta_{11} + 20 * \beta_7 = 0.037$, 95% CI = [−0.034, 0.108], $p = .30$, nor did males exposed to no/low maternal depressive symptoms, $\beta_3 + 20 * \beta_7 = -0.010$, 95% CI [−0.036, 0.016], $p = .44$, or females exposed to no/low maternal depressive symptoms, $\beta_3 + \beta_8 + 20 * \beta_7 = -0.009$, 95% CI = [−0.039, 0.021], $p = .54$. At ages younger than 20 months, the negative association between surgency/extraversion and relative telomere length among males exposed to elevated maternal depressive symptoms was even more robust (i.e., more negative). In males exposed to elevated maternal depressive symptoms, the negative association of surgency/extraversion and relative telomere length remained statistically significant up to age 27 months (−0.070, 95% CI [−0.139, −0.001], $p = .046$). The previously reported (Bosquet Enlow et al., 2023) main effect of regulation/effortful control on relative telomere length remained significant in the model, $\beta_5 = 0.027$, 95% CI = [0.005, 0.049], $p = .016$, independent of the maternal depressive symptoms × surgency/extraversion × sex effect. The previously reported (Bosquet Enlow et al., 2023) age × surgency/extraversion interaction term also remained significant in the current model, $\beta_7 = 0.002$, 95% CI = [0.0002, 0.003], $p = .023$, indicating that, in the sample as a whole (i.e., without regard to child sex or maternal depressive

Table 4. Fixed effects from the linear mixed model predicting child relative telomere length

		Coefficient	95% confidence interval	*p*-value
β_0	Constant	1.297	1.080, 1.515	< .001
β_1	Age (months)	−0.012	−0.019, −0.006	< .001
β_2	Female	0.068	−0.121, 0.257	.481
β_3	Surgency/extraversion	−0.041	−0.076, −0.006	.022
β_4	Negative affectivity	0.008	−0.011, 0.028	.395
β_5	Regulation/effortful control	0.027	0.005, 0.049	.016
β_6	Elevated maternal depressive symptoms	0.356	−0.003, 0.715	.052
β_7	Age × surgency/extraversion	0.002	0.0002, 0.003	.023
β_8	Female × surgency/extraversion	0.001	−0.038, 0.040	.967
β_9	Female × elevated maternal depressive symptoms	−0.588	−1.104, −0.072	.026
β_{10}	Surgency/extraversion × elevated maternal depressive symptoms	−0.071	−0.143, 0.002	.055
β_{11}	Female × surgency/extraversion × elevated maternal depressive symptoms	0.117	0.012, 0.223	.029

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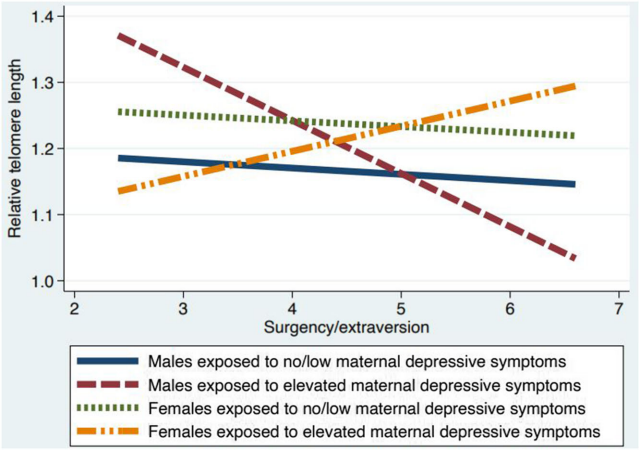

Figure 1. Model predictions of child relative telomere length based on the temperament domain score for surgency/extraversion, maternal depressive symptoms, and child sex. Predictions were evaluated at the mean age across study assessments of 20 months and adjusted for the temperament domains of negative affectivity and regulation/effortful control. Among males with exposure to elevated maternal depressive symptoms, there was a negative association between surgency/extraversion and relative telomere length ($p = .02$). No association between surgency/extraversion and relative telomere length was observed among males exposed to no/low maternal depressive symptoms ($p = .44$) or among females exposed to elevated maternal depressive symptoms ($p = .30$) or no/low maternal depressive symptoms ($p = .54$).

symptoms), greater surgency/extraversion was associated with decreased telomere attrition rate between infancy and age 3 years.

Further examination of the findings (not shown in Table 4) indicated that maternal depressive symptoms by themselves were not related to child relative telomere length in the sample as a whole (i.e., the effect assessed at mean values of surgency/extraversion and child sex), $\beta = 0.003$ [−0.031, 0.038], $p = .842$, or in males versus females (i.e., the child sex interaction assessed at the mean value of surgency/extraversion), $\beta = -0.020$ [−0.087, 0.048], $p = .564$. The interaction between maternal depressive symptoms and surgency/extraversion also was not associated with child relative telomere length (i.e., the interaction assessed at the "average" child sex), $\beta = -0.016$ [−0.068, 0.037], $p = .565$. Thus, effects of maternal depressive symptoms on child relative telomere length were only observed when considering both child sex and temperament, specifically surgency/extraversion.

Figure 1 demonstrates the association between surgency/extraversion and relative telomere length, stratified by sex and maternal depressive symptom group, at the mean age across study assessments of 20 months. As visualized in Figure 1, the line representing males exposed to elevated maternal depressive symptoms shows a relatively steep slope between surgency/extraversion and relative telomere length, whereas the line representing males not exposed to elevated maternal depressive symptoms shows a relatively flat slope between surgency/extraversion and relative telomere length, consistent with the findings described above that, among males, the association between greater surgency/extraversion and shorter telomere length was only observed in those exposed to elevated maternal depressive symptoms. Similarly, a comparison of the lines for males exposed to elevated levels of maternal depressive symptoms and either of the lines for females (i.e., those exposed and those not exposed to elevated levels of maternal depressive symptoms) reveals relatively flatter lines for females, consistent with the findings reported above of a lack of any observed associations between surgency/extraversion and relative telomere length among females, regardless of level of exposure to maternal depressive symptoms. Thus, Figure 1 demonstrates the results of the significant 3-way interaction (sex × maternal depressive symptoms × temperament) on relative telomere length at the mean age of 20 months, specifically showing that greater surgency/extraversion was associated with shorter telomere length only among males exposed to elevated maternal depressive symptoms.

In regard to our approach to operationalizing child exposure to maternal depressive symptoms, we chose to dichotomize exposure using a clinically relevant cutoff score. This approach accounted for the skewness in BDI scores and produced more easily understandable results, particularly in the context of interpreting interaction effects. In a secondary analysis, we utilized the continuous BDI score, which yielded similar results to our primary analysis. Specifically, the female × surgency/extraversion × maternal depressive symptoms effect was statistically significant (0.013, 95% CI [0.004, 0.021], $p = .005$).

Discussion

The overall goal of the current study was to examine whether child temperament and sex moderated associations between exposure to maternal depressive symptoms and telomere length in the first three years of life. The analysis plan was driven by (a) research demonstrating that temperament and biological sex may influence a child's susceptibility to the effects of environmental exposures, such as maternal depression, on developmental outcomes and (b) emerging data suggesting that telomere dynamics in early life may be differentially affected by the interplay of these variables. We specifically hypothesized that (1) in the context of exposure to elevated maternal depressive symptoms, higher levels of negative affectivity and surgency/extraversion and lower levels of regulation/effortful control would be associated with shorter telomere length; (2) in the context of exposure to elevated maternal depressive symptoms, higher levels of negative affectivity and surgency/extraversion and lower levels of regulation/effortful control would be associated with an increased rate of telomere attrition from infancy to age 3 years; and (3) that the joint effects of maternal depression exposure and temperament on telomere length would be more pronounced among male children compared to female children.

The results suggest that child sex and the temperament characteristic of surgency/extraversion jointly influenced susceptibility to the effects of exposure to maternal depression on child telomere length. Specifically, in the context of elevated maternal depressive symptoms, greater surgency/extraversion was associated with shorter telomere length among males. These effects were particularly prominent in the first two years, coinciding with a developmental period when telomere attrition occurs especially rapidly and when telomeres may be particularly susceptible to environmental exposure effects (Bosquet Enlow et al., 2020). Females failed to show an association between surgency/extraversion and telomere length, regardless of maternal depression status. Males whose mothers did not endorse elevated maternal depressive symptoms also did not evidence a relation between surgency/extraversion and telomere length. As previously reported (Bosquet Enlow et al., 2023), regulation/effortful control was independently associated with telomere length, and negative affectivity was not associated with telomere length. With the exception of the surgency/extraversion effects previously reported (Bosquet Enlow et al., 2023) and replicated here (i.e., significant age

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× surgency/extraversion term), the current analyses did not provide evidence that the study predictors were associated with differences in telomere attrition rate across the first three years.

Prior work in this sample found that surgency/extraversion was associated with a reduced rate of telomere attrition when examined in the sample as a whole, without reference to maternal depressive symptoms (Bosquet Enlow et al., 2023). We previously concluded that more "reactive" children (e.g., high on surgency/extraversion) might demonstrate longer telomere length/decreased rate of attrition under supportive conditions and shorter telomere length/increased rate of attrition under stressful conditions. The current sample was well resourced and consequently may have been positioned generally to provide a high level of environmental supports, which may explain our previous findings linking higher surgency/extraversion to reduced rate of telomere attrition in males and females outside of consideration of adverse contextual variables. However, the subsample of children exposed to elevated maternal depressive symptoms may have experienced a more stressful environment in which being more temperamentally reactive was a risk factor for telomere shortening. The current analyses explored this possibility and found supportive evidence, with higher surgency/extraversion associated with shorter telomere length in the context of exposure to elevated maternal depressive symptoms among males. That is, the results of the current study support a diathesis-stress model, suggesting that greater surgency/extraversion among males increases susceptibility to the detrimental effects of exposure to a stressful environment, specifically elevated maternal depressive symptoms, on telomere length dynamics in early life. The previous findings in this cohort suggested, albeit indirectly, that higher levels of surgency/extraversion increased susceptibility to the positive (protective) effects of a supportive environment on telomere attrition rate. Together, the pattern of findings across the two studies suggest that surgency/extraversion may function as a differential susceptibility factor in relation to telomere dynamics in early life, with high surgency/extraversion conferring protective effects in the context of supportive environments but increased risk in the context of stressful environments. Admittedly, the interpretation that the findings of the previous study showed evidence that higher levels of surgency/extraversion conferred differential susceptibility to positive environmental exposures is speculative at this point, as we did not have available a positive environmental variable to test in analyses (the absence of elevated maternal depressive symptoms is not indicative of a supportive, positive environment); rather, the positive environment was assumed in the prior study given the known characteristics of the study sample as a whole. Additional research is needed to test this hypothesis more fully, including studies that (a) examine the interactive effects on telomere length dynamics of surgency/extraversion and multiple forms of environmental exposures that range from highly supportive to highly stressful and (b) perform formal statistical tests relevant for confirming that findings support a differential susceptibility to context model (e.g., regions of significance; Roisman et al., 2012).

The findings of an apparently positive (i.e., protective) association of surgency/extraversion on telomere erosion in the first study and the negative association of this temperament characteristic with telomere length in the current study are consistent with reports in the literature that this temperament characteristic is predictive of both adaptive and maladaptive developmental outcomes. For example, surgency/extraversion has been associated with both better self-regulation and positive emotionality and with externalizing problems/ADHD (Foss et al., 2022). Together, these findings suggest that surgency/extraversion may be an important individual characteristic that confers differential susceptibility to environmental influences on a range of outcomes, with more optimized development under supportive conditions and more maladaptive outcomes under more stressful conditions.

The results of the current study further suggest that the effects of exposure to maternal depression on telomere length may be specifically evident among males with elevated surgency/extraversion. Such findings are consistent with much of the prior literature examining the effects of stress exposures, including maternal depression, on a range of early life outcomes, including telomere length, with increased susceptibility among males frequently observed (Bosquet Enlow et al., 2018; Bosquet Enlow, Sideridis, et al., 2019; Van den Bergh et al., 2017). Thus, environmental exposures may interact differently with temperament characteristics in males versus females, with consequences for telomere biology. Notably, if analysis of the association between maternal depression and child telomere length had not taken into account both sex and temperament in the current study, the results would have suggested no effects of maternal depression symptoms on child telomere length. As predicted by theories of differential susceptibility, our findings indicate that failure to consider individual characteristics that confer vulnerability may obscure important associations between exposures and developmental outcomes.

Unlike surgency/extraversion, regulation/effortful control demonstrated a main effect on telomere length, with higher scores on this temperament dimension associated with longer telomere length, regardless of child sex or maternal depressive symptoms. In the previous study with this cohort, regulation/effortful control was consistently associated with longer telomere length across assessed ages in the sample as a whole (Bosquet Enlow et al., 2023). These findings suggest that regulation/effortful control may represent a protective factor for telomere length dynamics, across sexes and environmental conditions, possibly through its positive influence on regulation of physiological stress systems implicated in telomere erosion processes (e.g., HPA axis, oxidative stress, autonomic nervous system; Donzella et al., 2000; Kroenke et al., 2011; Zerach et al., 2020). Additional studies that examine this temperament domain in the context of a range of environmental conditions would shed more light on the role of this trait on telomere processes in early childhood.

The only other study, to the best of our knowledge, to apply a differential susceptibility model to examine associations between temperament and telomere length in early childhood failed to find an association; more specifically, there was no evidence that children with greater levels of negative affectivity were more susceptible to the effects of parenting quality on telomere length (Beijers et al., 2020). Notably, this study only considered the temperament domain of negative affectivity in infancy, which also was not associated with telomere outcomes in the current study. Other studies that have examined the role of negative emotionality as a differential susceptibility factor in relation to a variety of developmental outcomes have produced mixed results, with evidence that both children with high and children with low negative emotionality show contextual sensitivity, but in different, sometimes opposite, ways in response to a given exposure and developmental outcome (Markovitch et al., 2023). These mixed findings may be due, in part, to the fact that negative emotionality alone may not influence environmental susceptibility but rather only in combination with other temperament traits, particularly

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activity level (Markovitch et al., 2023). Some have suggested that temperament profiles, comprising multiple temperament traits, are more appropriate and robust when operationalizing temperament as a marker of environmental susceptibility (Markovitch et al., 2023). In our prior study examining associations between temperament and telomere dynamics in this cohort, we operationalized temperament both as temperament traits, as done in the current study, and as temperament profiles (Bosquet Enlow et al., 2023). We did not find any evidence for associations between temperament profiles and telomere dynamics and thus did not include temperament profiles in the current analyses for the sake of parsimony. The extant literature on relations between temperament and telomere length is extremely limited. More studies are required to elucidate the specific temperament characteristics most robustly associated with telomere dynamics. At minimum, findings to date point to the importance of considering multiple temperament domains in this line of research.

As noted above, there is considerable evidence that the effects of a wide range of exposures on an array of developmental outcomes are moderated by various individual characteristics (Markovitch et al., 2023). However, work to date frequently has implied that environmental susceptibility is a unidimensional, dichotomous trait, with individuals either susceptible or not susceptible to all types of environmental influences (Markovitch et al., 2023). Emerging evidence directly testing this notion suggests not only that environmental susceptibility is continuous and multidimensional, but also that different individuals are susceptible to different exposures in relation to different developmental outcomes (Markovitch et al., 2023). The current study focused on two potential environmental susceptibility factors (temperament and sex), one environmental exposure (maternal depressive symptoms), and one outcome (telomere dynamics). More research is needed to identify other susceptibility factors that influence the effects of maternal psychological functioning on child telomere attrition and to identify other environmental exposures whose effects on telomere dynamics are moderated by child temperament.

This study's hypotheses assumed directionality of effects, specifically that temperament and sex influence the effects of maternal depression on telomere dynamics. Some have suggested that rates of epigenetic aging may serve as a cause, rather than effect, of differential susceptibility to the environment. One study reported that children with higher levels of accelerated methylation aging demonstrated more unpredictable temperament in infancy and more externalizing symptoms in early childhood if their mothers endorsed more hostile parenting behaviors but fewer problems if their mothers endorsed less hostile parenting; children with lower levels of accelerated methylation aging did not show associations between maternal hostility and infant temperament or child psychological symptoms (Manczak et al., 2023). The study authors concluded that these findings may suggest that individuals with accelerated cellular aging are more likely to demonstrate psychological dysfunction under adverse conditions but greater maturity under more supportive conditions (Manczak et al., 2023). The findings also may be interpreted to suggest that some individuals are more biologically sensitive beginning in utero, reflected in both accelerated epigenetic aging evident at birth and greater vulnerability to positive and negative environmental exposures in childhood (Manczak et al., 2023). Currently, the directionality of effects between telomere dynamics and child psychological and physical health are not well understood. Thus, more research is needed to determine more definitively the extent to which telomere dynamics in early life (a) are vulnerable to the effects of environmental exposures, (b) are a biomarker of sensitivity to the environment, and/or (c) are causally involved in differential susceptibility to context.

Strengths and limitations of the current study deserve consideration. The relatively large sample consisted of healthy children recruited in infancy and followed to age 3 years; longitudinal studies, particularly in early childhood, are rare in the telomere literature. The use of saliva samples for assaying telomere length offers numerous advantages, including low risk and ease and acceptability to both caregivers and children. Previous work has validated the methods used here for extracting DNA from saliva and assessing telomere length (Goldman et al., 2018; Montpetit et al., 2014; Ridout et al., 2018). However, because the method produces relative telomere length rather than absolute kilobase length estimates, it limits comparability with findings from other studies (Montpetit et al., 2014)

The sample was primarily non-Hispanic White and of middle to high socioeconomic status. These sample characteristics are both a strength and a limitation. Some previous studies have found differences in telomere length by race and socioeconomic status. The reasons for such associations are not established but may be related to racial/ethnic differences in polygenetic adaptation (Hansen et al., 2016) and to higher rates of stress exposures, systemic racism, and other health risk factors among both minority racial groups and low socioeconomic status groups (Geronimus et al., 2015). Using a sample of relatively high socioeconomic status reduces the potential variability in telomere length due to exposure to stressors associated with economic adversity, allowing for a more targeted examination of maternal depression exposure effects. However, the limited representation of individuals of minority racial/ethnic backgrounds and varied socioeconomic status restricts the generalizability of the findings. The current findings should be explored in samples representing a range of sociodemographic characteristics.

This study did not consider the mechanisms by which maternal depression, child temperament, and child sex influence child telomere biology. Exposure to maternal depression may serve as a contextual stressor that activates physiological stress systems implicated in telomere attrition processes, including the HPA axis and autonomic nervous system (Bosquet Enlow, Sideridis, et al., 2019; Epel et al., 2009; Gotlib et al., 2015; Nelson et al., 2018; Quigley et al., 2023). In fact, there is limited evidence that the association between exposure to maternal depression and telomere shortening in early life is mediated by increased child cortisol reactivity (Nelson et al., 2018). Maternal depression has also been associated with a more stressful caregiving environment (e.g., increased marital conflict; Goodman & Gotlib, 1999), which may contribute to alterations in child stress reactivity and, consequently, telomere attrition processes. The effects of psychosocial stress and associated physiological dysregulation on telomere length dynamics may be magnified in males compared to females (Bosquet Enlow et al., 2018; Zalli et al., 2014). Temperament traits also may interact with, magnify, or mitigate maternal depression exposure effects on relevant physiological processes. For example, surgency/extraversion is associated with greater cortisol reactivity to the environment in early life, particularly among children low in effortful control (Donzella et al., 2000; Tervahartiala et al., 2021). Higher levels of effortful control may regulate autonomic nervous system stress reactivity, dampening stress effects on telomere biology (Calkins & Fox, 2002; Huffman et al., 1998; Jones et al., 2018). Maternal depression may exert influence on child

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physiological, emotional, and behavioral stress reactivity specifically through disruptions to the provision of sensitive caregiving, with stronger effects on children with certain temperament profiles (Belsky et al., 1998; Belsky & Pluess, 2009; Bosquet Enlow, Petty, et al., 2019; Zhang et al., 2022). Notably, more responsive, sensitive parenting has been shown to diminish the effects of early psychosocial risk on child telomere length shortening (Asok et al., 2013; Beijers et al., 2020). Finally, there is evidence that child temperament and maternal depression bidirectionally influence each other in early life, presumably through the quality and emotional tone of maternal-child interactions over time (Bridgett et al., 2009; McGrath et al., 2008). Future studies should consider assessing potential mechanisms that may drive associations among maternal depression, child temperament, child sex, and child telomere length dynamics, including child stress reactivity and caregiving quality.

This study focused on elevated maternal depressive symptoms as the stress exposure. Exposure to other forms of adversity may produce different results in both direction and magnitude. Future research may benefit from considering a comprehensive assessment of various types of stress exposures in a sample with varying levels of adversity, including samples assessed for clinical diagnoses of maternal depression. Relatedly, some of the exclusion criteria for the parent study that provided data for the current analyses have been associated with higher rates of maternal depression (e.g., preterm birth, low birthweight, other birth complications). Consequently, our sample may have underrepresented the level of depression/depressive symptoms in mothers of young children in the general population. Notably, effects were observed in this sample despite the fact that elevated maternal depressive symptoms were primarily in the range suggestive of mild depression. Thus, there may be negative effects of maternal depression on child telomere dynamics even in the presence of relatively low levels of maternal symptoms, at least among more susceptible children. Moreover, these findings suggest that even in a non-clinical, community sample, maternal psychological functioning may influence child telomere length in early life. Additional research that examines the effects of a wider range of maternal depression symptoms and clinical diagnoses on child telomere biology is warranted.

A measure of maternal depressive symptoms in pregnancy was not administered in this sample. Given that maternal depressive symptoms showed moderate stability over time, children exposed to elevated maternal depressive symptoms postnatally were at increased likelihood of having been exposed prenatally. Research suggests that maternal depression in pregnancy is associated with telomere length in newborns, with some studies showing a negative association and others a positive association; moreover, there is evidence that such associations may be specific to males (Bosquet Enlow et al., 2018, 2021). Additionally, prenatal stress has been associated with greater susceptibility to postnatal parental caregiving quality when predicting childhood telomere erosion, with those exposed to high levels of prenatal stress demonstrating greater erosion in the context of insensitive parenting and less erosion in the context of sensitive parenting and those exposed to low levels of prenatal stress showing no relation between parenting quality and telomere erosion (Beijers et al., 2020). Exposure to prenatal stress has been identified as a factor that increases child postnatal plasticity to the environment, possibly via epigenetic modifications, neural and physiological developmental effects, and influences on the microbiome, factors that may influence postnatal regulation of telomere dynamics (Beijers et al., 2020). We could not assess potential contributions of prenatal programing processes here, which may have contributed to the findings. We also did not consider the role of genetic factors/heritability in analyses (Broer et al., 2013).

Another potential limitation of the current study is the reliance on maternal report of child temperament, as maternal depression may bias reporting of child behavior. We believe that any such bias would have had limited impact on our specific hypotheses, as we were not testing whether maternal depressive symptoms and child temperament domain scores were correlated, but rather whether the association between child temperament and child telomere length (an objective measure not possibly biased by maternal report) was influenced by the presence of elevated maternal depressive symptoms. However, future research may benefit from consideration of observational measures of child temperament to avoid this limitation. An approach that combines the strengths of parent-report (e.g., leveraging of caregivers' knowledge of their children's functioning across a range of contexts) and observational measures (e.g., standardized, objective) may provide the most robust test of the proposed hypotheses (Morris et al., 2020).

A very small minority of parental respondents identified as fathers (e.g., $n = 6$ or 1% of the sample at T1). We elected to retain data from these families to maximize sample size and power and maintain consistency with our prior study, which utilized child temperament data regardless of parental respondent. Moreover, these fathers likely completed the questionnaires because they were the child's primary caregiver, which may be more relevant for the current analyses than limiting to maternal respondents only. That being said, because the respondents were almost exclusively mothers, we describe the data in relation to maternal depressive symptoms. Future work may benefit from assessing influences of all of the child's caregivers.

Conclusion

Models of differential susceptibility to context posit that there are various characteristics that influence an individual's sensitivity to the effects of both positive and negative aspects of their environment on developmental and health outcomes. Findings from the current study suggest that temperament and sex moderate the effects of exposure to elevated maternal depressive symptoms on child telomere length in early life, such that exposure to maternal depression is associated with shortened telomere length among males with elevated levels of surgency/extraversion. Regulation/effortful control, however, appears to function as a protective factor in relation to child telomere length, regardless of child sex or context. The current findings may have particular import given that they were observed in the first years of life, when children may be especially susceptible to the effects of psychological and environmental exposures on telomere erosion, with implications for health across the lifespan. Specifying the complex interplay of factors that influence telomere biology in early life may enhance our understanding of the developmental origins of health and disease and our ability to identify at-risk individuals who may benefit from interventions that optimize health outcomes.

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Competing interests. The authors declare none.

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