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Maternal psychological resilience during pregnancy and newborn telomere length: a prospective study

Glenn Verner, MPH[1], **Elissa Epel, PhD**[2], **Marius Lahti-Pulkkinen, PhD**[3], **Eero Kajantie, MD, PhD**[4,5,6,7], **Claudia Buss, PhD**[1,8,9], **Jue Lin, PhD**[10], **Elizabeth Blackburn, PhD**[10,11], **Katri Räikkönen, PhD**[3], **Pathik D. Wadhwa, MD, PhD**[8,9,12,13,14], **Sonja Entringer, PhD**[1,8,9]

[1]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health (BIH), Institute of Medical Psychology, Berlin, Germany [2]Department of Psychiatry, San Francisco School of Medicine, University of California, San Francisco, California, USA [3]Department of Psychology and Logopedics, University of Helsinki, Finland [4]Department of Public Health Solutions, THL National Institute for Health and Welfare, Helsinki and Oulu, Finland [5]PEDEGO Research Unit, MRC Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland [6]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway [7]Children's Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland [8]Department of Pediatrics, University of California, Irvine, Irvine, California [9]UC Irvine Development, Health and Disease Research Program, University of California, Irvine, Irvine, California [10]Department of Biochemistry and Biophysics, University of California, San Francisco, California, USA [11]Department of Microbiology and Immunology, University of California, San Francisco, California, USA [12]Department of Psychiatry & Human Behavior, University of California, Irvine, School of Medicine, Irvine, California, USA [13]Department of Obstetrics & Gynecology, University of California, Irvine, School of Medicine, Irvine, California, USA [14]Department of Epidemiology, University of California, Irvine, School of Medicine, Irvine, California, USA

Abstract

Address correspondence to: Sonja Entringer, PhD, Institute for Medical Psychology, Charité Universitätsmedizin Berlin, Luisenstr. 57, 10117 Berlin, Germany, Tel: +49 30 450 529 222, Fax: +49 30 450 529 990, sonja.entringer@charite.de; Pathik D. Wadhwa, MD, PhD., Professor of Psychiatry & Human Behavior, Obstetrics & Gynecology, Pediatrics, and Epidemiology, Director, UC Irvine Development, Health and Disease Research Program, University of California, Irvine, School of Medicine, 3117 Gillespie Neuroscience Research Facility (GNRF), 837 Health Sciences Road, Irvine, CA 92697, Tel: (949) 824-8238, Fax: (949) 824-8218, pwadhwa@uci.edu.

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Neuroscience Research Center
Charité Universitätsmedizin Berlin
Hufelandweg 14
10117 Berlin
Germany

Objective—In the context of the importance of elucidating the determinants of the initial, newborn setting of telomere length (TL) it is increasingly evident that maternal stress and stress-related processes during pregnancy play a major role. Although psychological resilience may function as a buffer, research in this area has not yet examined its potential role vis-à-vis that of stress. We, therefore, examined the relationship between maternal psychological resilience during pregnancy and newborn TL.

Methods—In a sample of 656 mother-child dyads from the *PREDO* cohort, multiple serial assessments were conducted over the course of pregnancy to quantify maternal stress, negative and positive emotional responses to pregnancy events, positive affect, and perceived social support. Principal component analysis (PCA) identified two latent factors: stress and positivity. A measure of resilience was computed by regressing the positivity factor on the stress factor, in order to quantify positivity after accounting for stress. TL was measured using qPCR in leukocytes extracted from cord blood shortly after birth. Linear regression was used to predict newborn TL from maternal resilience during pregnancy, adjusting for other potential determinants.

Results—Maternal stress predicted shorter newborn TL ($\beta=-0.079$, $p=0.044$), and positivity predicted longer TL ($\beta=0.135$, $p=0.001$). Maternal resilience (positivity accounting for stress) was significantly and positively associated with newborn TL ($\beta=0.114$, $p=0.005$, 95% CI [0.035, 0.189]), with each standard deviation increase in resilience predicting 12% longer newborn TL.

Conclusions—Our results indicate that maternal psychological resilience may exert a salubrious effect on offspring telomere biology and highlight the importance of enhancing maternal mental health and wellbeing during pregnancy.

Keywords

psychological resilience; fetal programming; telomere; pregnancy; positive psychology; social support; stress

Introduction

The critical importance of telomere biology for health, disease risk, and longevity is well established. The telomere system, consisting of telomeres, repeated double strands of DNA that serve to protect chromosomal ends during replication, and telomerase, the enzyme capable of elongating telomeres, is one of the key regulatory systems of cellular aging and senescence (1). Shortened telomere length (TL) is a not only a biomarker but appears to play a causal role in a wide range of physical and psychological disorders and mortality risk (2).

The initial, newborn setting of the telomere biology system has important implications for the trajectory of cellular aging and long-term health and susceptibility to common age-related disorders (3). We and others have reported that this initial setting of the system exhibits developmental plasticity, and that the effects of suboptimal developmental conditions appear to be mediated, in part, by the programming actions of maternal-placental-fetal biological processes (4-6).

Among the suboptimal developmental conditions that have been associated with newborn telomere length, maternal stress and stress-related biological processes feature prominently.

Maternal psychological stress during pregnancy (and even prior to becoming pregnant) has been linked to offspring TL at the time of birth, during childhood, and adult age (7-12). The focus, to date, has been almost exclusively on negative exposures and risk factors (summarized in (13)), despite the growing recognition of the independent impact of positive emotions (over and beyond that of the mere absence of negative emotions) on biological substrates that underlie health and disease risk. Thus, although positive emotions and psychological resilience have been shown to exert a protective effect on health and disease risk, and in the specific context of pregnancy maternal positive affect (14) and social support (15) have been positively associated with obstetric and infant outcomes, fetal programming research on telomere biology has not yet addressed the important question of the potential salubrious effects of maternal positivity and resilience. To our knowledge, this is the first study of the potential programming effects of maternal resilience and positive psychological state in pregnancy on the initial (newborn) setting offspring telomere length.

Theories of psychological resilience emphasize the importance of positive traits, state, or affect that can buffer the impact of stress. Induction of positive emotions or positivity can lead individuals to recover more quickly from the negative physiological sequelae of stress (16), reduce the allostatic wear-and-tear of repeated or prolonged exposure to stress, turn on positive restorative mechanisms, and perhaps even prevent or attenuate telomere shortening (17). Positive states of mind have furthermore been theorized to be a driving force in our development of key resilience resources including rewarding social relationships (16), which have been shown to provide psychological and neurobiological resilience to stress (18).

A relatively small number of studies have examined the effects of positive affect on adult TL. Positivity and optimism have been associated in some (19-21), but not other ((22, 23), studies with telomere length. Of note, these effects on TL were evident even after adjustment for depression (19), PTSD symptoms, and traumatic life events (20), suggesting that positivity and resilience represent constructs that are not merely the absence of negative psychological states. Social support has also been associated with TL among adults in multiple studies, with greater levels of perceived social support predicting longer telomeres (24-27), including during pregnancy (28), though one study has found the opposite association (29). However, as stated above, the question of the role of positive psychological states in telomere biology, also understudied in adults as compared to negative states, have yet to be addressed in the context of fetal programming of the telomere system.

This is also the first study in this (i.e., the PREDO) cohort to examine potential programming effects of maternal psychology on telomere biology. Previous studies in this cohort have linked maternal psychological state during pregnancy to placental functioning (30) and birth (31) and child outcomes (32, 33). Each of these outcomes have been linked in other studies (but not in this cohort) to newborn TL, supporting the scientific premise underlying our hypotheses. Especially relevant is the finding in this cohort that maternal positive affect during pregnancy was inversely associated with risk of preterm birth (31). Our study builds on this foundation to hypothesize and explore the ways in which maternal positive emotional state may influence the development of her offspring’s telomere system during the intrauterine period.

The goal of our study was to examine a hypothesized positive relationship between maternal psychological resilience during pregnancy and newborn telomere length. We conceptualized resilience as the extent to which an individual is able to maintain positivity and satisfying social relationships in the face of stress. Our study is a secondary analysis conducted using data from a large prospective mother-child cohort, in whom serial measures of maternal psychological state were collected across pregnancy, and DNA was isolated from cord blood to assess newborn TL.

Methods

Participants and procedure

The study population consisted of pregnant women enrolled between 2006 and 2010 in the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) cohort at ten hospitals in Finland and their live-born singleton children (see (34) for study protocol). Of the N=4777 women-child dyads recruited to the study, TL data was available for N=688 newborns. Participants were enrolled at antenatal clinics early in gestation (12+0 to 13+6 weeks) and followed up extensively through pregnancy and beyond. The PREDO cohort was enriched for women with at least one risk factor for preeclampsia (clinical sample, N=602). The cohort also included women recruited from the community irrespective of obstetric risk status (community sample, N=54). Data from both samples was combined and analyzed together as the two groups did not differ significantly in newborn TL, stress, positivity or resilience factor scores. The study was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District and by participating hospitals, and written, informed consent was obtained from all participants (34).

Sociodemographic, health, and lifestyle data were collected at baseline. As there was no variation in race in this sample (this was an all-white sample representative of the Finnish population), we have not adjusted for race. Psychological questionnaires were administered throughout pregnancy, and newborn cord blood samples were obtained at birth. Questionnaires relating to resilience (positivity, social support, and stress) are described in detail below, and the timeline of their administration is presented in Table 1. The final sample for the current report included N=656 mother-child pairs for whom psychosocial measurements during pregnancy and newborn cord blood TL were available.

Psychological measures

We quantified positive affectivity using three scales: affect from the Positive and Negative Affect Schedule (PANAS), positive state from the State-Trait Anxiety Inventory (STAI) and positive mood reactivity to pregnancy related events from the Pregnancy Experience Scale (uplifts, PES). Social support satisfaction was determined using a visual analog scale for social support (VAS-SS). Similarly, we quantified negative affectivity using three scales: perceived stress from the Perceived Stress Scale (PSS), biweekly perceived stress from a visual analog scale for stress (VAS-S), and negative mood reactivity to pregnancy related events from the PES (hassles, PES). The entire course of pregnancy was well represented, with the affect and social support measures being repeated up to fourteen times, and hassles and uplift measures being repeated up to four times across early, mid and late gestation.

For each assessment, a within-subject mean was calculated for each subject who completed at least 50% of the questionnaire in question. A summed score across pregnancy was then computed as a product of the within-subject mean and number of assessments completed by the subject. The average completion rate across all waves for all the questionnaires used in the principal component analysis was approximately 90%. In both the principal component analysis and linear regression analysis, incomplete cases were deleted listwise.

Principal component analysis (PCA) was used to isolate two latent factors, positivity and stress, as described below (Statistical Analysis section). The questionnaires used to yield the factors are detailed below.

A **positivity factor** was created from positive emotion/affect-related items from the following questionnaires and a social support scale:

i) Positive affect from the positive scale of the Positive and Negative Affect Schedule (PANAS) (35): Participants rated a list of 10 positive emotions (e.g. “interested”, “excited”) on a 5-point Likert scale according to how strongly they felt the emotion in the moment (state affect). Responses were summed to create positive affect scores.

ii) Positive state sum scores from the State-Trait Anxiety Inventory (STAI) (36): The STAI comprises 10 positive items (e.g.. “I feel pleasant”, “I feel secure”), rated on a 4-point scale and summed. The state version of the instrument, which asks about feelings in the moment, was administered at each visit.

iii) Pregnancy-related uplifts from the Pregnancy Experience Scale (PES) (37): The PES consists of 41 pregnancy-related items (e.g. “how much the baby is moving”, “discussions with spouse about pregnancy/childbirth issues”), which respondents rate on two 4-point Likert scales. One scale asks them to what degree the item was uplifting, the other to what degree it was experienced as a hassle (described below). Responses to the question “How much has this made you feel happy, positive, or uplifted?” were used to determine frequency and intensity of uplifts. Frequency of uplifts was determined by totaling the number items on the positive scale that were rated above 0 (“not at all”). Intensity of uplifts was calculated by summing the responses from 1-3 and dividing the result by the frequency.

iv) Social support satisfaction over last 2 weeks, from a Visual Analog Social Support Scale (VAS-SS): Participants were asked to rate how much support they felt they had received from loved ones over the past two weeks by marking the level along a 65 mm horizontal scale from “no support at all” to “a great degree of support”. The responses were scored by measuring the distance in millimeters from the starting point to the line drawn.

A **stress factor** was computed from the following scales:

Perceived stress in the past month (PSS) (38): The (PSS-4) includes 4-stress items rated on a 5-point scale from “never” to “very often”. Two items were reverse scored, then all responses were summed.

Pregnancy-related hassles from the Pregnancy Experience Scale (PES) (37), using the responses to the question “How much has this made you feel unhappy, negative, or upset?”, scored on a 4-point Likert scale. Frequency and intensity of hassles were computed as described above.

Perceived stress over last 2 weeks, from a Visual Analog Stress Scale (VAS-S): Participants were asked to rate their overall stress level over the past two weeks by marking how much stress they felt along a 65 mm horizontal scale from “no stress at all” to “very high levels of stress”. The distance in millimeters from the starting point to this line was measured and served as a score. The same scale was administered four times, with each repetition focusing on a different aspect of stress: 1) work or studying; 2) close interpersonal relationships; 3) taking care of children/household duties; 4) pregnancy-related stress. The scores on each subscale were combined to create a total stress score.

To control for the potential effect of personality on the experience of positive emotions and stress, in a subsequent analysis we further adjusted the resilience regression for trait neuroticism measured at 12 weeks gestation using the Finnish version of the NEO Personality Inventory (NEO-PI) (39).

Obstetric risk conditions and birth outcomes

Obstetric risk conditions, including chronic hypertension, gestational hypertension, preeclampsia, and gestational and type 1 diabetes, were obtained from medical records and the Finnish Medical Birth Register. For women in the high obstetric risk group, diagnoses were confirmed by an expert jury (34). We created dummy variables to indicate presence of chronic/gestational hypertension, preeclampsia and diabetic disorders.

Body mass index (BMI), maternal age, parity, and smoking status were extracted from the Finnish Medical Birth Register (FMBR). Birth outcomes were also obtained from the FMBR, including child sex, birth weight, and gestational age at birth (34).

Telomere length

Telomere length was analyzed in leukocytes from cord blood samples collected at birth. DNA was isolated from whole blood. Leukocyte telomere length (LTL) is the most commonly used measure of TL in human epidemiological studies, and it has been postulated that TL dynamics in leukocytes mirror those of the entire hematopoietic stem cell population (HSCs) (40), the original pool of which is formed early in pregnancy and serves as the progenitor for cells in all blood lineages (41).

Relative telomere length was measured by quantitative polymerase chain reaction (qPCR), expressed as the ratio of telomere to single-copy gene abundance (T/S ratio), as previously described (42). The telomere qPCR primers were tel1b [5'-CGGTTT(GTTTGG)5GTT-3'], used at a final concentration of 100 nM, and tel2b [5'-GGCTTG(CCTTAC)5CCT-3'], used at a final concentration of 900 nM. The single-copy gene (human beta-globin) qPCR primers were hbg1 [5'-GCTTCTGACACAACTGTGTTCACTAGC-3'], used at a final concentration of 300 nM, and hbg2 [5'-CACCAACTTCATCCACGTTCACC-3'], used at a final concentration of 700 nM. The final reaction mix consisted of the following: 20 mM Tris-

hydrochloride, pH 8.4; 50 mM potassium chloride; 200 μM each deoxyribonucleotide triphosphate; 1% dimethyl sulfoxide; 0.4x SYBR green I; 22 ng Escherichia coli DNA; 0.4 Units of platinum Taq DNA polymerase (Invitrogen Inc., Carlsbad, CA), and approximately 6.6 ng of genomic DNA per 11 microliter reaction. A 3-fold serial dilution of a commercial human genomic DNA containing 26, 8.75, 2.9, 0.97, 0.324 and 0.108ng of DNA was included in each PCR run as the reference standard. The quantity of targeted templates in each sample was determined relative to the reference DNA sample by the maximum second derivative method in the Roche LC480 program. The reaction was carried out in a Roche LightCycler 480 in 384-well plates, with triplicate wells for each sample. Dixon Q test was used to exclude outliners from the triplicates. The average of the T and S triplicate wells after outliner removal was used to calculate the T/S ratio for each sample. The same reference DNA was used for all PCR runs.

We applied a telomere (T) thermal profile consisting of denaturing at 96°C for 1 minute followed by 30 cycles of denaturing at 96°C for 1 second and annealing or extension at 54°C for 60 seconds with fluorescence data collection and a single copy gene (S) thermal profile consisting of denaturing at 96°C for 1 minute followed by 8 cycles of denaturing at 95°C for 15 seconds, annealing at 58°C for 1 second, and extension at 72°C for 20 seconds, followed by 35 cycles of denaturing at 96°C for 1 second, annealing at 58°C for 1 second, extension at 72°C for 20 seconds, and holding at 83°C for 5 seconds with data collection. The T/S ratio for each sample was measured in duplicate runs, each with triplicate wells. When the duplicate T/S values disagreed by more than 7%, the sample was run in triplicate and the two closest values were used.

Eight control genomic DNA samples were included to calculate a normalizing factor for each run. In each batch, the T/S ratio of each control DNA was divided by the average T/S ratio for the same DNA from 10 runs to generate a normalizing factor that was then used to correct the participant DNA samples to generate the final T/S ratio. Assays were performed with the same lot of reagent throughout the whole experiment. All samples that were included for telomere length measurements passed quality control criteria of an OD 260/280 ratio of between 1.7 and 2.0. The majority of samples had a DNA concentration of 30 ng/dl with a few exceptions at concentrations of 20 ng/ml (1% of samples). The average inter-assay coefficient of variation (CV) for this study was 2.3%.

DNA was extracted from N=344 samples via NucleoSpin, N=293 via the phenol-chloroform, and N=19 via the Automated Gentra extraction methods. Although it is possible that DNA extraction method can lead to systematic differences in measured TL (43), it has been shown that the rank order of TL in a population is not affected by the DNA extraction method (43). We therefore created standardized (z) scores of the TL measurements and furthermore adjusted the model for DNA extraction method. The observation that DNA extraction method was a significant predictor of TL in one of our subgroup analyses [specifically, the subgroup with resilience and neuroticism data] highlights the importance of accounting for the effect of this factor.

Statistical analysis

Analyses were conducted using SPSS 25.0 for Windows.

Pregnancy sum scores—In order to obtain a measure of cumulative levels of maternal stress, positivity, and resilience, scores from each questionnaire were averaged across pregnancy. The intercorrelation between the scores at different time points supports using an average (correlations for all instruments between 0.328 and 0.732). The average score of the PES intensity of hassles scale was transformed to achieve a normal distribution (natural log plus one transformation).

Principal component analysis of the positive and negative affectivity measures—We created two composite variables, positivity and stress, from the various questionnaires described above. The scores of the individual measures that went into each composite were weighted using principal component analysis (PCA). PCA allows the number of covariates to be reduced by transforming inter-correlated variables into a new set of uncorrelated principal components encompassing the variation of the original variables, allowing models to be simplified while retaining maximum variance and predictive value. This strategy was particularly suitable for our data, as multiple questionnaires measured similar constructs, yielding correlated scores. PCA was deemed preferable to principal axis factoring as no *a priori* hypothesis was made regarding the number of underlying factors (44). Incomplete cases were deleted listwise so that only women who had completed more than half of each component questionnaire at at least one time point were included.

A positivity factor was computed using the PANAS and STAI positive subscales, PES frequency and intensity of uplifts, and the VAS for social support. Factorability of these scales was supported on several grounds. All scores were significantly correlated (at least $r=0.27$, $p<0.001$,) and Bartlett's test of sphericity was significant ($\chi^2(10)=1130.67$, $p<0.001$), indicating covariance between the scales. Furthermore, the diagonals of the anti-image correlation matrix were all greater than 0.658 (above the accepted cut off of 0.50) and Kaiser-Meyer-Olkin (KMO) sampling adequacy was above the established threshold of 0.50 (KMO=0.709)(44). One component had an eigenvalue above the standard Kaiser criterion cutoff of 1 ($\lambda=2.71$) and explained 54.01% of the total variation. A scree plot revealed a sharp drop in predictive value and subsequent leveling off for further components, supporting the recognition of a single factor (44). As only one component was extracted, a rotated factor matrix could not be produced. We identified this component as the positivity factor.

A stress factor was similarly constructed from PES hassle frequency, hassle intensity, PSS, and VAS stress scores using PCA. Interrelatedness of the variables was established by correlation (at least $r=0.45$, $p<0.001$) and Bartlett's test of sphericity ($\chi^2(6)=837.49$, $p<0.001$). Sample adequacy was confirmed by a KMO statistic of 0.76 and anti-image correlation matrix diagonals of above 0.71. A single component was extracted with an eigenvalue of $\lambda=2.50$ and visually confirmed by scree plot, indicating that including further components would not increase predictive value of the model (44). This component explained 62.51% of the total variance in the data and was considered the stress factor.

PCA factors were centered with a mean of zero and a standard deviation (SD) of one. The positivity factor had a range of −3.34 to 2.68. The stress factor ranged from −2.75 to 3.49.

The stress and positivity factors were significantly inversely correlated ($r^2 = -0.514$, $p<0.001$).

Resilience Factor—To create a resilience factor, we regressed the positivity factor against the stress factor. This approach quantifies for each subject the variation in positivity that is *not* accounted for by the variation in stress. Thus, at a given level of stress, individuals who exhibit higher positivity have more resilience. The resilience factor was also zero-centered with a standard deviation of one, and had a minimum value of −4.18 and a maximum of 2.66.

Regression models—Linear regression models were developed to predict newborn telomere length from maternal resilience, positivity, and stress, with adjustment for the effects of other potential determinants of newborn TL. Cases were deleted listwise so that only women with pregnancy sum scores for each of the psychological measures composing the factors and complete covariate data were included.

Repeated measure ANOVAs revealed no significant within-subject effects for either the resilience ($F(2,1088)=0.036$, $p=0.850$), positivity ($F(2,1128)=0.170$, $p=0.681$), or stress ($F(2,1090)=0.058$, $p=0.810$) factors. Due to this lack of inter-individual variation across time, we performed analyses using the average scores of these factors across pregnancy.

Covariates were specified *a priori* based on previously published determinants of newborn telomere biology and included child sex, gestational age at birth, birth weight, maternal age at childbirth, maternal pre-pregnancy BMI, maternal educational attainment (classified as primary, secondary, lower tertiary, or upper tertiary, scored 1-4), obstetric risk conditions (hypertension, preeclampsia, and diabetes), and maternal smoking status during pregnancy. Parity was also included as a covariate due to its expected influence on maternal emotional state during pregnancy.

Results

Data on newborn telomere length and maternal prenatal resilience were available for N=656 mother-child dyads. Sociodemographic and clinical characteristics of the sample are presented in Table 2. Newborn T/S ratio ranged from 1.58 to 3.35, with a mean of 2.39 ± 0.24. Score on the individual questionnaires prior to collapse into positivity and stress factors are presented in Table 3.

Consistent with findings from previous studies, maternal stress during pregnancy was significantly and inversely associated with newborn TL ($\beta= -0.079$, $p=0.044$, 95% CI [−0.155, −0.002], $R^2=0.044$, $F(13, 642)=2.272$, $p=0.006$). A one standard deviation (SD) change in maternal stress was associated with a 4% difference in average newborn TL. Among the covariates included in the model, sex of the child (TL was longer in girls: $\beta=0.099$, $p=0.013$, 95% CI [0.022, 0.177]) and maternal age at childbirth ($\beta=0.095$, $p=0.024$, 95%CI [.011, 0.179]) were also significant predictors of TL at birth.

Maternal positivity during pregnancy was significantly and positively associated with newborn TL ($\beta =0.135$, $p=0.001$, 95% CI [0.059, 0.211], $R^2=0.055$, $F(13,642)=2.786$,

p<0.001). Each SD change in maternal positivity was associated with a 13% difference in average newborn TL.

Lastly (and most importantly), maternal resilience during pregnancy was significantly and positively associated with newborn telomere length (model R^2=0.050, F(13,642)=2.500, p=0.002; β (resilience)=0.112, p=0.004, 95% CI [0.035, 0.189]). Each SD change in maternal resilience was associated with a 12% difference in newborn TL. As in previous models, sex of the child (girls had longer telomeres: β=0.093, p=0.020, 95% CI [0.015, 0.171]) and maternal age at childbirth (β=0.099, p=0.019, 95% CI [0.017, 0.182]) remained significant predictors of TL. These findings persisted when our model was further adjusted for maternal trait neuroticism (β=0.148, p=0.001, 95% CI [0.060, 0.235], R^2=0.080, F(14,481)=2.979, p<0.001).

Detailed results of the resilience regression are shown below in Table 4. Output of the other regressions (stress, positivity, and resilience with adjustment for neuroticism) can be found in Supplement 1.

Several subsequent sensitivity analyses were performed on the resilience regression. To examine a potential ceiling or floor in the effect of maternal prenatal resilience on newborn TL, we stratified the regression according to stress factor tertile. We found a stronger effect of resilience among those in the highest tertile of stress (β=0.159, p=0.018) than in the bottom two tertiles (β=0.085 p=0.893, β=0.086, p=0.225, tertiles one and two, respectively).

To further investigate the robustness of this relationship, models were run excluding all women with obstetric conditions (hypertensive conditions, preeclampsia, and diabetes). This reduced the sample size from N=656 to N=366. Although no longer statistically significant, associations between maternal psychological factors and newborn TL length continued to be observed in the expected directions (maternal resilience was positively associated with newborn TL: (β=0.072); maternal positivity was positively associated with newborn TL: β=0.087; and maternal stress was inversely associated with newborn TL: β=−0.049).

We found no interaction between child sex and either resilience (β=0.139, p=0.263), positivity (β=0.151, p=0.233), or stress (β=−0.076, p=0.535) on child telomere length.

Discussion

The principal and novel finding of our study is that in a comparably large cohort of mother-child dyads assessed serially over the course of early, mid and late pregnancy, maternal psychological resilience, conceptualized and operationalized as maternal positive affect and social support satisfaction adjusted for maternal stress during pregnancy, was prospectively associated with newborn TL. To our knowledge, this is the first time that maternal resilience and positivity have been studied in the context of prenatal programming, and this study therefore adds a new perspective to this field of research. The magnitude of the effect of resilience was considerable, with each standard deviation increase in maternal resilience being associated with a 12% difference (increase) in newborn telomere length. Our findings also replicated previous reports linking maternal stress during pregnancy with offspring TL. We were further able to demonstrate that resilience evinced a stronger association with

newborn TL among those women in our sample with the highest levels of stress, a result which indicates that the benefits of maternal positive emotions may be especially pronounced among the most stressed individuals.

In this study, the impact of maternal resilience on newborn TL was greater than that of maternal stress alone. Given our conceptualization and operationalization of resilience as a multidimensional measure that incorporates positive affect and perceived social support as well as stress, our finding suggests that effects of positivity are not merely the opposite or inverse of those of stress, as well as evincing that these positive states can even exert transgenerational effects. Positive emotion, independently and also after accounting for stress, significantly influenced aspects of fetal development that regulate the initial, newborn setting of telomere length. We also note that although we observed the expected inverse relationship between positivity and stress, this relationship accounted for only about 25% of their shared variance. This suggests there is considerable between-subject variability in the level of positivity at the same or equivalent level of stress, thereby supporting the importance of assessing both positive and negative affect and responsivity in the context of development and health.

There are several plausible mechanisms by which maternal resilience could influence newborn telomere length, broadly by either promoting telomere elongation and/or by protecting against telomere attrition. Resilience, positivity, and social support have been shown to impact biological pathways involved in the neuroendocrine stress response (46), which, in turn, has well-documented effects on telomere biology. Several measures of positive psychological functioning and social support (47) have been associated with reduced or healthier patterns of cortisol output, including among pregnant women (48). Conversely, excess hypothalamic-pituitary-adrenal (HPA) axis activation and cortisol release have been implicated in telomere shortening (49). Cortisol also has been shown to reduce telomerase activity *in vitro* (50); thus, lower cortisol levels as a consequence of greater resilience may support the maintenance or even elongation of telomeres by promoting telomerase activity.

Resilience also may exert a protective effect on telomere length *via* the immune system. Resilient individuals and those experiencing satisfying social support seem to exhibit immune profiles that contrast to those of chronically stressed individuals (who, for their part, are at a higher likelihood of developing unfavorable health outcomes) (46, 51). Positive psychological states and social support have been associated with lower levels of cytokines, inflammatory markers (51, 52) and reduced risk of infection (53), which, in the context of prenatal development, may result in the embryo/fetus being exposed to a lower inflammatory load and consequent telomere erosion (54).

Resilience, positivity, and social support are known to diminish basal and stress-related autonomic arousal and lead to a more rapid and complete recovery from stress, and may even directly preserve or promote restorative physiology (16, 55). Improved vagal tone is associated with the experience of positive emotions (56) and social support (51) and, in turn, may be linked to greater telomerase activity (57). Higher levels of estrogen, which may be protective against negative mood (58), also have been shown to predict longer TL (59).

Clearly, additional research is warranted to better identify and characterize the pathway(s) by which maternal positivity and resilience promote fetal development and influence the initial setting of the telomere biology system.

In additional to the above-discussed strength in our conceptualization and operationalization of maternal resilience, other strengths of our study are the comparably large sample size and the breadth and depth of prenatal psychological data, some of which was collected as often as every two weeks throughout the course of pregnancy. Some of the limitations of this study include the non-availability of maternal or paternal TL and paternal age. One of the study findings was an independent and positive association between maternal age and newborn TL. Paternal age is a well-established predictor of newborn TL (60), and this may account for the observed association between maternal age and newborn TL, as older mothers are more likely to have older partners. It is also important that these findings be replicated in a cohort with clinically relevant levels of stress to better understand the robustness of the protective effects of resilience and positivity. Based, in part, on our finding that the magnitude of the association between maternal resilience and newborn TL was greater among women experiencing a higher level of stress than among women with medium or lower levels of stress, we suggest that the effect size observed is our study is likely a conservative estimate of what might be expected in a population with higher levels of stress.

Another important limitation is the lack of data in this cohort on negative life events, including baseline (prior to occurrence) and subsequent (following occurrence) psychological state and functioning. Such data facilitate examination of the temporal elements of the development of resilience (61). However, the focus of our study is on ascertainment of the transgenerational (mother to child) effects of maternal resilience in pregnancy, and not on how the mothers came to develop psychological resilience. Moreover, other theories of resilience, such as the broaden-and-build hypothesis, specifically emphasize the role of positive emotions in creating resilience, from the immediate biological effects of a positive state of mind to the coping, social, and lifestyle resources that such emotions confer on individuals (62). In this context, we submit that the experience of positive emotions in everyday life after accounting for stress is a reflection of both an individual's current resilience as well as of their future capacity to react to adverse circumstances. Given the growing evidence of the direct role that positivity plays in combatting stress and building resilience, we believe that there is much insight to be gained from studying resilience even when temporal data on negative life events is not available.

Potential biological mediators of stress and resilience, such as cortisol or pro-inflammatory cytokines, were also not measured. Future research should seek to identify specific pathways by which maternal resilience may act on the developing fetal telomere biology system.

Our study contributes new insight into the role of maternal prenatal psychological resilience in the initial setting of her offspring's telomere system, with potential life-long consequences for the offspring's health, disease risk, and the aging process. This beneficial effect of resilience underscores the importance of attending to mothers' mental as well as physical health during pregnancy to optimize mother and child health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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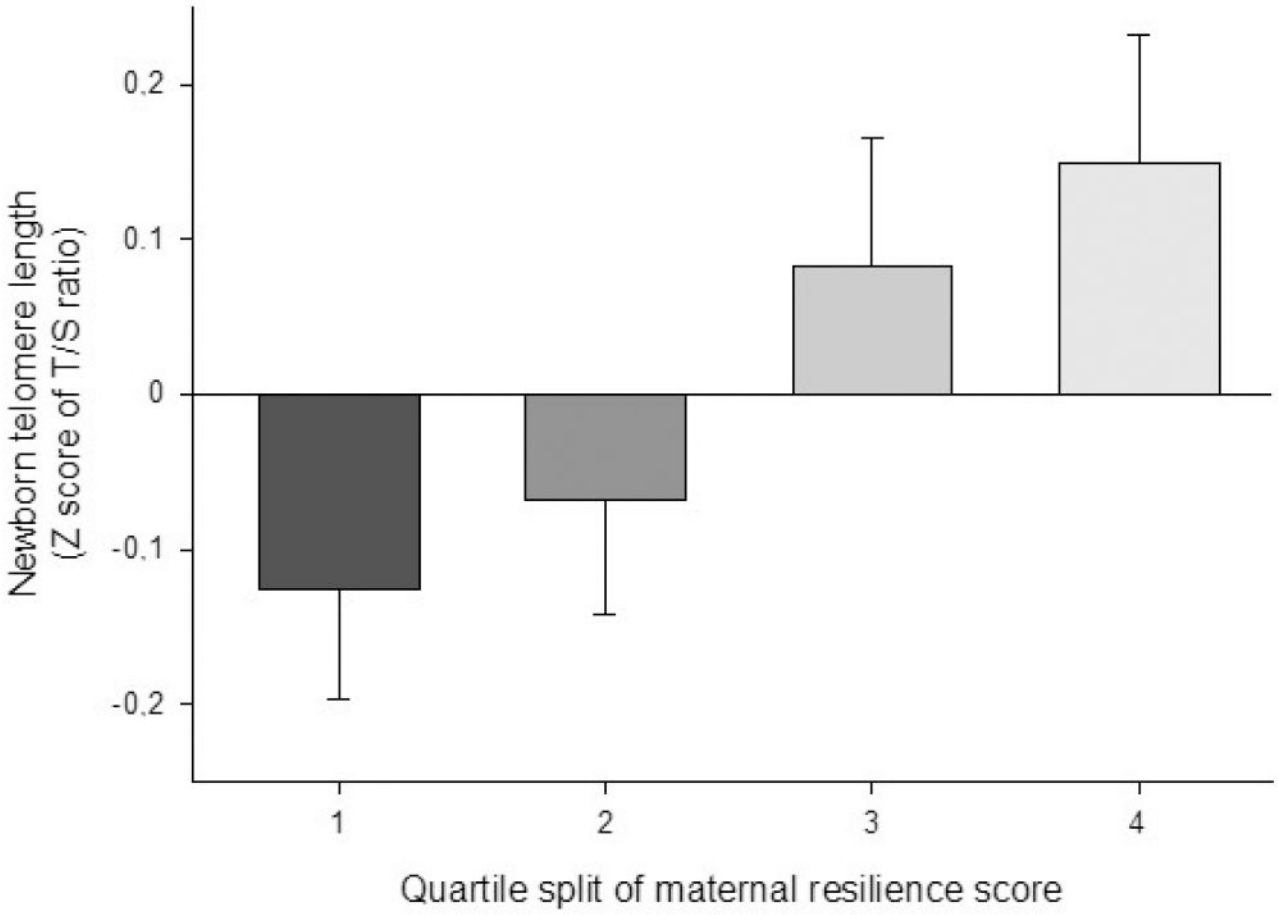

Figure 1:
Association between maternal resilience factor during pregnancy (in quartiles) and newborn TL. Newborn telomere length is reported as the Z score of T/S ratio. Standard errors (SEM) are shown with bars. Resilience was conceptualized as positivity in the face of stress. Factor score centered at zero.

Table 1

Timeline of psychological and psychosocial measures collected from the PREDO cohort

	Week of pregnancy													
Instrument	**Early pregnancy**		**Mid pregnancy**						**Late pregnancy**					
	12	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**
PANAS	x	x	x	x	x	x	x	x	x	x	x	x	x	x
STAI Positive – State		x	x	x	x	x	x	x	x	x	x	x	x	x
VAS Social Support	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PES Frequency of uplifts	x			x				x			x			
PES Intensity of uplifts	x			x				x			x			
PES Frequency of hassles	x			x				x			x			
PES Intensity of hassles	x			x				x			x			
PSS	x	x	x	x	x	x	x	x	x	x	x	x	x	x
VAS Stress	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Measures depicted PANAS – Positive and Negative Affect Schedule; STAI – State/Trait Anxiety Inventory; VAS Social Support – Visual analog scale for social support; PES –Pregnancy Experience Scale; PSS – Perceived Stress Scale; VAS Stress – Visual analog scale for stress

Table 2

Socio-demographic and clinical characteristics of the study population

Maternal factors		**Mean**	**St. Dev**	**N**	**%**
Maternal age at childbirth, years		33.24	5.48		
Maternal pre-pregnancy BMI		26.97	6.31		
Educational attainment	Primary			27	4.1
	Secondary			269	41.0
	Lower tertiary			152	23.1
	Upper tertiary			208	31.8
Parity	0			205	31.3
	1			293	44.7
	2			117	17.8
	3			27	4.1
	4+			14	2.2
Obstetric factors					
Hypertension	Chronic hypertension			101	15.4
	Gestational hypertension			57	8.7
Preeclampsia				47	7.2
Diabetes	Type 1			8	1.2
	Gestational diabetes			131	20
Smoking during pregnancy	No smoking			626	95.4
	Any smoking			30	4.6
Child factors					
Sex of the child	Male			341	52.0
	Female			315	48.0
Gestational age at birth, weeks		39.73	1.71		
Birth weight, grams		3541.20	569.44		

Valid percentages reported for maternal educational attainment, parity, hypertension, diabetes, and smoking during pregnancy

Table 3

Psychological questionnaire data prior to collapse into factors by principal component analysis

Instrument	N	Mean	St. Dev.	Range	Max. Score
PANAS	656	29.98	7.43	38.29	50.00
STAI Positive subscale	656	30.43	5.24	25.29	40.00
VAS Social support	656	42.80	11.82	58.36	65.00
PES Frequency of uplifts	656	27.89	7.38	40.50	41.00
PES Intensity of uplifts	656	1.85	0.39	2.60	3.00
PES Frequency of hassles	656	16.35	6.79	36.70	41.00
PES Intensity of hassles	656	1.39	0.28	1.80	3.00
PSS	656	5.33	2.55	15.76	20.00
VAS Stress	656	75.50	36.73	208.71	260.00
NEO-PI Neuroticism	496	71.71	23.05	142.00	192.00

Sample size, mean, standard deviation, range, maximum score depicted for: PANAS – Positive and Negative Affect Schedule; STAI – State/Trait Anxiety Inventory; PES – Pregnancy Experience Scale; VAS-SS – Visual analog scale for social support; PSS – Perceived Stress Scale; VAS Stress – Visual analog scale for stress NEO-PI Neuroticism – NEO Personality Inventory Neuroticism

Means in healthy pregnant samples for PES and PSS scales are as follows: PES Frequency of uplifts: 28.33 (37); PES Intensity of uplifts: 1.91 (37); PES Frequency of hassles: 19.12 (37); PES Intensity of hassles: 1.39 (37); PSS 3.88 (scoring adjusted for consistency) (46)

Table 4:

Linear regression predicting newborn telomere length from maternal resilience during pregnancy adjusted for maternal and child determinants of telomere length

	B	SE B	β	t	p	CI_L	CI_U
Intercept	−1.327	1.063		−1.248	0.212	−3.415	0.761
Resilience factor	0.111	0.039	0.112	2.875	0.004	0.035	0.187
DNA extraction method	0.091	0.070	0.050	1.290	0.197	−0.047	0.228
Sex of the child	0.184	0.079	0.093	2.341	0.020	0.030	0.339
Gestational age at birth	0.025	0.029	0.043	0.849	0.396	−0.033	0.083
Child birthweight	−9.032E-5	0.000	−0.052	−1.022	0.307	0.000	0.000
Maternal age at childbirth	0.018	0.008	0.099	2.360	0.019	0.003	0.033
Parity	−0.014	0.043	−0.013	−0.320	0.749	−0.097	0.070
Maternal pre-pregnancy BMI	−0.012	0.007	−0.075	−1.749	0.081	−0.025	0.001
Maternal education level	−0.046	0.046	−0.043	−1.017	0.310	−0.136	0.043
Hypertension in pregnancy	0.151	0.093	0.065	1.625	0.105	−0.032	0.334
Preeclampsia	0.217	0.156	0.056	1.388	0.166	−0.090	0.524
Diabetes in pregnancy	−0.032	0.100	−0.013	−0.319	0.750	−0.228	0.164
Smoking in pregnancy	−0.052	0.186	−0.011	−0.278	0.781	−0.418	0.314

Notes: B= unstandardized coefficient, *SE B*= standard error of the unstandardized coefficient, β=standardized coefficient, CI_L 95% Confidence Interval of *B* lower bound, CI_U 95% Confidence Interval of *B* upper bound.