Aus dem Institut für Medizinische Psychologie
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D I S S E R T A T I O N

Maternal psychological resilience and fetal programming of the telomere system

Mütterliche Resilienz in der Schwangerschaft und fetale Programmierung von Telomerbiologie

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List of Abbreviations

BMI	-	Body mass index
CI	-	Confidence interval
CRP	-	C–reactive protein
EMA	-	Electronic momentary assessment
FMBR	-	Finnish Medical Birth Record
HPA	-	Hypothalamic-pituitary-adrenal axis
HRV	-	Heart rate variability
HSC	-	Hematopoietic stem cell
IL-6	-	Interleukin 6
KMO	-	Kaiser-Meyer-Olkin
LTL	-	Leukocyte telomere length
NEO-PI	-	Neuroticism-Extraversion-Openness Personality Inventory
OS	-	Oxidative stress
PANAS	-	Positive and Negative Affect Schedule
PCA	-	Principal component analysis
PES	-	Pregnancy Experience Scale
PREDO	-	Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction Cohort
PSS	-	Perceived Stress Scale
PTSD	-	Post-Traumatic Stress Disorder
qPCR	-	Quantitative polymerase chain reaction
ROS	-	Reactive oxygen species
S	-	Single gene copy
SD	-	Standard deviation
STAI	-	State-Trait Anxiety Inventory
T	-	Telomere
TA	-	Telomerase activity
TL	-	Telomere length
TNF α	-	Tumor necrosis factor alpha
VAS-S	-	Visual analog scale for stress
VAS-SS	-	Visual analog scale for social support

Abstract – English

Theoretical Background. Age-related, non-communicable diseases contribute ever-increasingly to the global burden of disease. Risk or resilience to these conditions begin to be shaped even before birth *via* alterations in maternal-placental fetal biology. The telomere system plays a central role in the development aging-related of non-communicable diseases and the aging process. Fetal telomere biology seems to be plastic to conditions in the womb. Previous studies have established that maternal prenatal stress is associated with shorter offspring telomere length (TL). This study seeks to investigate whether maternal positive psychological factors and psychological resilience during pregnancy may function as a protective factor in the context of fetal programming of the telomere system.

Study Aims. The study had the following four aims:

1. To replicate past findings on the association between higher levels of stress during pregnancy and shorter newborn telomere length.
2. To investigate the association between maternal social support during pregnancy and newborn telomere length.
3. To test the association between maternal positivity during pregnancy and newborn telomere length.
4. To investigate the association between maternal psychological resilience during pregnancy and newborn telomere length.

Methods. The study sample was drawn from a large, prospective pregnancy cohort study that was extensively characterized in terms of stress, social support, and positivity throughout pregnancy. Prenatal psychological data and newborn TL data (measured using quantitative polymerase chain reaction (qPCR) from leukocytes isolated from cord blood cells) was available for N=656 mother-child dyads. Principal component analysis (PCA) was used to isolate latent maternal positivity and stress factors. These were regressed to create a resilience factor representing the degree of positivity a woman experienced during pregnancy taking into account her level of stress. Linear regression models were created predicting newborn TL from maternal psychological factors and other known determinants of TL at birth.

Results. Maternal stress significantly predicted shorter newborn TL ($\beta = -0.079$, $p=0.044$), social support ($\beta = 0.080$, $p=0.040$) and positivity significantly predicted longer TL ($\beta = 0.135$, $p=0.001$). Maternal resilience (positivity accounting for stress) was significantly and positively associated with newborn TL ($\beta = 0.114$, $p = 0.005$) with each standard deviation increase in resilience predicting 12% longer newborn TL.

Conclusions. Maternal psychological resilience during pregnancy seems to exert beneficial effects on the fetal telomere system. Children of mothers with greater resilience during pregnancy may begin life with a head start on a path towards healthy aging and longevity. This underscores the importance of supporting maternal mental health during pregnancy to improve health for her and her child, combat health disparities, and improve population health for decades into the future.

Abstrakt – Deutsch

Theoretischer Hintergrund. Altersbedingte, nichtübertragbare Krankheiten tragen maßgeblich zur globalen Krankheitslast bei. Das Ausmaß des Krankheitsrisikos oder auch der Widerstandsfähigkeit gegenüber diesen Erkrankungen wird möglicherweise bereits vor der Geburt bestimmt. Das Telomersystem spielt eine zentrale Rolle bei physiologischen Alterungsprozessen und der Entwicklung altersbedingter nicht übertragbarer Krankheiten. Die fetale Telomerbiologie scheint plastisch, d.h. durch Bedingungen im Mutterleib veränderbar zu sein. Frühere Studien haben gezeigt, dass mütterlicher vorgeburtlicher Stress mit einer kürzeren Telomerlänge (TL) der Nachkommen verbunden ist. In der aktuellen Studie wird untersucht, welche Rolle positive psychologischen Faktoren und die psychische Resilienz (Widerstandsfähigkeit) der Mutter während der Schwangerschaft für die frühe Programmierung des fetalen Telomersystems spielen.

Ziele. Die Studie hat folgende Forschungsziele:

1. Die Replikation früherer Forschungsbefunde zum Zusammenhang zwischen höherem Stress der Mutter während der Schwangerschaft und kürzerer Telomerlänge bei Neugeborenen.
2. Die Untersuchung des Zusammenhangs zwischen der sozialen Unterstützung der Mutter während der Schwangerschaft und der Telomerlänge des Neugeborenen.
3. Den Zusammenhang zwischen der positiven Einstellung der Mutter (Positivität) während der Schwangerschaft und der Telomerlänge der Neugeborenen zu testen.
4. Die Untersuchung des Zusammenhangs zwischen der psychologischen Resilienz der Mutter während der Schwangerschaft und der Telomerlänge des Neugeborenen.

Methode. In einer großangelegten prospektiven Längsschnittstudie in Finnland bestehend aus 656 Mutter-Kind Dyaden aus wurden mütterlicher Stress, positive und negative emotionale Reaktionen auf Ereignisse in der Schwangerschaft, positiver Affekt und wahrgenommene soziale Unterstützung wiederholt über die Schwangerschaft hinweg gemessen. Mittels Hauptkomponentenanalyse wurden basierend auf den verschiedenen Fragebögen zu mütterlichem Wohlbefinden zwei Faktoren extrahiert: mütterliche Positivität und mütterlicher Stress. Ein Maß für psychische Resilienz wurde berechnet, in dem Positivität zum Ausmaß von Stress ins

Verhältnis gesetzt wurde. Der so ermittelte Resilienzfaktor stellt die verbleibende Positivität unter Stress dar. Telomerlänge der Neugeborenen wurde mithilfe der quantitativen Polymerase-Kettenreaktion in Leukozyten aus Nabelschnurblut quantifiziert. Unter Einschluss von relevanten Kovariaten wurde in vier separate multiplen linearen Regressionsmodellen der Effekt von mütterlicher Resilienz, Positivität und Stress in der Schwangerschaft auf die Telomerlänge der Neugeborenen getestet.

Ergebnisse. Höherer mütterlicher Stress ging mit kürzerer Telomerelänge der Neugeborenen (β = -0.079, p=0.044) einher. Höhere soziale Unterstützung der Mutter (β = 0.080, p=0.040) und höhere mütterliche Positivität (β = 0.135, p=0.001) waren mit längerer TL der Nachkommen verbunden. Mütterliche Resilienz (Positivität unter Berücksichtigung von Stress) war positiv mit Telomerlänge der Neugeborenen assoziiert (β = 0.114, p = 0.005).

Fazit. Die psychische Resilienz der Mutter während der Schwangerschaft hat positive Effekte auf die frühe Programmierung des fetalen Telomersystems. Da die Telomere zentral sind für zelluläre Gesundheit und mit einem höheren Risiko für altersbedingten Erkrankungen assoziiert sind, haben Kinder von Müttern mit höherer Widerstandfähigkeit gegenüber Stress möglicherweise bereits zu Beginn ihres Lebens günstigere Ausgangs-Bedingungen bezüglich der Gesundheit über die Lebensspanne. Die Ergebnisse dieser Studie unterstrichen die Bedeutung der psychischen und sozialen Unterstützung von Schwangeren, um die Gesundheit und Entwicklung der Mütter und der Kinder zu verbessern. Durch die verbesserte Unterstützung von Schwangeren könnte so die transgenerationale Übertragung von gesundheitlichen Ungleichheiten verhindert und die Belastung durch nichtübertragbare Krankheiten auf Bevölkerungsebene reduziert werden.

1 Introduction

1.1 Early-life determinants of healthy aging

Lifelong trajectories of resilience and vulnerability to disease begin their course even before birth, shaped not only by our genes but also by the environment in which we grow. Prenatal life is a period of precipitous development and great plasticity, meaning that conditions in the womb can play an outsize role in shaping an individual's health and disease risk across the lifespan. Outcomes ranging from obstetric conditions to the risk of developing common, complex, age-related disorders decades later have been linked time and again to factors influencing the intrauterine environment (Barker, 2004). Age-related cardiovascular, endocrine, immune, and metabolic disorders make up an increasing portion of the global burden of disease and are of growing importance for population health in low, middle, and high-income countries alike (Global Health Observatory, 2020). A growing body of evidence indicates that maternal psychosocial factors during pregnancy can also embed themselves biologically during fetal development and influence health and disease risk across generations. Understanding the early origins of such conditions enables a focus on prevention, which can lower the burden on health systems and help individuals live longer, healthier lives.

1.2 The fetal programming hypothesis

The phenotype that an organism exhibits is due not only to its genetic code, but to factors that influence which and how genes are expressed. From an evolutionary perspective, it is of clear advantage to an organism to be able to adapt to the greatest possible degree to the unique environment in which it finds itself to maximize its chances to survive and thrive in these specific conditions. An organism that even before its birth can respond to environmental signals and begin to modify its genetic expression accordingly can begin life on a trajectory best adapted to the challenges it will face (Ellison, 2005). This realization and ensuing observations of the long-term effects of prenatal environmental factors on offspring health form the basis of the theory of the fetal programming hypothesis, which is central to the questions addressed in this thesis.

The theory of fetal or developmental programming proffers that intrauterine conditions exert programming effects on the developing organism that can permanently influence fetal physiology and subsequent health. Because the fetal period is especially sensitive, with critical windows during which certain systems develop quickly and cells divide rapidly, maternal factors, in interplay with the placenta and the fetus itself, can permanently alter the structure and function

of tissues and systems (Godfrey & Barker, 2001). Genes alone do not determine an individual's risk, for example, for age-related diseases, but act in a complex interplay with environmental factors. These provide the developing embryo, fetus, and infant with valuable information about the world in which it will live and enable it to prepare for these conditions – the earlier (further "upstream") the exposure, the more developmental plasticity exhibited, the more pronounced the effect (Entringer, de Punder, Buss, & Wadhwa, 2018).

The Dutch Famine Study is a seminal work in this field that established the link between a mother's nutritional state during pregnancy and her child's risk of developing chronic non-communicable diseases when the child itself has reached middle or old age decades later. During the last winter of the Second World War, the Nazis, in retribution for Dutch resistance to occupation, instituted a blockade against the country that caused widespread shortages and famine among the population. In following up on children whose mothers experienced food deprivation in various stages of pregnancy, it became evident that these children continued to suffer negative effects throughout their lives, included higher rates of diabetes, cardiovascular disease, obesity, and other non-communicable diseases (Roseboom, de Rooij, & Painter, 2006). This observation formed the basis of the fetal programming hypothesis, and in subsequent years more and more maternal states and exposures during pregnancy have been linked to child health status throughout the lifespan.

Age, body mass index (BMI), parity, factors related to life style (i.e. physical activity, alcohol consumption, smoking), exposure to environmental toxins, and, relevantly for this thesis, psychological state/ stress are among the maternal factors that have been associated with offspring outcomes as disparate as cognitive functioning, insulin sensitivity, and cardiovascular disease (e.g.(Bertram & Hanson, 2002; Carolan-Olah, Duarte-Gardea, & Lechuga, 2015; Sandman, Davis, Buss, & Glynn, 2011; Seckl & Holmes, 2007)). Suboptimal prenatal exposures do not often cause disease in and of themselves, but shape the developing fetus in such a way as to increase or decrease susceptibility later in life (Entringer, Buss, & Wadhwa, 2015).

1.3 Theoretical framework for fetal programming of the telomere system

Common, complex age-related diseases present complicated etiologies that have yet to be fully discerned, though understanding of important risk factors is growing. Different individuals may in fact develop the same or similar disease phenotypes *via* different pathways, and dysfunction in multiple systems is typically implicated in the development of such diseases (Barouki, Gluckman, Grandjean, Hanson, & Heindel, 2012). The widespread effects of the intrauterine

environment on numerous systems hint at a common underlying mechanism linking prenatal adversity to a higher risk for developing non-communicable diseases later in life. The telomere system has been proposed as a potential mediator bridging the gap between prenatal exposures and later health outcomes (Entringer et al., 2018). The telomere system, factors influencing telomere biology, and potential mechanisms of fetal programming of the telomere system are described in the following sections.

Fetal programming of the telomere system is of particular interest in the investigating of the developmental origins of non-communicable diseases for several reasons (as presented in (Entringer et al., 2018) and further explained in the sections below:

1. Shortened telomere length plays a potentially causal role in the etiology of most, perhaps even all, age-related disorders, as well as aging itself.
2. The newborn setting of the telomere seems to play a determinative role in lifelong telomere dynamics.
3. The initial setting of the telomere system exhibits developmental plasticity and seems to be influenced by prenatal conditions.

Given these circumstances and the potential mechanisms for the intergenerational transmission of maternal psychological state *via* alterations in the telomere system outlined in the following sections, this thesis addresses the hypothesis that maternal psychological resilience, social support, and positive psychology during pregnancy may exert a salubrious influence on lifelong offspring health.

Figure 1 illustrates the theory of the fetal programming of the telomere system (as elaborated on in (Entringer et al., 2018); figure adapted from (Buss et al., 2017)). According to this hypothesis, maternal psychological factors such as resilience and stress influence maternal biology, in particular neuroendocrine, inflammatory, oxidative stress, and the autonomic nervous systems. These alterations in turn have an impact on maternal-placental-fetal stress biology, leading to changes in the fetal compartment which "program" fetal telomere biology and contribute to disease risk or resilience throughout the lifespan.

Figure 1.

Theoretic model of the fetal programming effects of maternal psychological resilience during pregnancy on the offspring telomere system.

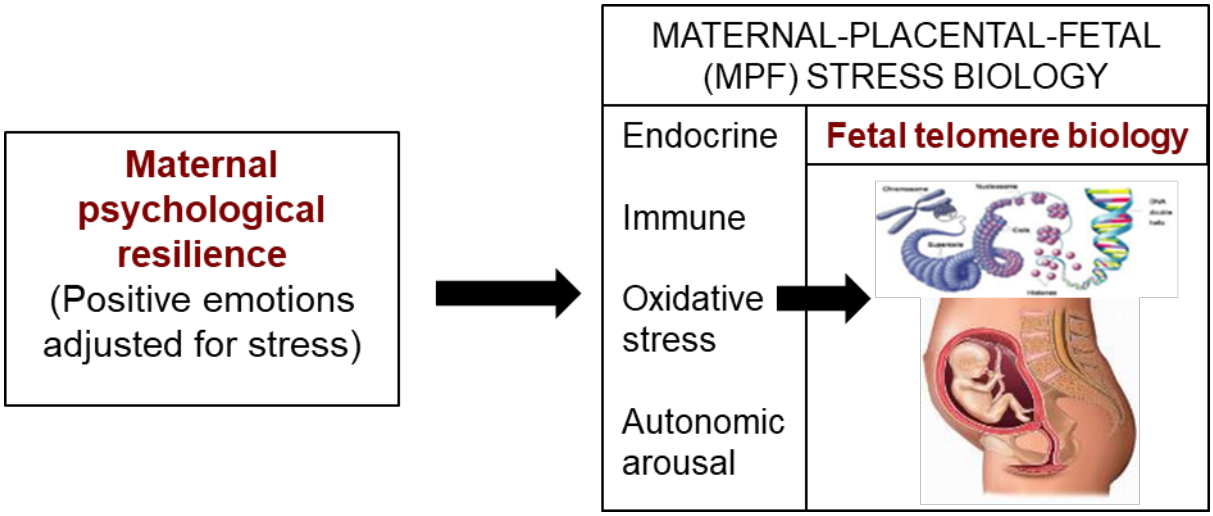


Figure 1. Theoretical framework for the fetal programming effect of maternal psychological state on the fetal telomere system during pregnancy. It is hypothesized that maternal resilience leads to changes in endocrine, immune, oxidative stress, and autonomic systems, which then act on fetal cells via maternal-placental-fetal biology to induce changes in the developing fetal telomere system.

1.4 The telomere system

Telomeres, tandem 5′-TTAGGG-3′ repeats at the ends of chromosome that protect the genome during cell division, and telomerase, an enzyme capable of extending telomeres, make up the telomere system. As cells divide, telomeres become shorter and shorter as base pairs are lost due to incomplete replication and not sufficiently replaced by telomerase until a critical threshold is reached, after which cells cease to divide and become senescent (Blackburn, 2001). Telomeres play vital roles in numerous cellular processes in addition to cellular senescence and apoptosis, including but not limited to transcription, chromosomal stability, mitochondrial function and cell differentiation (Blackburn, Epel, & Lin, 2015; Zhu, Liu, Ding, Wang, & Geng, 2019). Proper telomere structure and functioning is therefore essential.

Telomerase, a reverse transcriptase enzyme, adds telomeric repeat sequences counteracting this decline and helping to maintain telomere length as cells divide throughout the lifespan. Telomerase is however inactive in most somatic tissues, being maintained in germ cells, proliferating stem cells, and, importantly, activated immune cells (Forsyth, Wright, & Shay, 2002). However, though telomerase activity (TA) is upregulated in many cell types following immune

challenge, telomerase may not be capable of fully replacing the DNA lost in the course of repeated proliferation (Huang et al., 2017).

1.4.1 Telomeres and healthy aging

Short telomere length (TL) has been associated with all-cause mortality and a wide array of age-related diseases (Wang, Zhan, Pedersen, Fang, & Hagg, 2018). Beyond being a biomarker of aging, short TL seems to play both a causal and exacerbating role in the development of common, complex age-related disorders (Blackburn et al., 2015). Above and beyond the well-established correlation between shorter TL and greater chronological age, animal models have been used to investigate whether telomere shortening in itself is sufficient to cause aging and its associated effects. For example, studies in knock-out mice missing essential telomere maintenance genes (i.e. telomerase components) illustrate how this is causative of mitochondrial dysfunction leading to age-related degeneration and disease (Sahin et al., 2011). Knock-out gene studies in zebra fish, a species with average telomere lengths closer to humans than those of mice, have led to similar findings. Zebra fish with induced telomere shortening also exhibit dysregulation in important cell cycle and mitochondrial processes and develop typical age-related degenerative phenotypes and shorten lifespans (Carneiro, de Castro, & Ferreira, 2016). That individuals with premature aging syndrome exhibit shorter telomeres, in a dose-response relationship with disease severity, provides indication of a similar mechanism being at work in humans (Armanios & Blackburn, 2012).

As telomere length at any given time is a function of the initial setting of the telomere system and the rate of attrition over time (loss of base pairs due to cell division and cellular challenges, plus base pairs added by telomerase), and TL rank order seems to remain fixed across adulthood (Benetos et al., 2013), telomere length at birth may both predict and shape the aging process itself (Heidinger et al., 2012). Factors influencing the telomere system in the womb are therefore of interest in promoting healthy aging (Aviv, Levy, & Mangel, 2003).

Figure 2 illustrates the role of telomeres in healthy aging, showing telomere attrition across the lifespan and the importance of the initial setting of the telomere system (figure adapted from (Stewart & Weinberg, 2006). The solid (black) line represent an individual who begins life with relatively longer TL. As time passes and the somatic cells continue to divide, TL (vertical axis) shortens until they reach point M1, after which the cell becomes genetically unstable and eventually M2, where the cell is at a crisis point and apoptosis occurs. The dashed (red) line represents an individual beginning life with relatively shorter telomeres. Given the same telomere attrition rate, this individual's cell will reach critical points M1 and M2 sooner, i.e. at a younger chronological age.

Figure 2.

Effect of initial setting of the telomere system on lifelong telomere dynamics.

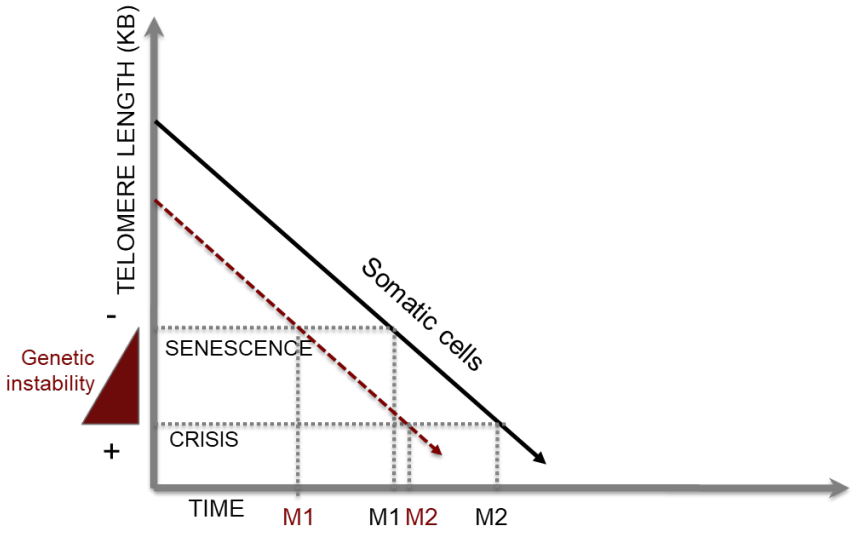


Figure 2. The importance of the initial setting of the telomere system and the rate of telomere attrition in the aging process. Given the same rate of telomere attrition, individuals who begin like with longer telomere length will reach the point of critically short telomere length, after which cells become senescent and stop dividing and eventually undergo apoptosis, at a chronically more advanced age than those who begin life with shorter telomeres (adapted from (Stewart & Weinberg, 2006).

1.4.2 Stress and the telomere system

A large body of research demonstrates that psychosocial conditions are important determinants of telomere length and impact telomerase activity (Epel et al., 2010). The link between stress and TL is by now well established not only in adults (i.e. (Mathur et al., 2016; Oliveira et al., 2016; Shalev et al., 2013)), but also in the context of fetal programming. This topic has been a central area of research in the writer's working group, and her doctoral supervisor, Professor Sonja Entringer, was the first to show a connection between maternal stress during pregnancy and newborn telomere length. Maternal perceived stress during gestation has been associated with offspring TL at birth (Entringer et al., 2013; Marchetto et al., 2016; Salihu et al., 2016; Send et al., 2017), and moreover, even into adulthood (Entringer et al., 2011), suggesting that the telomere system is plastic to intrauterine programming effects. Maternal-placental-fetal stress-related processes during pregnancy (specifically, immune, neuroendocrine, and oxidative stress factors, which are known to affect telomere biology (Wadhwa, 2005)) seem to mediate these effects, providing the link between maternal psychological state during pregnancy and later offspring health outcomes (Entringer et al., 2015).

1.5 Biological embedding of stress and maternal-placental-fetal stress signals

There are several mechanisms by which psychological stress can get "under the skin" *via* effects on the telomere system. Evidence for the effects of two of these stress-related biological processes on telomeres, the neuroendocrine stress response and the immune response/inflammation, is summarized below. As neuroendocrine stress can induce and promote inflammation, (Tsigos & Chrousos, 2002) these mechanisms should be considered as acting in conjunction in their influence on the dynamic telomere system.

1.5.1 The neuroendocrine stress response

The stress response involves a cascade of biological reactions that prepare an individual to respond to a stressful situation and then return to equilibrium once a stressor has been successfully addressed (allostasis). The hypothalamic-pituitary-adrenal (HPA) axis, which results in the secretion of the glucocorticoid cortisol in humans, is a primary element of this response. Though HPA activation is adaptive in response to acute stress, chronic stress can results in dysregulation of the system and long-term exposure to detrimental levels of cortisol and other stress hormones, which many studies have linked to telomere shortening (Jiang et al., 2019). .

Telomerase, the main regulator of telomeres *in vivo*, may underlie the observed effects of stress on TL. Chronic stress impacts telomerase activity, though the relationship appears to be complex – some studies have found lower levels of basal telomerase activity among stressed individuals (Epel et al., 2004; Epel et al., 2010) while others observe an increase in basal telomerase activity but a reduced ability to upregulate TA in response to an immune challenge (Damjanovic et al., 2007). Though telomerase and stress seem to interact in complex ways, *in vitro* exposure to cortisol has been shown to inhibit telomerase activity in lymphocytes, diminishing their ability to replenish telomere repeats lost during immune activation and subsequent cell division (Choi, Fauce, & Effros, 2008). Maternal cortisol levels in pregnancy can - in part - pass through the placenta and contribute to fetal concentrations (Benediktsson, Calder, Edwards, & Seckl, 1997; Rehman, Sirianni, Parker, Rainey, & Carr, 2007), providing a mechanism for the programming effect of maternal psychological state during pregnancy on fetal telomere length (through inhibition of telomerase).

1.5.2 Immune response and inflammation

Chronic stress can also lead to protracted activation of the immune system (Kiecolt-Glaser et al., 2003) and a pro-inflammatory state associated with many common, complex age-related diseases (Zhang et al., 2016). This results in deleterious overexposure to an inflammatory milieu and increases proliferation of immune cells, both of which induce telomere shortening (Aviv,

2004). C - reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) are among those inflammatory mediators which have been implicated in reduced TL in adults (Bekaert et al., 2007; Kiecolt-Glaser et al., 2011; Osler, Bendix, Rask, & Rod, 2016).Pro-inflammatory cytokines may transfer from mother to fetus across the placenta (Aaltonen, Heikkinen, Hakala, Laine, & Alanen, 2005), or induce inflammatory processes in the placenta that – in turn - may contribute to a more pro-inflammatory milieu in the fetal compartment. The effects of immune activation/inflammation on TL may also be mediated by telomerase. Inflammation alters telomerase activity, increasing its action in the short term to maintain telomere length as immune cells proliferate. Adaptive in the short term, this action is however insufficient to prevent TL shortening and resultant cell senescence in the long run, such as under conditions of chronic stress - immune cells with very short TL then also demonstrate lower telomerase activity, limiting their replicating capacity (Akbar & Vukmanovic-Stejic, 2007). This immunosenescent state leaves individuals both more vulnerable to infection, due to a diminished ability to mount an immune defense, and damaging chronic low-levels of inflammation (de Punder, Heim, Wadhwa, & Entringer, 2019). Maternal inflammation during pregnancy has in fact recently been associated with shorter newborn TL by another member of the writer's working group (Lazarides et al., 2019), providing evidence that a mother's stress load during pregnancy exerts programming effects on her child's telomeres via the immune system.

1.5.3 Oxidative stress

Another potential mechanism of the biological embedding of prenatal maternal stress in the developing fetal telomere system is *via* oxidative stress. Oxidative stress (OS) results from an excess of oxygen free radicals (ROS-radical oxygen species) generated during oxygen metabolism – serving important cellular functions at appropriate levels, they become toxic at elevated levels (Pizzino et al., 2017). In addition to important environmental (i.e. toxins) and dietary factors that can provoke an imbalance of oxygen free radicals, psychological stress is also associated with greater oxidative stress (Epel et al., 2004). Oxidative stress shortens telomeres *in vitro* (von Zglinicki, 2002) and has been associated with shorter TL and lower TA, providing evidence of this mechanism *in vivo* (Epel et al., 2004). This link has been further substantiated in a pregnant sample, with stressful life events being linked to greater measures of oxidative stress (Eick et al., 2018). Though due to their extremely short half-lives, ROS cannot cross the placenta, they have been found to negatively impact placental function and are linked to pregnancy complications (Schoots, Gordijn, Scherjon, van Goor, & Hillebrands, 2018) and have been proposed to function in conjunction with other stress parameters to program fetal development (Rakers et al., 2020).

1.6 Stress and well-being in pregnancy

Given the detrimental programming effects induced by psychological stress, reducing stress and supporting well-being during pregnancy would benefit both mother and child. However, stress is not always avoidable. For women faced with stress during pregnancy, elucidating factors that can mitigate stress or its negative ramifications is of great importance. The potential role of positive factors in protecting against or perhaps even reversing the detrimental effects of stress is currently understudied (Seligman, 2008), leaving our understanding of the programming effects of maternal psychological state incomplete and hindering efforts to design and implement interventions that could improve outcomes. Psychological resilience may promote positive outcomes and serve to psychologically and physiologically buffer the negative sequela of stress, including their impact on the initial setting of the telomere system.

1.7 Psychological resilience

What keeps us healthy is just as important as the things that can make us sick. Some people are resilient – even in the face of stressful or traumatic events, they are able to maintain a state of health and well-being. Though an exact definition of resilience and the traits or processes that it encompasses is still much discussed, research from across disciplines coalesces around a concept of resilience that includes "healthy, adaptive, or integrated positive functioning over the passage of time in the aftermath of adversity" (Southwick, Bonanno, Masten, Panter-Brick, & Yehuda, 2014). For the purposes of this dissertation, resilience is defined as the capacity to maintain a positive emotional state and rewarding social connections in the face of stress. The following will outline the reasoning behind this definition and its utility in investigating the potential role of resilience in the fetal programming of the telomere system.

1.7.1 Positive emotions and psychological resilience

There is growing recognition that positive psychology and good health consist of more than the mere absence of disease or psychopathology, and that they are not only valuable in and of themselves but are phenomena with distinct psychological and biological repercussions (Seligman, 2008). This dissertation seeks to address this important knowledge gap in the context of fetal programming and examine the role of positive emotions and resilience independently of that of stress.

The broaden-and-build hypothesis (Fredrickson, 2001) emphasizes the essential role of positivity, the practice of being or tendency to be positive or optimistic in attitude (Oxford English

Dictionary), in creating resilience. Psychological resilience is posited to arise from the use of positive emotions to interpret, cope with, and recover from negative experiences (Tugade & Fredrickson, 2004). By diminishing autonomic arousal, positive emotions put us in a calm state of mind, allowing us to broaden our perspectives and find benefits or silver linings in our experiences, think creatively and develop new coping strategies, and build lasting personal and psychological resources to handle future stressors (Fredrickson, 2001; Tugade, Fredrickson, & Barrett, 2004; Van Cappellen, Rice, Catalino, & Fredrickson, 2018). Positivity is thus posited to serve as a base for the development of further resilience traits.

Resilient individuals' positivity also elicits positive emotions in others, vitalizing and reinforcing social ties that provide further resilience resources (Kok et al., 2013). Positivity and social support can thus been seen as interacting in a feedforward loop, boosting each other, augmenting resilience, and counteracting negative psychological states (Garland et al., 2010; Ozbay et al., 2007). Physical activity (Wichers et al., 2012), sleep quality (Finan, Quartana, & Smith, 2015), and a healthy diet (Steptoe, Dockray, & Wardle, 2009), other factors considered resilience-building, also bolster and are bolstered by positive affect. Positive emotions and social connections, therefore, may underlie many of the traits often included under the umbrella of resilience and mediate the health outcomes associated with resilience (Van Cappellen et al., 2018).

17.2 Resilience, stress recovery, and allostatic load

Recovery from stress, both physically and psychologically, is a central aspect of resilience. This dissertation is focused on resilience in the context of biological embedding and healthy aging, an important aspect of which is protecting cells from the wear-and-tear that repeated or prolonged stress exerts on the body. The ability of the body to respond to challenges and afterwards return to a state of homeostasis is called allostasis; allostatic load refers to long term damage or dysregulation of systems that can ensue after prolonged or repeated exposure to stress and impede an individual's ability to achieve healthy allostasis (McEwen, 1998). Resilience is hypothesized to promote health by protecting individuals from reaching allostatic load, even under stressful conditions (Puterman & Epel, 2012).

Increasing evidence demonstrates that positivity and resilience can buffer against stress, counteract its physiological consequences, and even activate restorative mechanisms that protect telomeres and other systems (Fredrickson, Mancuso, Branigan, & Tugade, 2000), shielding individuals from the allostatic load and subsequent vulnerability accumulated under conditions of chronic stress (Epel, Daubenmier, Moskowitz, Folkman, & Blackburn, 2009). Experiencing positive emotions and social support has been linked to lower activation of stress-responsive neuroendocrine, autonomic, and immune systems (Dockray & Steptoe, 2010), mechanisms by

which resilience may benefit health, and which have also been shown to influence the telomere system (see above). These positive states are also associated with improved short- and long-term health outcomes, including experimental studies showing that this effect is not merely due to positive affect being associated with the absence of negative affect (Chida & Steptoe, 2008; Howell, Kern, & Lyubomirsky, 2007) and pointing to an important role for positivity in stress recovery. It is therefore important that both sides of the resilience coin, positive function and experienced adversity, be incorporated in models of resilience.

1.7.3 Resilience and telomeres

Despite the central role played by resilience in supporting healthy aging (Lavretsky & Irwin, 2007), very few studies have examined the relationship between resilience resources and telomere length, an important biomarker of cell senescence and aging. With regards to positive affective state and optimism, some studies have found that positive emotions were associated with longer TL (Connolly et al., 2018; Puterman et al., 2013; Schutte, Palanisamy, & McFarlane, 2016), while others, both studies on older adults, reported no association (O'Donovan et al., 2009; Rius-Ottenheim et al., 2012). Importantly for the work presented here, however, the positive effects on TL were observed following adjustment for depression (Puterman et al., 2013), post-traumatic stress disorder (PTSD) symptoms, and traumatic life events (Connolly et al., 2018), supporting the notion that resilience and the balance of positive and negative states, rather than positivity or negativity alone, may be exerting these effects on the telomere system. Social support has been reliably linked to longer TL (Barger & Cribbet, 2016; Carroll, Diez Roux, Fitzpatrick, & Seeman, 2013; Mitchell, Kowalsky, Epel, Lin, & Christian, 2018; Stein et al., 2018; B. N. Uchino et al., 2015; Bert N. Uchino et al., 2012; Zalli et al., 2014) ; with exception of (Lincoln, Lloyd, & Nguyen, 2019), which found the opposite association), including among pregnant women (Mitchell et al., 2018). However, the potential link between resilience and telomeres has yet to be addressed in the context of fetal programming of the telomere system.

1.7.4 Maternal resilience during pregnancy

To date, fetal programming research has largely focused on possible negative effects of maternal psychological state on prenatal development. However, a mother's characteristics have a corresponding potential to positively influence her unborn child's long-term health and development (Seligman, 2008). In fact, maternal positive emotion (Pesonen et al., 2016; Voellmin, Entringer, Moog, Wadhwa, & Buss, 2013) (Hernandez-Martinez, Val, Murphy, Busquets, & Sans, 2011) (Lobel, DeVincent, Kaminer, & Meyer, 2000), social support (Feldman, Dunkel-Schetter, Sandman, & Wadhwa, 2000) and resilience (Bender & Castro, 2000) have all been associated with favorable pregnancy and birth outcomes. Very few studies have examined maternal prenatal

resilience in conjunction with long term child health outcomes, but those that due find benefits that persist into childhood (McManus, Khalessi, Lin, Ashraf, & Reich, 2017; van den Heuvel, Donkers, Winkler, Otte, & Van den Bergh, 2015; van den Heuvel, Johannes, Henrichs, & Van den Bergh, 2015). These findings underline a potential for intergenerational transmission of the biological effects of resilience, though the mechanism by which this occurs remains to be investigated. One strong potential candidate mechanism is *via* programming of the initial setting of the fetal telomere system during gestation.

1.8 Biological embedding of resilience and positivity

Research to date provides evidence for several mechanisms by which resilience and positivity may get "under the skin" and leave their mark on the telomere system. Three prominent possibilities are outlined below: neuroendocrine stress processes, immune activity/inflammation, and autonomic arousal (assessed via heart rate variability/vagal tone). As described above with respect to the biological embedding of stress, these processes seem to interact and mutually enforce each other and should be considered in combination in understanding the biological effects of resilience and positivity. These associations support the hypothesis that psychological resilience may play a role, not only in the attrition of telomeres over time, but in programming the initial setting of the telomere system.

1.8.1 The neuroendocrine stress response

As detailed above, neuroendocrine stress, culminating in the secretion of cortisol, is associated with telomere shortening and reduced telomerase activity (Choi et al., 2008; Tomiyama et al., 2012). Positive psychology, on the other hand has been associated with lower cortisol levels (at awakening (Brummett, Boyle, Kuhn, Siegler, & Williams, 2009; Lai et al., 2005; Lindfors & Lundberg, 2002) also when adjusting for concurrent depression (Steptoe, O'Donnell, Badrick, Kumari, & Marmot, 2008; Steptoe, Wardle, & Marmot, 2005). Similarly, social support has been shown to suppress HPA axis reactivity, lowering cortisol secretion (DeVries, Glasper, & Detillion, 2003). Furthermore, negative affect was not a predictor of cortisol when positive affect was also controlled for, indicating that positive factors may be more important than negative ones in predicting cortisol levels (Lai et al., 2011). The relationship between positive psychology and cortisol levels has also been demonstrated in pregnant women (Pluess et al., 2012), which can in turn impact fetal cortisol levels.

1.8.2 Immune response and inflammation

Resilience may also exert a positive effect on the developing fetal telomere system *via* immune factors. Positive psychology has been linked to both lower baseline immune system activation (IL-6 and CRP levels) (Steptoe, Wardle et al. 2005) and increased immune activation, lower levels of infection, and diminished symptoms response to exposure to viruses (Cohen, Doyle et al. 1999, Cohen, Alper et al. 2006, Doyle, Gentile et al. 2006) and following vaccination (Marsland, Cohen et al. 2006), demonstrating improved overall immune functioning among individuals with greater positive affect. Similar patterns of improved immune functioning have also repeatedly been associated with higher levels of social support (reviewed in (Uchino, 2006)), providing further support for this potential mechanism for the biological embedding of resilience on the telomere system.

1.8.3 Autonomic arousal

Positive emotions are associated with higher vagal tone, also called heart rate variability (HRV) (Oveis, 2009). Vagal tone is the difference in heart rate during inhalation and exhalation and reflects the functioning of the vagal nerve, which is a core component of the parasympathetic nervous system, a reflection of autonomic arousal that can be used as a proxy for a state of mental well-being and allostatic stress response potential (Porges, 2007). Increases in positive emotions have been shown to correspond to increases in HRV and, conversely, individuals with more HRV seem to experiences greater increases in positive emotions following a mediation intervention, evincing an "upward spiral" of positive emotions and autonomic state (Kok et al., 2013). The same pattern has been documented in terms of social support, with social connections increasing HRV and the greater capacity for emotional regulation associated with HRV in turn helping build social connection (Petrocchi & Cheli, 2019). Improved vagal tone is linked to a wide range of endocrine and immune parameters (Thayer & Sternberg, 2006), whose alteration could also impact the telomere biology system. Links between HRV and telomere system have also been demonstrated: In a group of 62 women, lower telomerase activity was related to lower resting vagal hear rate and greater vagal suppression in response to a standardized laboratory stressor (Epel et al., 2006).

Given the evidence of the beneficial effects of maternal resilience and positivity in pregnancy and potential mechanisms for the biological embedding of maternal resilience and positivity in the fetal telomere system, this thesis seeks to investigate the following aims in the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) cohort, a large, comprehensive prospective birth cohort.

1.9 Aims

1. To replicate past findings on the association between higher levels of stress during pregnancy and shorter newborn telomere length.

Hypothesis: Higher levels of maternal stress during pregnancy are associated with shorter offspring telomere length at birth.

2. To investigate the association between maternal social support during pregnancy and newborn telomere length.

Hypothesis: Children of mothers who experienced more satisfying social support during pregnancy will have longer telomeres at birth than children of mothers lacking adequate social support.

3. To test the association between maternal positivity during pregnancy and newborn telomere length.

Hypothesis: Mothers who experience more positive emotions during pregnancy will give birth to children with longer telomeres.

1. To investigate the association between maternal psychological resilience during pregnancy and newborn telomere length.

Hypothesis: The balance of positive and negative psychological state during pregnancy, namely the degree of positivity (positive affect, uplifting emotions, rewarding social support) experienced by pregnant women while taking into account their level of stress exposure, is associated with longer offspring newborn TL.

1.10 Contribution of this dissertation

1.10.1 Contribution to the field of fetal programming

This dissertation presents the first study to examine the potential role of maternal resilience, positivity, and social support during pregnancy in programming the initial, newborn setting of the telomere system and therefore offers a novel contribution to the field (Aims 2-4). It builds specifically on research on the programming effects of maternal stress during pregnancy on the telomere system (Aim 1). In addressing stress effects, this thesis offers the benefit of examining this question among a sample significantly larger than previous studies. Contributing to the strength of the study in addressing all four aims is the quality and amount of data. The psychological state of women in this cohort is extremely well characterized, with positive and negative states being assessed up to 14 times throughout the course of pregnancy, and the cohort

offers excellent sources of data on birth and obstetric outcomes (clinical assessments by study doctors and access to detailed health records).

1.10.2 Contribution regarding other findings and publications in this cohort

This thesis also expands previous research conducted on the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) cohort on the long-term effects of maternal psychological state during pregnancy on offspring health and development. Most of these studies have focused on the negative effects exerted by maternal depression and anxiety during pregnancy, including with respect to stress processes in the placenta (Reynolds et al., 2015) and child psychological outcomes (Lahti et al., 2017; O'Donnell et al., 2017). Importantly, an inverse relationship was also found between maternal positive affect during pregnancy and the risk of preterm birth in this cohort (Pesonen et al., 2016). However, this is the first study in this cohort to consider newborn TL as an outcome of interest.

1.10.3 Contribution of this author

As the first author of the paper, I conducted background research on the impacts of resilience and positivity on the telomere system as well as on other obstetric and child outcomes. I integrated the telomere data that was analyzed at a laboratory at UC San Francisco with the large PREDO data set. I conceptualized and computed the measure of maternal resilience using principal component analysis and formulated the hypotheses and conducted the statistical analyses. I composed the first draft of the manuscript and incorporated suggestions from coauthors and reviewers through several rounds of revision. I also presented the findings in poster presentations and short talks at several conferences and colloquia.

1.10.4 Contribution of this dissertation.

This dissertation expands significantly on the work presented in the published paper. Numerous additional analyses and results are presented that are not included in the publication in addition to a more extensive background leading to the hypotheses investigated in the paper and dissertation. The following Methods and Results sections include some extracts, tables, and figures taken from the original publication related to this dissertation of which I am the sole first author (Verner et al., 2020). All such instances have been cited. The subsequent discussion of the findings is much more comprehensive than the discussion of the published paper and includes greater consideration of the public health and clinical implications of the findings, their importance with respect to potential positive psychology interventions during pregnancy, and an extensive outlook for future research in the field.

2 Methods

2.1 Study design and participants

The study sample for this dissertation constitutes a sub-cohort of the Prevention and Prediction of Preeclampsia (PREDO) study. This large cohort study, conducted at 10 participating hospitals in Finland, includes women pregnant between 2005 and 2009 and their live-born, singleton children (N=4,777). All participants were recruited amongst women attending prenatal ultrasound screenings at study clinics between 12 and 14 weeks gestation (Girchenko et al., 2017). The study was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District and all participating hospitals, and participants provided written, informed consent. Pre-pregnancy and obstetric health data and birth data were extracted from patient case reports and the Finnish Medical Birth Registry (FMBR).

The goal of the PREDO study was to learn more about the development and presentation of preeclampsia and intrauterine growth restriction (IUGR) among a large population, including both at-risk women (clinical sample, N=1,083) and those without known risk factors (community sample, N=3,702). The study sought to elucidate associations between these conditions and maternal biomarkers as well as child health and developmental outcomes (Girchenko et al., 2017). The cohort was also designed to explore the impact of maternal prenatal stress, depression, and anxiety during pregnancy on these parameters, and to that end maternal psychological state was assessed in detail throughout the course of pregnancy.

One such biological marker was newborn TL, measured in leukocytes extracted from cord blood samples collected shortly after birth (data available for N=688 newborns). The study sample for this dissertation consisted of those women for whom offspring TL and stress, positivity, and social support psychological measures (see descriptions below) were available (N=656 mother-child dyads). A flow chart of women from the PREDO cohort included in the analyses of this dissertation is shown below (Figure 3).

Telomere length was measured in a subsample drawn predominantly from the clinical sample (N=630 from the clinical sample, N=58 from the community sample). Since the majority of women of the current sample was drawn from the clinical sample, due to the intentional recruitment of women with risk factors for preeclampsia in this group, the sample in this study differs significantly from the overall cohort, which combined the clinical and community cohorts. Pre-pregnancy BMI ($t(4749)=-13.753$, $p<0.001$), hypertensive disorders ($\chi^2(3, N=4751)=348.035$, $p<0.001$) and gestational diabetes ($\chi^2(1, N=4751)=70.487$, $p<0.001$) were all higher or more prevalent in the subsample in which TL was measured. Maternal age at childbirth was also

significantly higher in the subsample (t(4769)=-9.489, p<0.001)), as would be expected, since several risk factors for clinical sample inclusion involve complications in previous pregnancies, making it more likely for the women in this group to be somewhat older, as well as maternal age over 40 being a risk factor in and of itself. There were also significantly fewer women who smoked in this sample, as smoking throughout pregnancy (but not quitting smoking during the first trimester) was an exclusion criteria for membership in the clinical sample as smoking has been found, perhaps counterintuitively, to in fact reduce the risk of preeclampsia (Karumanchi & Levine, 2010). These descriptives are presented below in Table 1.

The study sample for this thesis consisted of N=656 mother-child pairs for whom newborn TL and maternal prenatal psychological data were available. No significant differences were found between women who were drawn from the clinical sample (N=602) and those drawn from the community sample (N=54) with respect to telomere length (t(654)=0.079, p=0.937) or any of this dissertation's psychological predictors of interest (stress (t(654)=-0.513, p=0.608), social support (t(654)=0.114, p=0.909), positivity (t(654)=1.079, p=0.281), and resilience (t(654)=0.951, p=0.342)). However, as was the case in comparing mother-child dyads for whom newborn TL was measured and the overall combined cohort (described above), there were significant differences in the prevalence of obstetric risk conditions and gestational length between the women recruited to the clinical compared to the community cohorts. Women from the clinical sample had significantly different (larger) pre-pregnancy BMI (t(654)=-7.964, p<0.001), were more likely to have pregnancies complicated with diabetes (t(654)=-4.716, p<0.001) and chronic hypertension (t(654)=-11.007, p<0.001), and their children were a significantly different (younger) gestational age at birth (t(654)=3.726, p<0.001). These factors were adjusted for in all final models included in this dissertation.

Table 1.

Comparison of subset of sample with newborn telomere length data and the overall PREDO cohort.

		Newborn telomere length subset				Remaining PREDO cohort members			
Maternal factors		*N*	*%*	*Mean*	*St. Dev.*	*N*	*%*	*Mean*	*St. Dev.*
Age at childbirth		688		33.12	5.66	4083		31.23	4.70
Pre-pregnancy BMI		686		26.96	6.32	4065		24.14	4.71
Educational attainment	Primary	28	4.2%			141	3.8%		
	Secondary	274	41.0%			1362	36.5%		
	Lower tertiary	155	23.2%			984	26.4%		
	Upper tertiary	211	31.6%			1241	33.3%		
Parity		686		1.02	0.97	4055		0.86	0.96
Obstetric factors									
Hypertensive disorders	Chronic hypertension	105	15.3%			83	2.0%		
	Gestational hypertension	59	8.6%			144	3.5%		
	Preeclampsia	50	7.3%			146	3.6%		
Diabetes	Type 1 diabetes	7	1.0%			18	0.4%		
	Gestational diabetes	137	20.0%			375	9.2%		
Smoking during pregnancy		34	5.0%			374	9.2%		
Child factors									
Sex of the child	Male	357	51.9%			2125	52.3%		
	Female	331	48.1%			1940	47.7%		
Gestational age at birth		687		39.72	1.71	4089		39.90	1.66
Birth weight		686		3542.23	563.47	4060		3528.35	521.26

Note. Maternal age at childbirth reported in years. Child gestational age at birth reported in weeks. Child birthweight reported in grams.

Figure 3.

PREDO study participation flowchart.

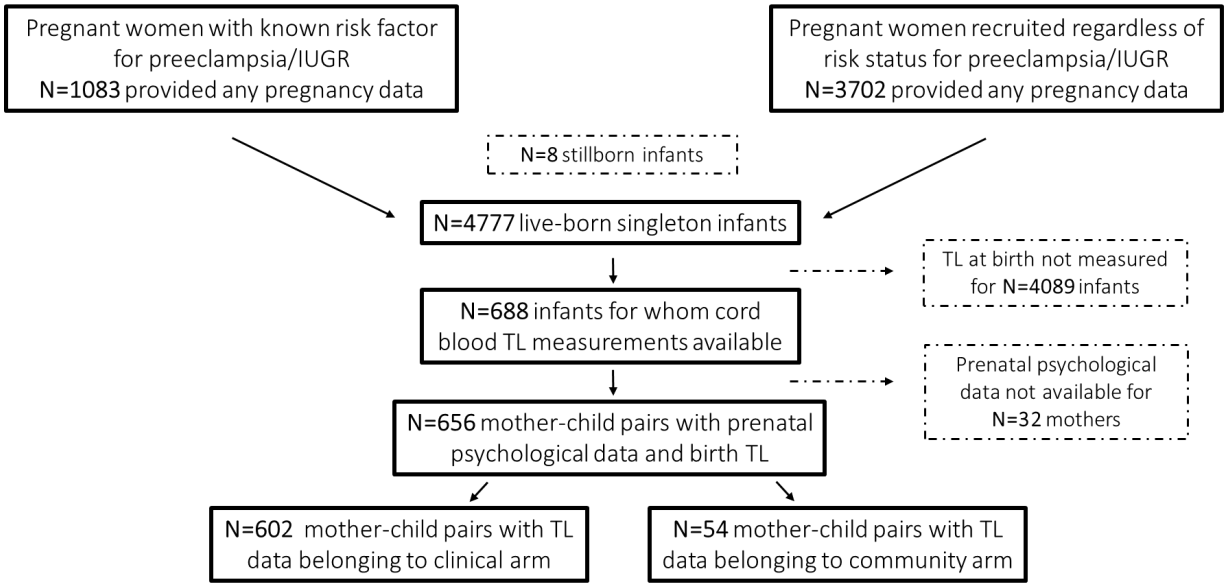


Figure 3. Of the N=4,777 live-born children included in the PREDO study, telomere length was measured from the cord blood of N=688 infants shortly after birth. For N=656 of these mothers, prenatal psychological data is available.

2.2 Prenatal psychological assessment

2.2.1 Approach, procedures, and compliance

Stress, social support, positivity, and resilience during pregnancy are the psychological constructs that were the main focus of this dissertation in terms of investigating their association with offspring telomere length. Psychological data during pregnancy was collected frequently in the PREDO cohort, with measures being obtained as often as every two weeks beginning at 12 weeks gestation. To maximize the amount of psychological information that could be incorporated into these analyses while simultaneously avoiding the problems of including too many covariates in a model, the scores from the relevant questionnaires were combined using principle component analysis (PCA). The questionnaires relevant to this dissertation are described below, and Table 2 depicts when they were administered throughout the study.

Compliance with filling out the questionnaires was very high. Approximately 90% of all women completed the questionnaires at each of the biweekly measurement points. Furthermore, the questionnaire scores were only included when at least half of the questions were answered. A within-subject mean was then created and averaged across all assessments. Missing cases were deleted listwise

This dissertation's statistical approach was to maximize the amount of variance between women by included as much relevant data as possible while simultaneously minimizing the

number of variables in any given model. The stress factor was constructed by combining the frequency and intensity of hassle experiences and two measures of perceived stress. This well-rounded stress measure was intended to capture both daily and pregnancy-related stress, which some studies have found to be a stronger predictor of obstetric outcomes than general stress (Lobel et al., 2008). Social support, a component of the positivity factor, was also analyzed independently as a predictor of newborn TL in a preliminary stage of analysis. As social support is a central component in the theoretical concept of resilience focused on in this thesis (Fredrickson, 2001), it was important that it be included the positivity and resilience constructs. It was therefore included in the positivity factor in addition to frequency and intensity of uplifting experiences during pregnancy, positive affect, and positive traits reported during pregnancy. A resilience factor was then computed by regressing the stress factor on the positivity factor, created a round measure of psychological state expressing the degree to which positive emotionality could be maintained in light of stress.

2.2.2 Psychological questionnaires descriptions

The questionnaires included, how they were administered in the study, and how PCA was used to create the factor scores, is described below in sections excerpted from the text on which this dissertation is based, of which I am the sole first author (Verner et al., 2020).

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

Positive affect from the positive scale of the Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988): 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.

Positive state sum scores from the State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, Lushene, & Vagg, 2010): 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.

Pregnancy-related uplifts from the Pregnancy Experience Scale (PES) (DiPietro, Ghera, Costigan, & Hawkins, 2004): 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.

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) (Cohen, 1988): 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) (DiPietro et al., 2004), 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) (Pulver, Allik, Pulkkinen, & Hämäläinen, 1995).

Table 2.

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

Note. 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

2.3 Maternal characteristics, obstetric risk conditions and birth outcomes

As the PREDO cohort was designed to investigate risk factors for the development preeclampsia and IUGR, detailed information on obstetric risk conditions, including health in previous pregnancies and birth outcomes, was available. This information was extracted from the FMBR for all participants, and an expert jury confirmed all diagnoses for women recruited via the clinical sample. Risk factors that led to participants being considered at-risk for the development of obstetric complications were as follows: preeclampsia in a previous pregnancy, IUGR in a previous pregnancy, gestational diabetes in a previous pregnancy, pre-pregnancy obesity (defined as a BMI of $\geq 30\ kg/m^2$), chronic hypertension, type 1 diabetes, maternal age at childbirth below 20 or greater than 40 years, systematic lupus erythematosus, Sjörgen's syndrome, or a previous pregnancy with fetal demise (> 22 gestational weeks or over 500 g) (Girchenko et al., 2017).

Of the array of data available, covariates of importance were drawn from the literature on prenatal determinants of TL. These included child sex, maternal age at childbirth, maternal education level, parity, gestational age at birth, birth weight, maternal pre-pregnancy BMI, chronic or gestational hypertension, preeclampsia, gestational or type 1 diabetes, and maternal smoking during pregnancy.

2.4 Determination of newborn telomere length

The following subsection is taken from the publication on which this dissertation is based (Verner et al., 2020).

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) (Kimura et al., 2010), the original pool of which is formed early in pregnancy and serves as the progenitor for cells in all blood lineages (Mikkola & Orkin, 2006).

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 (Cawthon, 2002). 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 Light Cycler 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 96ºC for 1 minute followed by 30 cycles of denaturing at 96ºC for 1 second and annealing or extension at 54ºC for 60 seconds with fluorescence data collection and a single copy gene (S) thermal profile consisting of denaturing at 96ºC for 1 minute followed by 8 cycles of denaturing at 95ºC for 15 seconds, annealing at 58ºC for 1 second, and extension at 72ºC for 20 seconds, followed by 35 cycles of denaturing at 96ºC for 1 second, annealing at 58ºC for 1 second, extension at 72ºC for 20 seconds, and holding at 83ºC 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 (Seeker et al., 2016), it has been shown that the rank order of TL in a population is not affected by the DNA extraction method (Seeker et al., 2016). 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.

2.5 Statistical analysis

The following section is taken from the publication on which this dissertation is based, of which I am the sole first author (Verner et al., 2020).

Analyses were conducted using SPSS 25.0 for Windows.

2.5.1 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 inter-correlation 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).

2.5.2 Principal component analysis of 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 (Jolliffe & Cadima, 2016). 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)(Jolliffe & Cadima, 2016). One component had an eigenvalue above the standard Kaiser criterion cutoff of 1 (λ=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 (Jolliffe & Cadima, 2016). 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 λ=2.50 and visually confirmed by scree plot, indicating that including further components would not increase predictive value of the model (Jolliffe & Cadima, 2016). 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).

2.5.3 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.

2.5.4 Telomere length Z score

DNA was extracted from 344 samples via the NucleoSpin system, 293 via the phenol-chloroform method, and 19 via the automated Gentra method. Although it is possible that DNA extraction method can lead to systematic differences in measured TL (Seeker et al., 2016), it has been shown that the rank order of TL in a population is not affected by the DNA extraction method (Seeker et al., 2016). 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.

2.5.5 Regression models

Multiple 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.

3 Results

This section includes the main results reported in the publication (positivity, stress, and resilience regressions) as well as additional results of analyses that were not included in the publication (social support analyses, graphs of positivity, stress, resilience, and social support findings, sensitivity analyses, gender analyses, supplemental tables).

Sociodemographic and health characteristics of the study sample of N=656 mother-child dyads are presented below in Table 3 and maternal psychological data obtained during pregnancy in presented in Table 4. The tables appeared in the publication upon which this dissertation is based, of which I am the sole first author (Verner et al., 2020). Results reported in that publication are restated below in addition to results addressing additional outcomes investigated in this thesis. Newborn T/S ratio ranged from 1.58 to 3.35, with a mean of 2.39 ± 0.24. Newborn T/S ratio according to gender is presented below in Figure 4.

Table 3.

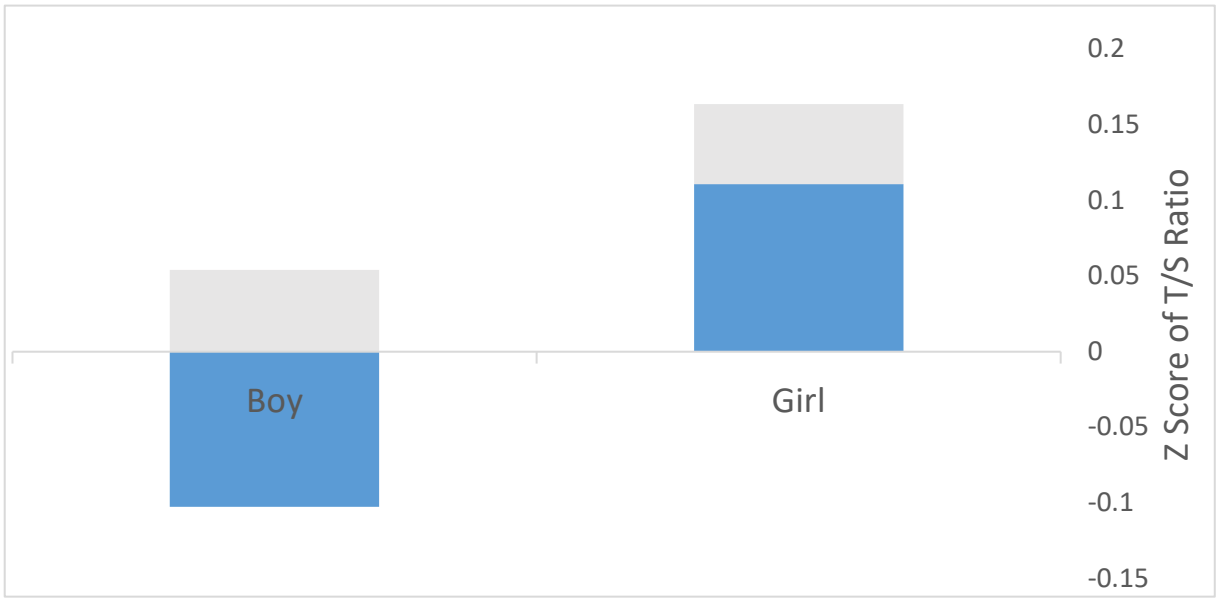
Socio-demographic and clinical characteristics of the study population.

Maternal factors		*M*	*SD*	*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		
Telomere length, T/S ratio		2.39	0.24		

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

Figure 4.

Telomere length at birth and child sex.



Note. TL was determined by measuring the T/S ratio, a ratio of the number of telomere repeats in a sample compared to a control gene. T/S ratio was then standardized by transformation into Z score, in which data is transformed to achieve a mean distribution of zero and a standard deviation of one. Data on child sex was extracted from health records. The blue bar represents the mean T/S ratio Z score of each child sex. Gray shading indicates the standard error of the mean (SEM).

Table 4.

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

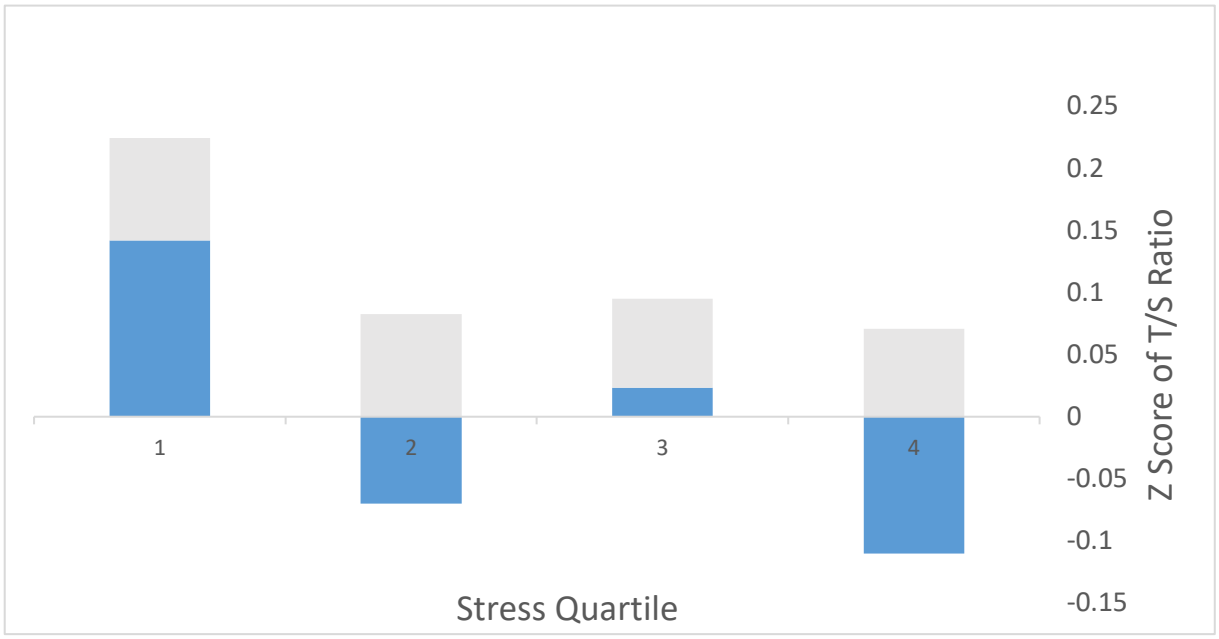
Note. Sample size, mean, standard deviation, range, maximum score depicted for: PANAS – Positive and Negative Affect Schedule; STAI – State/Trait Anxiety Inventory; PES – Pregnancy Experience Scale; VAS-SS – Visual analog scale for social support; PSS – Perceived Stress Scale; VAS Stress – Visual analog 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 (DiPietro et al., 2004); PES Intensity of uplifts: 1.91 (DiPietro et al., 2004); PES Frequency of hassles: 19.12 (DiPietro et al., 2004); PES Intensity of hassles: 1.39 (DiPietro et al., 2004); PSS 3.88 (scoring adjusted for consistency) (Karam et al., 2012).

3.1 Aim 1: Maternal stress and newborn telomere length

Consistent with findings from previous studies, maternal stress during pregnancy was significantly and inversely associated with newborn TL (β= -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 (decrease) in average newborn TL. Among the covariates included in the model, sex of the child (TL was longer in girls: β=0.099, p=0.013, 95% CI [0.022, 0.177]) and maternal age at childbirth (β=0.095, p=0.024, 95%CI [.011, 0.179]) were also significant predictors of TL at birth (full regression results in Supplementary Table S1). These findings are presented in Figure 5, which shows newborn TL as a function of maternal stress factor quartile.

Figure 5.

Maternal stress during pregnancy and newborn telomere length.



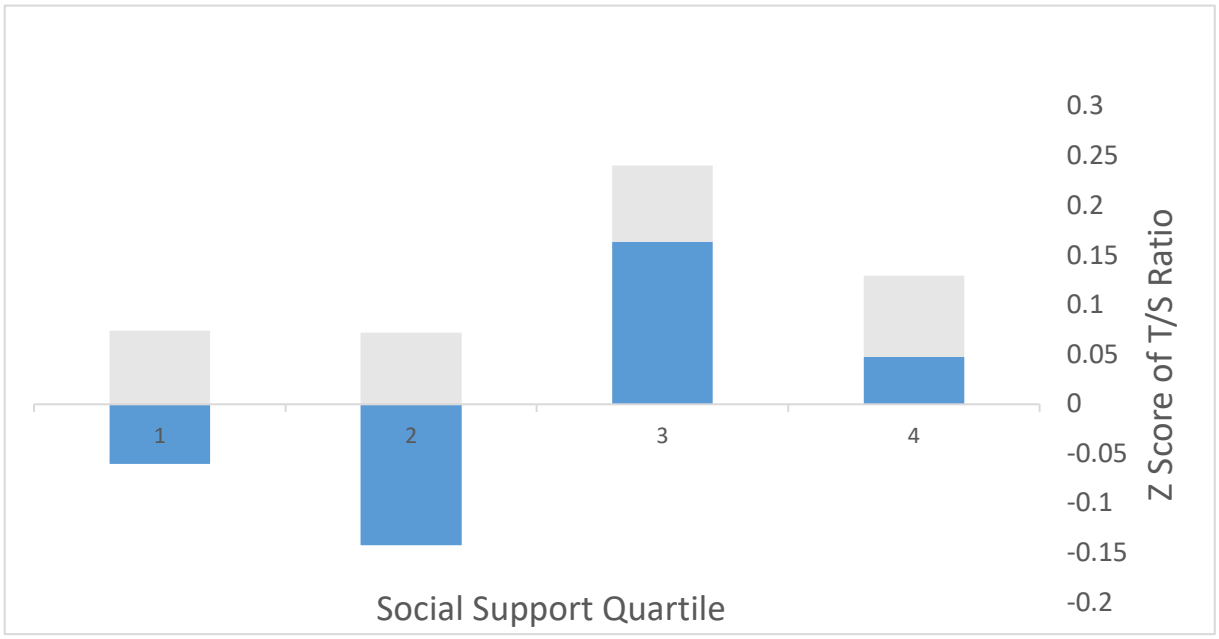
Note. TL was determined by measuring the T/S ratio, a ratio of the number of telomere repeats in a sample compared to a control gene. T/S ratio was then standardized by transformation into Z score, in which data is transformed to achieve a mean distribution of zero and a standard deviation of one. The Z score of the T/S ratio was then residualized for model covariates to isolate the impact of maternal psychological state during pregnancy on newborn TL. Mean Z score of the T/S ratio is shown in blue according to quartile of the maternal prenatal stress score. Gray shading indicates the standard error of the mean (SEM).

3.2 Aim 2: Maternal social support and newborn telomere length

Social support satisfaction was significantly, positively associated with newborn TL (β=0.080, p=0.040, 95% CI [0.000, 0.012]), R^2=0.048, F(13, 652) =2.525, p=0.002. Each standard deviation (SD) increase in average social support satisfaction across pregnancy was associated only with a 1% increase in newborn TL. The following covariates were also significant: sex of the child (TL was longer in girls: β=0.096, p=0.015), maternal age at childbirth (β=0.103, p=0.014), and maternal pre-pregnancy BMI (β=-0.086, p=0.047) (full regression results in Supplementary Table S2). Figure 6 shows newborn TL according to maternal prenatal social support satisfaction quartile.

Figure 6.

Maternal social support during pregnancy and newborn telomere length.



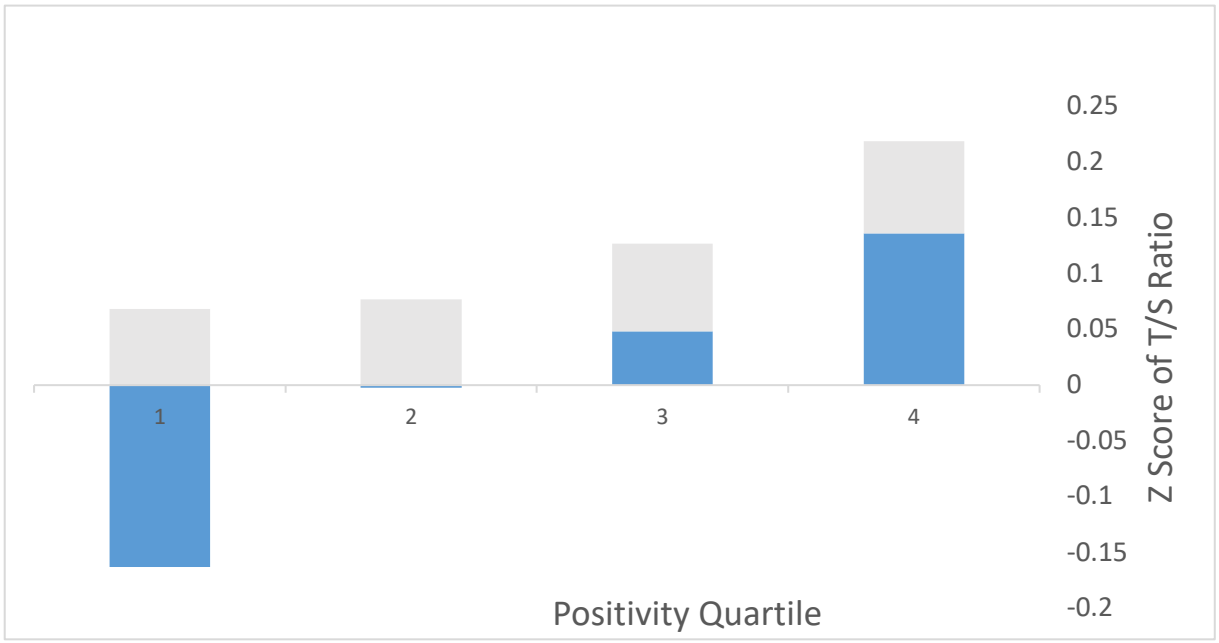
Note. TL was determined by measuring the T/S ratio, a ratio of the number of telomere repeats in a sample compared to a control gene. T/S ratio was then standardized by transformation into Z score, in which data is transformed to achieve a mean distribution of zero and a standard deviation of one. The Z score of the T/S ratio was then residualized for model covariates to isolate the impact of maternal psychological state during pregnancy on newborn TL. Mean Z score of the T/S ratio is shown in blue according to quartile of the maternal prenatal social support satisfaction score. Gray shading indicates the standard error of the mean (SEM).

3.3 Aim 3: Maternal positivity and newborn telomere length

Maternal positivity during pregnancy was significantly and positively associated with newborn TL (β =0.135, p=0.001, 95% CI [0.059, 0.211], R^2=0.055, F(13,642)=2.786, p<0.001) (full regression results in Supplementary Table S3). Each SD change in maternal positivity was associated with a 13% difference in average newborn TL. This result is displayed graphically in Figure 7 according to positivity quartile. Maternal positivity and stress were inversely correlated, with an R^2 value of 0.265.

Figure 7.

Maternal positivity during pregnancy and newborn telomere length.



Note. TL was determined by measuring the T/S ratio, a ratio of the number of telomere repeats in a sample compared to a control gene. T/S ratio was then standardized by transformation into Z score, in which data is transformed to achieve a mean distribution of zero and a standard deviation of one. The Z score of the T/S ratio was then residualized for model covariates to isolate the impact of maternal psychological state during pregnancy on newborn TL. Mean Z score of the T/S ratio is shown in blue according to quartile of the maternal prenatal positivity score. Gray shading indicates the standard error of the mean (SEM).

3.4 Aim 4: Maternal resilience and newborn telomere length

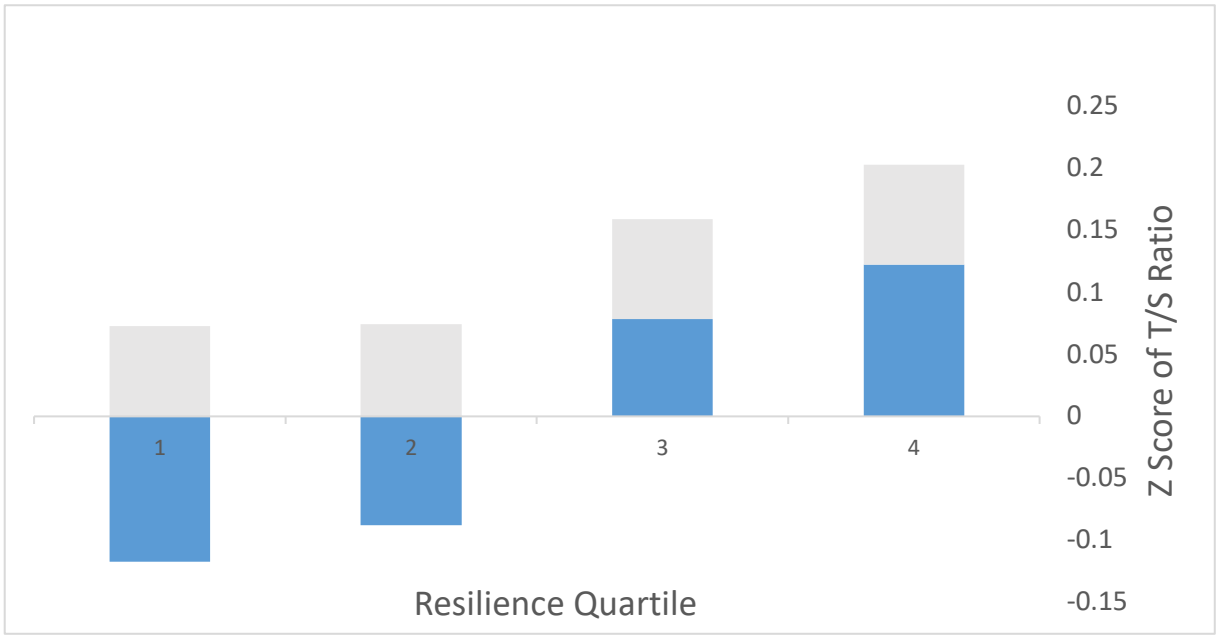
This analysis addressed this thesis's central goal. Maternal resilience during pregnancy was significantly and positively associated with newborn telomere length (model R^2=0.050, F(13,642)=2.500, p=0.002; β (resilience)=0.112, p=0.004, 95% CI [0.035, 0.189]). Each SD change in maternal resilience was 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. Figure 8 presents these results, depicting newborn TL according to maternal prenatal resilience quartile.

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) (full regression results in Supplementary Table S4).

Detailed results of the resilience regression are shown below in Table 5. Output of the other regressions (stress, social support, positivity, and resilience with adjustment for neuroticism) can be found in Supplement 1.

Figure 8.

Maternal resilience during pregnancy and newborn telomere length.



Note.. TL was determined by measuring the T/S ratio, a ratio of the number of telomere repeats in a sample compared to a control gene. T/S ratio was then standardized by transformation into Z score, in which data is transformed to achieve a mean distribution of zero and a standard deviation of one. The Z score of the T/S ratio was then residualized for model covariates to isolate the impact of maternal psychological state during pregnancy on newborn TL. Mean Z score of the T/S ratio is shown in blue according to quartile of the maternal prenatal psychological resilience score. Gray shading indicates the standard error of the mean (SEM).

3.5 Sensitivity analyses

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.

Table 5.

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

Note. 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.

4 Discussion

The study on which this dissertation is based is, to the authors' knowledge, the first to study psychological resilience and positivity in the context of fetal programming of the telomere system and therefore represents an important, novel contribution to the field. Previous research, not only on fetal programming but generally across disciplines, including research on pregnancy outcomes, has been preoccupied with negative exposures and risk factors (e.g. (Corno et al., 2019)). This study is therefore one of a growing number recognizing an independent and significant role for positive states in influencing health and disease risk. The study's multidimensional measure of resilience, integrating positive emotions, positive reactivity, social support, and stress, also represents a meaningful addition to the expanding body of scientific work on resilience, which continues to seek and develop useful definitions of resilience to facilitate its study. These and other strengths of the study, as well as limitations, are outlined below, along with further evaluation of the results.

Beyond this, the findings have significant public health and clinical relevance and suggest that non-invasive, inexpensive, and quick-to-roll out psychological interventions during pregnancy may, by boosting maternal wellbeing and resilience, meaningfully contribute to positive outcomes not only during pregnancy and birth, important in and of itself, but also throughout a child's life by helping to kick start his or her telomere system on a trajectory toward healthy longevity. The findings also point to important areas for further research, including potential ceiling effects of resilience in shielding at-risk women from the negative sequelae of stress, the biological mediators of the transgenerational embedding of psychological state, and effective interventions to increase resilience among women of childbearing age. These practical population heath implications and important directions for future scientific research are also discussed in the following.

4.1 Study contribution and strengths

4.1.1 Replication of maternal stress and offspring telomere length association

This thesis replicated the finding of previous studies that maternal psychological stress during pregnancy is associated with shorter offspring telomere length at birth. A unique contribution of this work is the large sample size, more than twice as large as the next largest sample (N=319 (Send et al., 2017)) and much larger than the initial studies in this domain (N=24 (Marchetto et al., 2016), N=27 (Entringer et al., 2013), N=71 (Salihu et al., 2016)). Additional strengths of this study include the detail in which the cohort was characterized. Questionnaires were administered serially up to fourteen times across pregnancy and a wealth of data on

maternal, obstetric, and child factors shown to play a role in determining TL was available and able to be controlled for, allowing the influence of psychological factors to be better isolated.

Though pregnant women in this sample reported typical levels of stress as compared to other studies of pregnant women (DiPietro et al., 2004; Karam et al., 2012), many (the clinical sample) were recruited due to the presence of risk factors for the development of preeclampsia or IUGR. These risk factors included current obstetric complications as well as women who had experienced such conditions in previous pregnancies. Due to this, one may suppose that these women were likely to have experienced a certain degree of pregnancy-specific stress, which, partly through its impact on health behaviors such as smoking, healthy eating, and caffeine consumption during pregnancy, has been associated with negative birth outcomes and may be more relevant in this context than general stress (Lobel et al., 2008). The presence of such stress makes this cohort particularly interesting to study in the context of stress-related fetal programming of the telomere system.

4.1.2 Novel finding of associations between positive maternal psychology and offspring telomere length

The multidimensional conceptualization of resilience discussed above, including positivity, positive affect, social support, and stress, is a strength of the study. This study found maternal psychological resilience during pregnancy to be prospectively associated with newborn cord blood TL. This represents a novel contribution to the field of fetal programming, as it is the first time that maternal resilience or positive psychology during pregnancy has been linked to offspring telomere length. The study found a clear, positive association between maternal psychological resilience during pregnancy, represented by positive emotional and social support experiences adjusting for stress, and offspring TL at birth - every standard increase in maternal resilience during pregnancy predicted 12% longer newborn telomeres, a significant effect in this context.

The findings of this study aide in teasing apart the influence of positive and negative psychological states on health. Though positivity and negativity are inversely related in this sample, as expected, this correlation explains only about 25% of their shared variance. This illustrates significant differences in the degree to which individuals experience positive emotions and rewarding social interactions even given a similar level of stress. The distinction between the presence of positive emotions and the absence of negatives ones, often overlooked, seems to be an essential one, as suggested by other researchers (Garland et al., 2010; Stellar et al., 2015). In fact, the effect of resilience on TL was greater than that of stress, a finding which

supports the assertion that it is important to consider positive emotions and traits alongside negative ones to better understand the biological embedding of psychological states.

Furthermore and importantly, the effect of resilience on TL was most pronounced among women who reported the greatest levels of stress (upper tertile of stress factor values). This suggests that the most stressed women, as opposed to those already evincing psychological well-being, may benefit the most from experiencing positive emotions during pregnancy, a finding with important implications for interventions and public health. As the participants in this study were generally healthy, with a very low prevalence of psychiatric diagnoses and typical levels of stress, these results may in fact underestimate the potential protective effect of resilience and positive emotions in the face of psychological distress.

Other aims of this thesis addressed the roles of both positive psychological state and social support on offspring telomere length at birth. Both were found to independently predict offspring telomere length. However, the effect the positivity construct was considerable larger than social support alone. This is striking, as social support is the positive exposure that to date has been most studied in the context of pregnancy (Hetherington et al., 2015). The apparent contribution in this study of social support satisfaction to overall psychological wellbeing and happiness support the framework of resilience developed in the broaden-and-build hypothesis, which theorizes that positive states play an active role in the development of future stress coping resources (Fredrickson, 2001).

4.1.3 Other predictors of newborn telomere length

This study replicated a previously-established association between female sex and longer telomeres (Gardner et al., 2014), including at birth (Aubert, Baerlocher, Vulto, Poon, & Lansdorp, 2012). Several hypotheses, including beneficial effects of estrogen exposure and reduced oxidative stress in women as compared to men have been proposed (Nawrot, Staessen, Gardner, & Aviv, 2004), which would be interesting for future studies to further explore in the context of fetal programming.

An association between maternal pre-pregnancy BMI and newborn telomere length was also observed in the analyses presented in this dissertation. Though BMI was a significant predictor of (shorter) newborn TL only in the social support model ($p=0.047$), it neared significant in two other models (stress: $p=0.053$; positivity; $p=0.058$) and was a borderline predictor in the final residence model ($p=0.081$). This replicates previous findings of an association between greater maternal pre-pregnancy BMI and shorter offspring TL (Martens, Plusquin, Gyselaers, De Vivo, & Nawrot, 2016). This association has also been found in adults, and pre-pregnancy overweight and obesity have been associated in previous studies with a wide

array of pregnancy complications and negative developmental outcomes (Siega-Riz & Laraia, 2006). These effects could be attributable to the pro-inflammatory state associated with obesity, which can contribute to telomere shortening (Aviv, 2004). The inflammatory mediator(s) involved and their role in telomere shortening and etiology of negative birth outcomes should be explored in future studies.

A positive association between maternal age at childbirth and newborn telomere length was also seen in all models in this study. Though the direction of the association is unexpected, it could be explained by the fact that older women are more likely to have older partners. Increasing paternal age is in a fact a strong predictor of newborn telomere length, as the sperm of older men tend to have longer TL (Eisenberg & Kuzawa, 2018).

The regression models in this study also did not find significant associations between telomere length at birth and the other model covariates (including the presence of obstetric complications (hypertension, preeclampsia, diabetes), maternal characteristics (education level, smoking during pregnancy), and fetal characteristics (gestational age at birth, birth weight)).

4.2 Study limitations

Limitations to this study include the following:

4.2.1 Missing data on potentially important predictors of newborn telomere length

Data on maternal and paternal TL was not available for this cohort, though TL is influenced by genetic factors (Factor-Litvak et al., 2016).Subsequent studies should include this important covariate. Paternal age data was also not available, though it has been associated with (longer) offspring TL (Eisenberg & Kuzawa, 2018).

4.2.2 No data on biological mediators of the embedding of maternal psychological state

As outlined above, several potential mechanisms may underlie the biological embedding of maternal resilience during pregnancy. Future studies should measure potential mediators, such as cortisol, inflammatory markers, and maternal autonomic arousal, during pregnancy and investigate their associations with newborn TL. Potential sensitive periods in the development of the fetal telomere system could also be explored. Dose- and time-dependent exposures may have an outsized effect as fetal development is composed of distinct phases wherein certain systems mature rapidly (Entringer et al., 2018). Measuring biological mediators serially throughout pregnancy could shine light into potential windows during which maternal resilience, positivity, or stress could permanently influence the development of the telomere system.

Telomerase activity may also play an important role in the biological embedding of maternal psychological state. As the enzyme capable of extending telomeres, it plays an important role in overall telomere dynamics but has to date been little studied in the context of fetal programming. Dysregulated telomerase activity has been associated with various obstetric complications and with maternal prenatal adversity, such as undernutrition (Fragkiadaki et al., 2016), hinting that telomerase activity may be partly implicated in the link between maternal psychological state during pregnancy and newborn TL. Maximal telomerase activity capacity (mTAC), a method of establishing telomerase responsivity to stress recently validated by a member of the author's working group (de Punder, Heim, Przesdzing, Wadhwa, & Entringer, 2018) is one potential measure of interest in this context.

4.2.3 The emergence of psychological resilience

This cohort also did not contain data on stressful or traumatic life events and psychological wellbeing prior to and following said event – such a focus on functioning over time in the face of adversity is emphasized in various theories of resilience (Bonanno, Romero, & Klein, 2015). However, as elaborated on in the Introduction, other theories, such as the broaden-and-build hypothesis, view positivity as a reflection of both current resilience and the psychological resources at an individual's disposal for facing future stressors (Fredrickson, 2001; Ong, Bergeman, Bisconti, & Wallace, 2006). An advantage of this study is that pregnancy itself is a life-changing event that often presents significant challenges – an informative context for studying resilience. Furthermore, the interest of this study was to examine the biological embedding of maternal resilience during pregnancy in the context of fetal programming rather than the process by which the mother herself may (or may not) have developed resilience.

4.3 Public health implications

4.3.1 Global burden of disease

The increasing incidence of non-communicable disease is a public health and health system crisis of increasing magnitude. These chronic conditions already account for close to two of three deaths worldwide, and this number is only projected to increase (Habib & Saha, 2010). These conditions threaten to reduce not only life expectancy but also quality of life, as populations become not only older (in developed countries) but less healthy around the world, as more and more people gain access to unhealthy processed foods and begin to lead more sedentary lives (Allen, 2017). In addition to these human costs, health care systems, some of which are already stretched to the limit to provide adequate care, will becoming increasingly overburdened and countries will be left struggling to manage ever-increasing health care costs

and the financial losses associated with individuals' reduced ability to contribute to the economy (Beaglehole et al., 2011). It is therefore of critical importance to combat this problem from all possible angles and with a focus on prevention.

4.3.2 Intergenerational transmission of health inequalities

Simultaneously, we are faced with growing health inequalities both within and between countries. People with lower socioeconomic status and member of minority groups have been found to suffer from higher rates of disease, and some regions of the world have been left behind in terms of the medical and lifestyle advances being made in other countries (Marmot, 2005). Birth and obstetric outcomes are an area where such inequalities are manifest along both socioeconomic (Blumenshine, Egerter, Barclay, Cubbin, & Braveman, 2010) and racial and ethnic lines. In the Unites States, for example, black women experience much higher rates of obstetric complications and fetal mortality than do white women (Lu & Halfon, 2003). Similar effects have been seen among migrants of non-native or minority ethnic backgrounds across western developed nations (Kim & Saada, 2013) including Germany (David, Pachaly, & Vetter, 2006).

An important finding of this study is that maternal positivity and resilience during pregnancy seem to exert positive effects on the fetal telomere system even when expectant mothers simultaneously experienced high stress levels. This shows the potential advantages of increasing maternal positive emotions, not only in conjunction with efforts to reduce stress, but perhaps even more so when stress reduction is not feasible. The stress of being a member of racial, ethnic, or social minority group facing stigma or discrimination presents just such a challenge. Such social disadvantage can be transmitted transgenerationally via maternal-placental-fetal stress biology (Scholaske et al., 2018), and stress-related neuroendocrine and inflammatory processes seem to underlie health disparities in birth outcomes (Christian, Glaser, Porter, & Iams, 2013). A focus on providing psychological and social support to these women, often among the most vulnerable and stressed, could have an outsize impact on population health and help combat health disparities.

4.4 Clinical implications

A growing body of evidence indicates that maternal psychosocial factors during pregnancy can also embed themselves biologically during fetal development and influence health and disease risk across generations. Understanding the early origins of such conditions enables a focus on prevention, which can lower the burden on health systems and help individuals live longer, healthier lives. Improving prenatal care is a task of central importance

and one which offers the double benefit of both caring for women at a vulnerable stage of their lives but also passing these benefits on to the next generation by striving to allow every child a healthy start in life. Addressing these inequalities and providing every individual with an equal change of a long and above all healthy life is a mission central to the next phase of human development. Public health, medical, and psychological professionals have an important role to play in achieving this goal.

4.4.1 Promoting resilience and positivity in pregnancy

The findings of this study provide impetus to promote positive emotions among pregnant women. This is an encouraging conclusion, as there is already a repertoire of low-cost, low impact interventions that could be applied to boost maternal positivity, which future research should seek to improve and expand. . Healthcare providers, especially obstetricians and midwives, can contribute simply by including simple mental health screening instruments as a routine component of prenatal care. When women with high levels of stress are identified, they can begin to receive care during pregnancy, with positive effects that would be passed on to the developing fetus.

4.4.2 Resilience and positivity interventions

Interest in and attention to positive psychology interventions among both the general population and pregnant women in particular is increasing (Corno et al., 2019). Importantly, many short duration, easy to implement interventions are proving to be effective - a meta-analysis of over 50 studies found that a range of positive psychology interventions can increase wellbeing in a sustainable way (Sin & Lyubomirsky, 2009). Interventions as simple as one-time online prompts to journals or reflect on one's own over the course of a week, for example, have led to significant increases in happiness and decreases in depression symptoms even six months later (Seligman, Steen, Park, & Peterson, 2005). In the context of pregnancy, a 5-week online intervention designed specifically for pregnant women with similar simple, self-led exercises also produced encouraging results across several cultural contexts (Corno et al., 2018; Corno et al., 2019). Such prompts, exercises, or other reminders could be made available via free-to-download apps for pregnant woman, encouraging them to continue to practice these activities, a significant predictor of lasting increases in positivity and stress resilience (Seligman et al., 2005; Sin & Lyubomirsky, 2009).

4.4.3 Mindfulness interventions and psychological wellbeing

Mindfulness interventions among pregnant women are showing a similar potential to positively influence maternal mental health, with subsequent beneficial influence on obstetric and postnatal mother and child outcomes, though further evidence and better-designed trials are

needed to support these conclusions (Dhillon, Sparkes, & Duarte, 2017). As with the positivity interventions discussed above, many of these efforts to increase mindfulness have the benefits of requiring few resources to implement and enabling flexible, independent use (i.e. an online platform women can freely access). Promisingly, a recent pilot study of a 3-week online mindfulness intervention demonstrated positive effects not only on perceived stress among participants, but was also associated with reduced cortisol levels, a candidate biological mediator of the effects of positivity on health (Matvienko-Sikar & Dockray, 2017).

4.5 Future research directions

This study indicates several important avenues for continued research on the fetal programming effects of maternal prenatal psychological state on the telomere system. Certainly, the association between maternal resilience during pregnancy and longer newborn TL should be replicated in other cohorts. This study was conducted in a sample drawn from the general population irrespective of psychiatric history: To examine possible ceiling effects in the capacity of resilience to shield against the negative effects of stress, these findings should be replicated in cohorts with clinically relevant levels of stress. The impact of psychological resilience among other women at high risk for high stress during pregnancy, such as those with psychiatric disorders, members of social minority groups, or who experienced childhood maltreatment, should also be examined in future studies.

Additional research is also warranted to identify potential time-dependent effects of prenatal exposure to maternal resilience, as the developing fetuses are more or less vulnerable/receptive to the physiological sequelae of maternal psychological state at certain phases of gestation (Davis & Sandman, 2010; Entringer et al., 2018). Electronic momentary assessment (EMA) protocols, which enable real-time assessment of psychological state throughout the course of daily life, would also contribute to our understanding and enable study of potential timing effects.

Importantly, future research should also measure potential biological mediators of the effects of stress and resilience, such as cortisol and inflammatory cytokines, ideally repeatedly throughout pregnancy, to better characterize the mechanism(s) by which maternal psychological state influences fetal telomere biology. Other markers of cellular aging, such as epigenetic changes, should also be studied in this context.

Finally, interventions to increase maternal resilience during pregnancy, such as those described above, should be the focus of ongoing research to create, implement, and maintain the most effective solutions for improving maternal mental wellbeing during pregnancy. The

results of this study indicate that evoking positive emotions and social support experiences could be especially relevant goals. The potential of such interventions to prevent negative obstetric, birth, and child outcomes makes them especially important, as prevention is always the best medicine to support health on a population level, and, by bolstering health prenatally, the intergenerational transmission of health disparities can be combatted. Ideally, resilience should be promoted in all women of childbearing age to maximize the benefit to current and future generations.

5 Conclusion

This study advances novel, important findings on the beneficial effects of maternal psychological resilience during pregnancy on the fetal programming of the telomere system. By demonstrating for the first time potential positive or protective effects of maternal wellbeing during pregnancy on developing fetal telomere biology. These findings contribute to a growing transdisciplinary awareness of the biological and psychological importance of resilience and positive psychology in shaping health and disease risk. Excitingly, the results demonstrate that positive maternal psychological characteristics, not only negative ones, may exert transgenerational effects.

The initial setting of the telomere system has long-term consequences for health and disease risk, potentially playing a deterministic role in life-long telomere dynamics. These in turn shape the risk of developing common, complex age-related disorders, challenges confronting an increasing number of individuals, and health systems, around the world. The findings of this study suggest that, not only is maternal resilience during pregnancy associated with longer newborn telomeres, but children of women experiencing the most stress might stand to gain the most from the experience of positive emotions during their pregnancies. The prenatal period therefore presents an ideal time for public health and clinical interventions supporting the health and wellbeing of both mother and child, to prevent negative outcomes and promote improved population health decades into the future.

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7 Supplement

Summary of adjusted models derived from linear regression

S1. Stress factor

	B	*SE B*	*β*	*t*	*p*	CI_L	CI_U
Intercept	-1.266	1.066		-1.187	0.236	-3.360	0.829
Stress factor	-0.079	0.039	-0.079	-2.016	0.044	-0.155	-0.002
DNA extraction method	0.074	0.071	0.041	1.045	0.297	-0.065	0.212
Sex of the child	0.198	0.079	0.099	2.501	0.013	0.043	0.353
Gestational age at birth	0.028	0.029	0.048	0.943	0.346	-0.030	0.086
Child birthweight	0.000	0.000	-0.069	-1.352	0.177	0.000	0.000
Maternal age at childbirth	0.017	0.008	0.095	2.260	0.024	0.002	0.032
Parity	-0.005	0.043	-0.004	-0.109	0.913	-0.088	0.079
Maternal pre-pregnancy BMI	-0.013	0.007	-0.084	-1.935	0.053	-0.027	0.000
Maternal education level	-0.049	0.046	-0.046	-1.069	0.285	-0.139	0.041
Hypertension in pregnancy	0.150	0.093	0.065	1.606	0.109	-0.033	0.333
Preeclampsia	0.234	0.157	0.061	1.492	0.136	-0.074	0.542
Diabetes in pregnancy	0.000	0.101	0.000	0.004	0.997	-0.197	0.198
Smoking in pregnancy	-0.033	0.187	-0.007	-0.174	0.862	-0.400	0.335

Note. *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.

S2. Social support satisfaction

	B	*SE B*	*β*	*t*	*p*	CI_L	CI_U
Intercept	-1.430	1.065		-1.342	0.180	-3.521	0.662
Stress factor	0.007	0.003	0.080	2.059	0.040	0.000	0.013
DNA extraction method	0.090	0.070	0.049	1.285	0.199	-0.048	0.228
Sex of the child	0.193	0.079	0.096	2.451	0.015	0.038	0.347
Gestational age at birth	0.020	0.029	0.034	0.687	0.492	-0.037	0.078
Child birthweight	-8.800E-5	0.000	-0.050	-0.995	0.320	0.000	0.000
Maternal age at childbirth	0.019	0.008	0.103	2.462	0.014	0.004	0.034
Parity	-0.004	0.042	-0.003	-0.083	0.934	-0.086	0.079
Maternal pre-pregnancy BMI	-0.014	0.007	-0.086	-1.994	0.047	-0.027	0.000
Maternal education level	-0.045	0.046	-0.041	-0.977	0.329	-0.134	0.045
Hypertension in pregnancy	0.135	0.093	0.058	1.443	0.149	-0.049	0.318
Preeclampsia	0.221	0.154	0.058	1.434	0.152	-0.082	0.532
Diabetes in pregnancy	-0.046	0.099	-0.019	-0.464	0.643	-0.241	0.149
Smoking in pregnancy	-0.082	0.185	-0.017	-0.442	0.659	-0.444	0.281

Note. 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.

S3. Positivity factor

	B	*SE B*	*β*	*t*	*p*	CI_L	CI_U
Intercept	-1.348	1.060		-1.271	0.204	-3.430	0.734
Positivity factor	0.134	0.038	0.135	3.495	0.001	0.059	0.209
DNA extraction method	0.082	0.070	0.045	1.178	0.239	-0.055	0.220
Sex of the child	0.193	0.078	0.097	2.457	0.014	0.039	0.347
Gestational age at birth	0.027	0.029	0.047	0.938	0.349	-0.030	0.085
Child birthweight	0.000	0.000	-0.058	-1.150	0.250	0.000	0.000
Maternal age at childbirth	0.018	0.008	0.099	2.369	0.018	0.003	0.033
Parity	-0.013	0.042	-0.012	-0.302	0.763	-0.096	0.070
Maternal pre-pregnancy BMI	-0.013	0.007	-0.082	-1.898	0.058	-0.026	0.000
Maternal education level	-0.051	0.045	-0.048	-1.127	0.260	-0.140	0.038
Hypertension in pregnancy	0.155	0.093	0.067	1.670	0.095	-0.027	0.337
Preeclampsia	0.218	0.156	0.056	1.395	0.164	-0.089	0.524
Diabetes in pregnancy	-0.015	0.100	-0.006	-0.155	0.877	-0.211	0.180
Smoking in pregnancy	-0.045	0.186	-0.009	-0.240	0.810	-0.410	0.320

Note. 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.

S4. Resilience factor plus neuroticism

	B	*SE B*	*β*	*t*	*p*	CI_L	CI_U
Intercept	-2.403	1.243		-1.933	0.054	-4.847	0.040
Resilience factor	0.141	0.042	0.148	3.317	0.001	0.057	0.224
Neuroticism	0.003	0.002	0.068	1.507	0.132	-0.001	0.006
DNA extraction method	0.154	0.077	0.088	1.990	0.047	0.002	0.306
Sex of the child	0.156	0.087	0.081	1.788	0.074	-0.015	0.326
Gestational age at birth	0.033	0.033	0.056	0.985	0.325	-0.033	0.098
Child birthweight	-8.902E-5	0.000	-0.052	-0.931	0.352	0.000	0.000
Maternal age at childbirth	0.025	0.008	0.138	2.918	0.004	0.008	0.041
Parity	0.027	0.049	0.025	0.542	0.588	-0.070	0.123
Maternal pre-pregnancy BMI	-0.007	0.007	-0.048	-0.964	0.336	-0.022	0.007
Maternal education level	-0.026	0.050	-0.025	-0.520	0.603	-0.125	0.073
Hypertension in pregnancy	0.169	0.103	0.076	1.646	0.100	-0.033	0.371
Preeclampsia	0.258	0.173	0.071	1.490	0.137	-0.082	0.599
Diabetes in pregnancy	-0.188	0.114	-0.077	-1.652	0.099	-0.411	0.036
Smoking in pregnancy	-0.123	0.205	-0.027	-0.599	0.550	-0.526	0.281

Note. 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.

8 Statutory Declaration

"I, Glenn Verner, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic ***Maternal psychological resilience and fetal programming of the telomere system/ Mütterliche Resilienz in der Schwangerschaft und fetale Programmierung von Telomerbiologie*** independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

Date Signature

Declaration of your own contribution to the publications

Glenn Verner contributed the following to the below listed publications:

I was the first author of this paper and contributed significantly to all stages of the process. Based on consultations with my supervisor about research in the field of prenatal programming, my interest in the resilience and positive psychology, and the existing literature, I developed hypotheses on the potential programming effects of these psychological states during gestation on the fetal telomere system. I conducted all statistical analysis myself using data from a large existing cohort of mother-child pairs. I wrote the first draft of the paper and, under supervision from my first supervisor, incorporated comments from coauthors and reviewers across several rounds of revision. I created all tables and figures included in the paper and dissertation.

Verner, G., Epel, E., Lahti-Pulkkinen, M., Kajantie, E., Buss, C., Lin, J., Blackburn, E., Räikkönen, K., Wadhwa, P., Entringer, S. (2020). Maternal Psychological Resilience During Pregnancy and Newborn Telomere Length: A Prospective Study. American Journal of Psychiatry, appi.ajp.2020.19101003.

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Signature, date and stamp of first supervising university professor / lecturer

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Signature of doctoral candidate

9 Extract from Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
Selected Categories: **"PSYCHIATRY"** Selected Category
Scheme: WoS
Gesamtanzahl: 214 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	World Psychiatry	5,426	34.024	0.014100
2	Lancet Psychiatry	4,887	18.329	0.022100
3	JAMA Psychiatry	10,894	15.916	0.055560
4	PSYCHOTHERAPY AND PSYCHOSOMATICS	3,892	13.744	0.005800
5	AMERICAN JOURNAL OF PSYCHIATRY	43,025	13.655	0.036370

Maternal Psychological Resilience During Pregnancy and Newborn Telomere Length: A Prospective Study

Glenn Verner, M.P.H., Elissa Epel, Ph.D., Marius Lahti-Pulkkinen, Ph.D., Eero Kajantie, M.D., Ph.D., Claudia Buss, Ph.D., Jue Lin, Ph.D., Elizabeth Blackburn, Ph.D., Katri Räikkönen, Ph.D., Pathik D. Wadhwa, M.D., Ph.D., Sonja Entringer, Ph.D.

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. The authors examined the relationship between maternal psychological resilience during pregnancy and newborn TL.

Methods: In a sample of 656 mother-child dyads from the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction 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 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 quantitative polymerase chain reaction 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 significantly predicted shorter newborn TL ($\beta = -0.079$), and positivity significantly predicted longer TL ($\beta = 0.135$). Maternal resilience (positivity accounting for stress) was significantly and positively associated with newborn TL ($\beta = 0.114$, 95% CI=0.035, 0.189), with each standard deviation increase in resilience predicting 12% longer newborn TL.

Conclusions: The 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 well-being during pregnancy.

AJP in Advance (doi: 10.1176/appi.ajp.2020.19101003)

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 not only a biomarker of 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 TL, 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 in adulthood (7–12). To date, the focus has been almost exclusively on negative exposures and risk factors (summarized in reference 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 of offspring TL.

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 with TL in some (19–21) but not other (22, 23) studies. Of note, these effects on TL were evident even after adjustment for depression (19), posttraumatic stress disorder 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 in adults in multiple studies, with greater levels of perceived social support predicting longer telomeres (24–27), including during pregnancy (28), although 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 with negative states, has yet to be addressed in the context of fetal programming of the telomere system.

This is also the first study in the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (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), birth outcomes (31), and child outcomes (32, 33). Each of these outcomes has 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 explore the ways in which a mother's positive emotional state may influence the development of her offspring's telomere system during intrauterine development.

Our goal in this study was to examine a hypothesized positive relationship between maternal psychological resilience during pregnancy and newborn TL. 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 which 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 PREDO cohort at 10 hospitals in Finland and their live-born singleton children (for the study protocol, see reference 34). Of the 4,777 mother-child dyads recruited to the study, TL data were available for 688 newborns. Participants were enrolled at antenatal clinics early in gestation (12 weeks to 13 weeks 6 days) 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 were 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 did not adjust 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 present analysis included 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) (35), positive state from the State-Trait Anxiety Inventory (STAI) (36), and positive mood reactivity to pregnancy-related events ("uplifts") from the Pregnancy Experience Scale (PES) (37). Social support satisfaction was determined using a visual analogue scale (VAS) for social support. Similarly, we quantified negative affectivity using three scales: perceived stress from the Perceived Stress Scale (PSS) (38), biweekly perceived stress from a visual analogue scale for stress, and negative mood reactivity to pregnancy-related events ("hassles") from the PES. The entire course of pregnancy was well represented, with the affect and social support measures being repeated up to 14 times, and the hassles and uplift measures up to four times, across early, mid, and late gestation.

TABLE 1. Timeline of psychological and psychosocial measures collected from the PREDO cohort[a]

	Week of Pregnancy													
	Early Pregnancy		Mid Pregnancy						Late Pregnancy					
Measure	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 for social support	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy Experience Scale														
Frequency of uplifts	x			x				x			x			
Intensity of uplifts	x			x				x			x			
Frequency of hassles	x			x				x			x			
Intensity of hassles	x			x				x			x			
Perceived Stress Scale	x	x	x	x	x	x	x	x	x	x	x	x	x	x
VAS for stress	x	x	x	x	x	x	x	x	x	x	x	x	x	x

[a] PANAS=Positive and Negative Affect Schedule; PREDO=Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction; STAI: State-Trait Anxiety Inventory; VAS=visual analogue scale.

For each assessment, a within-subject mean was calculated for each participant 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 participant. 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 was used to isolate two latent factors, positivity and stress, as described below, in the 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:

1. Positive affect from the positive scale of the PANAS: 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.
2. Positive state sum scores from the STAI: 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.
3. Pregnancy-related uplifts from the PES: 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 of items on the positive scale that were rated above 0 ("not at all"). Intensity of uplifts was calculated by summing the responses scored from 1–3 and dividing the result by the frequency.
4. Social support satisfaction over the past 2 weeks, from the visual analogue scale for social support: Participants were asked to rate how much support they felt they had received from loved ones over the past 2 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:

1. Perceived stress in the past month from the PSS: The PSS-4 includes four stress items rated on a 5-point scale from "never" to "very often." Two items were reverse scored, then all responses were summed.
2. Pregnancy-related hassles from the PES, 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.
3. Perceived stress over the past 2 weeks, from the visual analogue scale for stress: Participants were asked to rate their overall stress level over the past 2 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: work or studying, close interpersonal relationships, taking care of children/household duties, and pregnancy-related stress. The scores on the subscales 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 (FMBR). 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 FMBR. Birth outcomes were also obtained from the FMBR, including child sex, birth weight, and gestational age at birth (34).

Telomere Length

TL was analyzed in leukocytes from cord blood samples collected at birth. DNA was isolated from whole blood. Leukocyte TL 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 (40), the original pool of which is formed early in gestation and serves as the progenitor for cells in all blood lineages (41).

Relative TL 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′-CACCAACTT CATCCACGTTCACC-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; 0.4×SYBR green I; 22 ng *Escherichia coli* DNA; 0.4 units of platinum Taq DNA polymerase (Invitrogen, Carlsbad, Calif.); and approximately 6.6 ng of genomic DNA per 11 μL reaction. A threefold serial dilution of a commercial human genomic DNA containing 26, 8.75, 2.9, 0.97, 0.324, and 0.108 ng 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. The Dixon Q test was used to exclude outliers from the triplicates. The average of the T and S triplicate wells after outlier 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 eight 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 TL measurements passed quality control criteria of an optical density 260 nm/280 nm ratio 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 interassay coefficient of variation for this study was 2.3%.

DNA was extracted from 344 samples via the NucleoSpin system, 293 via the phenol-chloroform method, and 19 via the automated Gentra method. 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 (IBM, Armonk, N.Y.).

Pregnancy sum scores. 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. Principal component analysis allows the

number of covariates to be reduced by transforming intercorrelated 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. Principal component analysis 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 least at one time point were included.

A positivity factor was computed using the PANAS and STAI positive subscales, the frequency and intensity of PES uplifts, and the visual analogue scale 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 ($\chi^2=1130.67$, df=10, $p<0.001$), indicating covariance between the scales. Furthermore, the diagonals of the anti-image correlation matrix were all greater than 0.658 (above the accepted cutoff of 0.50), and Kaiser-Meyer-Olkin sampling adequacy was above the established threshold of 0.50, at 0.709 (44). One component had an eigenvalue of 2.71, above the standard Kaiser criterion cutoff of 1, 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). Because 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 visual analogue scale stress scores using principal component analysis. Interrelatedness of the variables was established by correlation (at least $r=0.45$, $p<0.001$) and Bartlett's test of sphericity ($\chi^2=837.49$, df=6, $p<0.001$). Sample adequacy was confirmed by a Kaiser-Meyer-Olkin statistic of 0.76 and anti-image correlation matrix diagonals of above 0.71. A single component was extracted with an eigenvalue of 2.50 and visually confirmed by scree plot, indicating that including further components would not increase the predictive value of the model (44). This component explained 62.51% of the total variance in the data and was considered the stress factor.

Principal component analysis factors were centered with a mean of zero and a standard deviation 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 TL 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-measures analyses of variance revealed no significant within-subject effects for the resilience ($F=0.036$, df=2, 1088, $p=0.850$), positivity ($F=0.170$, df=2, 1128, $p=0.681$), or stress ($F=0.058$, df=2, 1090, $p=0.810$) factors. Given this lack of interindividual 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 prepregnancy BMI, maternal educational attainment (classified as primary, secondary, lower tertiary, or upper tertiary and scored from 1 to 4), obstetric risk conditions (hypertension, preeclampsia, and diabetes), and maternal smoking status during pregnancy. Parity was also included as a covariate because of its expected influence on maternal emotional state during pregnancy.

RESULTS

Data on newborn TL and maternal prenatal resilience were available for 656 mother-child dyads. The sociodemographic and clinical characteristics of the sample are summarized in Table 2. Newborn T/S ratio ranged from 1.58 to 3.35, with a mean of 2.39 (SD=0.24). Scores on the individual questionnaires (before they were collapsed 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, $R^2=0.044$, $F=2.272$, df=13, 642, $p=0.006$). A one standard deviation 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=0.011, 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, $R^2=0.055$, $F=2.786$, df=13, 642, $p<0.001$). Each one standard deviation change in maternal positivity was associated with a 13% difference in average newborn TL.

TABLE 2. Sociodemographic and clinical characteristics of participants in a study of maternal psychological resilience during pregnancy and newborn telomere length

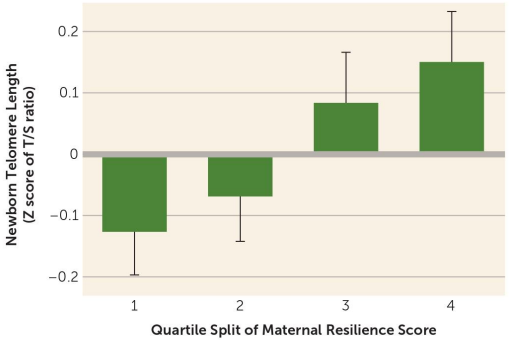
Maternal, Obstetric, and Child Factors		
Maternal factors		
	Mean	SD
Age at childbirth (years)	33.24	5.48
Prepregnancy BMI	26.97	6.31
	N	%
Educational attainment		
Primary	27	4.1
Secondary	269	41.0
Lower tertiary	152	23.1
Upper tertiary	208	31.8
Parity		
0	205	31.3
1	293	44.7
2	117	17.8
3	27	4.1
≥4	14	2.2
Obstetric factors		
Hypertension		
Chronic hypertension	101	15.4
Gestational hypertension	57	8.7
Preeclampsia	47	7.2
Diabetes		
Type 1 diabetes	8	1.2
Gestational diabetes	131	20.0
Smoking during pregnancy		
No smoking	626	95.4
Any smoking	30	4.6
Child factors		
Sex		
Male	341	52.0
Female	315	48.0
	Mean	SD
Gestational age at birth (weeks)	39.73	1.71
Birth weight (grams)	3,541.20	569.44

TABLE 3. Psychological questionnaire data prior to collapse into factors by principal component analysis, in a study of maternal psychological resilience during pregnancy and newborn telomere length[a]

Measure	Mean	SD	Range	Maximum Score
PANAS	29.98	7.43	38.29	50
STAI, positive state	30.43	5.24	25.29	40
VAS for social support	42.80	11.82	58.36	65
Pregnancy Experience Scale				
Frequency of uplifts	27.89	7.38	40.50	41
Intensity of uplifts	1.85	0.39	2.60	3
Frequency of hassles	16.35	6.79	36.70	41
Intensity of hassles	1.39	0.28	1.80	3
Perceived Stress Scale	5.33	2.55	15.76	20
VAS for stress	75.50	36.73	208.71	260
NEO-PI, trait neuroticism	71.71	23.05	142.00	192

[a] N=656 for all measures except the NEO-PI, for which N=496. Mean scores on the Pregnancy Experience Scale in a healthy pregnant sample (37) were as follows: frequency of uplifts, 28.33; intensity of uplifts, 1.91; frequency of hassles, 19.12; and intensity of hassles, 1.39. The mean score on the Perceived Stress Scale in a healthy pregnant sample (45) was 3.88 (scoring adjusted for consistency). NEO-PI=NEO Personality Inventory; PANAS=Positive and Negative Affect Schedule; STAI=State-Trait Anxiety Inventory; VAS=visual analogue scale.

FIGURE 1. Association between maternal resilience factor during pregnancy (in quartiles) and newborn telomere length[a]



[a] Newborn telomere length is reported as the Z score of the ratio of telomere to single-copy gene abundance (T/S ratio). Resilience was conceptualized as positivity in the face of stress. Factor score is centered at zero. Error bars indicate standard error.

Lastly (and most importantly), maternal resilience during pregnancy was significantly and positively associated with newborn TL (model R^2=0.050, F=2.500, df=13, 642, p=0.002; β (resilience)=0.112, p=0.004, 95% CI=0.035, 0.189) (Figure 1). Each one standard deviation 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=2.979, df=14, 481, p<0.001).

Detailed results of the resilience regression are presented in Table 4. Results of the other regressions (stress, positivity, and resilience with adjustment for neuroticism) are provided in the online supplement.

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

TABLE 4. Linear regression predicting newborn telomere length from maternal resilience during pregnancy adjusted for maternal and child determinants of telomere length

Variable	B	SE	95% CI	β	t	p
Intercept	−1.327	1.063	−3.415, 0.761		−1.248	0.212
Resilience factor	0.111	0.039	0.035, 0.187	0.112	2.875	0.004
DNA extraction method	0.091	0.070	−0.047, 0.228	0.050	1.290	0.197
Sex of the child	0.184	0.079	0.030, 0.339	0.093	2.341	0.020
Gestational age at birth	0.025	0.029	−0.033, 0.083	0.043	0.849	0.396
Child birth weight	−9.032E−5	0.000	0.000, 0.000	−0.052	−1.022	0.307
Maternal age at childbirth	0.018	0.008	0.003, 0.033	0.099	2.360	0.019
Parity	−0.014	0.043	−0.097, 0.070	−0.013	−0.320	0.749
Maternal prepregnancy BMI	−0.012	0.007	−0.025, 0.001	−0.075	−1.749	0.081
Maternal education level	−0.046	0.046	−0.136, 0.043	−0.043	−1.017	0.310
Hypertension in pregnancy	0.151	0.093	−0.032, 0.334	0.065	1.625	0.105
Preeclampsia	0.217	0.156	−0.090, 0.524	0.056	1.388	0.166
Diabetes in pregnancy	−0.032	0.100	−0.228, 0.164	−0.013	−0.319	0.750
Smoking in pregnancy	−0.052	0.186	−0.418, 0.314	−0.011	−0.278	0.781

TL, we stratified the regression according to stress factor tertile. We found a stronger effect of resilience among mother-child dyads in the highest tertile of stress (β=0.159, p=0.018) than in the lower tertiles (lowest tertile: β=0.085, p=0.893; middle tertile: β=0.086, p=0.225).

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 656 to 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 resilience (β=0.139, p=0.263), positivity (β=0.151, p=0.233), or stress (β=−0.076, p=0.535) on child TL.

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 TL. Our findings also replicate 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, 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 demonstrating that these positive states can even exert transgenerational effects. Positive emotion, independently of and after accounting for stress, significantly influenced aspects of fetal development that regulate the initial, newborn setting of TL. 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 that there is considerable between-subject variability in the level of positivity at the same or an 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 TL, broadly by promoting telomere elongation and/or by protecting against telomere attrition. Resilience, positivity, and social support have been shown to have an impact on 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, excessive 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 TL via the immune system. Resilient individuals and those who experience satisfying social support seem to exhibit immune profiles that contrast with 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 and inflammatory markers (51, 52) and a 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 consequently less 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), have also been shown to predict longer TL (59). Clearly, additional research is warranted to better identify and characterize the pathways by which maternal positivity and resilience promote fetal development and influence the initial setting of the telomere biology system.

In addition 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 were collected as often as every 2 weeks throughout the course of pregnancy. Some of the limitations of this study include the nonavailability 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 higher levels of stress than among those with medium or lower levels of stress, we suggest that the effect size observed in 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 was 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 and of their future capacity to react to adverse circumstances. Given the growing evidence of the direct role that positivity plays in combating 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 are not available.

Potential biological mediators of stress and resilience, such as cortisol or proinflammatory 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 the offspring telomere system, with potential lifelong consequences for the offspring's health, disease risk, and aging process. This beneficial effect of resilience underscores the importance of attending to mothers' mental as well as physical health during pregnancy to optimize the health of both mother and child.

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11 Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

12 List of Publications

Verner, G., Epel, E., Lahti-Pulkkinen, M., Kajantie, E., Buss, C., Lin, J., Blackburn, E., Räikkönen, K., Wadhwa, P. D., & Entringer, S. (2020). Maternal Psychological Resilience During Pregnancy and Newborn Telomere Length: A Prospective Study. American Journal of Psychiatry, appi.ajp.2020.19101003. Retrieved from https://doi.org/10.1176/appi.ajp.2020.19101003. doi:10.1176/appi.ajp.2020.19101003

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Entringer, S., de Punder, K., **Verner, G.,** Wadhwa, P. (2017). Fetal programming of telomere biology: Role of maternal nutrition, obstetric risk factors and suboptimal birth outcomes in Diet, nutrition, and fetal programming, Nutrition and Health pp.569-593. Springer International Publishing AG.

Verner, G., Schütte, S., Knop, J., Sankoh, O., & Sauerborn, R. (2016). Health in climate change research from 1990 to 2014: positive trend, but still underperforming. Global Health Action, 9, 30723-30723. Retrieved from https://pubmed.ncbi.nlm.nih.gov/27339855 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4917601/. doi:10.3402/gha.v9.30723

Herlihy, N., Bar-Hen, A., **Verner, G.**, Fischer, H., Sauerborn, R., Depoux, A., Flahault, A., & Schütte, S. (2016). Climate change and human health: what are the research trends? A scoping review protocol. BMJ Open, 6(12), e012022. Retrieved from http://bmjopen.bmj.com/content/6/12/e012022.abstract. doi:10.1136/bmjopen-2016-012022

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