Stress exposure in intrauterine life is associated with shorter telomere length in young adulthood

Sonja Entringer, Elissa S. Epel, Robert Kumsta, Jue Lin, Dirk H. Hellhammer, Elizabeth H. Blackburn, Stefan Wüst, and Pathik D. Wadhwa

Department of Pediatrics, University of California, Irvine, Irvine, CA 92697; Department of Psychiatry, University of California, San Francisco, CA 94143; Department of Psychology, University of Freiburg, 79104 Freiburg, Germany; Department of Biochemistry and Biophysics, University of California, San Francisco, CA 94143; Department of Clinical and Physiological Psychology, University of Trier, 54290 Trier, Germany; Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, 68159 Mannheim, Germany; and Departments of Psychiatry and Human Behavior, Obstetrics and Gynecology, and Epidemiology, University of California, Irvine, Irvine, CA 92697

AUTHOR SUMMARY

A rapidly growing body of empirical evidence suggests that the origins of susceptibility for many common age-related disorders can be traced back to the intrauterine period of life (i.e., the concept of fetal, or developmental, origins of health and disease risk) (1). Exposure to psychosocial stress and/or biological stress mediators during gestation has been identified as one salient condition that may underlie the long-term effects of the intrauterine environment (2). The link between psychosocial stress exposure and adverse health outcomes is well established, and the elucidation of biological processes underlying this relationship is of ongoing interest. In recent years, accumulating evidence supports an important role for telomere biology as a potential mechanism linking stress and disease risk (3). Telomeres are DNA–protein complexes that cap chromosomal ends and promote chromosomal stability. They shorten in all replicating somatic cells, including white blood cells, with age and with conditions that produce oxidative stress. Declines in the telomere/telomerase maintenance system can produce variations in telomere length, thereby potentially setting up a long-term trajectory at birth that contributes to individual susceptibility for age-related common diseases. Evidence linking other adverse conditions during fetal development (e.g., intrauterine growth restriction, poor maternal nutrition during pregnancy) with telomere length provides biological plausibility for this relationship.

The objective of the present study was to test the hypothesis that maternal psychosocial stress exposure during pregnancy is associated with shorter telomeres in their offspring during adult life. Because it is not possible to randomly assign exposure to stress during pregnancy, we approximated experimental exposure by enrolling young adults whose mothers happened to have experienced a high level of psychosocial stress during pregnancy (a major negative life event; the prenatal stress group) and comparing them with a group of subjects whose mothers had not been exposed to negative life events during pregnancy (comparison group). The potential confounding effects of other sociodemographic, obstetric, medical, and behavioral risk factors were addressed by using a stringent set of exclusionary criteria. Moreover, because prenatal stress exposure may be associated with subsequent conditions that may influence telomere length, such as presence of postnatal early-life adversity, inadequate parental care, or concurrent stress level, we assessed these constructs to statistically account for their possible confounding effects.

Prenatal stress exposure was a significant predictor of subsequent adult telomere length in the offspring (Fig. P1). The effect was substantially unchanged after adjusting for potential confounders (subject characteristics, birth weight percentile, postnatal early-life adversity, and concurrent stress level), and was more pronounced in women. The magnitude of the observed difference in leukocyte telomere length between the prenatal stress exposure group and the comparison group is striking. The leukocyte telomere length of individuals in the prenatally stressed individuals was, on average, 178 bp shorter than that of individuals in the comparison group (and 295 bp shorter in female subjects). This effect equates to a difference of 0.41 SDs in telomere length in the prenatal stress exposure group relative to the comparison group (and 0.68 SDs in female subjects). Based on the most recent and comprehensive review of studies of age-related attrition in telomere length (4), translating telomere shortening of this observed difference to years of aging indicates that the leukocytes

Author contributions: S.E., D.H.H., S.W., and P.D.W. designed research; S.E. and R.K. performed research; S.E., J.L., and E.H.B. analyzed data; S.E., E.S.E., E.H.B., and P.D.W. wrote the paper.

Conflict of interest statement: E.S.E., J.L., and E.H.B. are co-founders of Telome Health, a company focused on telomere measurement. This article is a PNAS Direct Submission. Freely available online through the PNAS open access option.

†To whom correspondence should be addressed. E-mail: pwadhwa@uci.edu.

See full research article on page E513 of www.pnas.org.

Cite this Author Summary as: PNAS 10.1073/pnas.1107759108.
of individuals in the prenatal stress group aged the equivalent of approximately 3.5 additional years (5 additional years in the women-only group) relative to those in the comparison group.

There are several pathways that may have led to the striking observation in the present study. Exposure to high levels of maternal stress during pregnancy is known to produce deleterious effects on the offspring’s developing endocrine, immune, and metabolic systems, and our previously published studies in this cohort have reported that the prenatally stressed individuals exhibited alterations in several of these parameters, including higher stimulated levels of IL-6, a cytokine that has been directly associated with shorter telomere length.

Our study has a few limitations. First, prenatal stress exposure was assessed retrospectively. Although retrospective assessments of psychosocial factors such as stress are prone to biases such as “after-the-fact” reporting (i.e., individuals who develop health disorders are more prone to retrospectively report higher levels of adverse exposures before the development of the disorder) and those produced by memory and current psychological state (affect/mood), we believe it is unlikely these biases significantly impacted our assessment of prenatal stress in the present study. All subjects were healthy young adults; they received identical information before and upon entering the study, they were not provided any information about the study hypotheses, and they (as well as the experimenters) were blinded to and had no a priori knowledge about the expected direction of study findings. Subjects in the two groups did not differ in their current baseline psychological state (depressive symptoms, perceived stress) or memory performance scores. Moreover, our use of major negative life events to retrospectively assess psychosocial stress exposure provides greater confidence for construct validity than would have been the case for retrospective assessments of other components of stress such as perceived severity of stress appraisals or stress symptoms. Second, men were underrepresented in our study. Some studies have reported sex-specific effects of prenatal stress exposure on certain outcomes. As the effect of prenatal stress on telomere length in the present study was largest in the women only group, this raises the intriguing possibility and speculation regarding potential sex-specific programming effects in this context. However, we did not have the statistical power to examine possible sex-specific programming effects.

To summarize, this study provides evidence in humans that maternal psychosocial stress exposure during gestation is a significant predictor of the offspring’s subsequent leukocyte telomere length, a marker of cellular aging, in young adulthood. This, in turn, suggests that the trajectory of cellular aging in humans may be influenced by stress in intrauterine life, thereby potentially increasing the susceptibility of prenatally stressed individuals for complex, common age-related diseases. Many questions remain concern the exact mechanisms underlying prenatal programming of telomere length and the directionality of the associations among prenatal stress, telomere length, and later health outcomes. Nonetheless, this study represents an important step, and these results add further evidence to the growing awareness that disease pathways for complex, common age-related disorders may have their foundations very early in life.