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Early-life stress and reproductive cost: A two-hit developmental model of accelerated aging?

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ABSTRACT

Two seemingly independent bodies of research suggest a two-hit model of accelerated aging, one highlighting early-life stress and the other reproduction. The first, informed by *developmental models of early-life stress*, highlights reduced longevity effects of early adversity on telomere erosion, whereas the second, informed by *evolutionary theories of aging*, highlights such effects with regard to reproductive cost (in females). The fact that both early-life adversity and reproductive effort are associated with shorter telomeres and increased oxidative stress raises the prospect, consistent with life-history theory, that these two theoretical frameworks currently informing much research are tapping into the same evolutionary-developmental process of increased senescence and reduced longevity. Here we propose a mechanistic view of a two-hit model of accelerated aging in human females through (a) early-life adversity and (b) early reproduction, via a process of telomere erosion, while highlighting mediating biological embedding mechanisms that might link these two developmental aging processes.

Introduction

Theories of aging have long addressed why and how we age [1], but heterogeneity in the pace of aging continues to raise questions. From a developmental view, as we age, various biological and environmental processes contribute to the functional decline of cells, tissues and organs rendering individuals more susceptible to disease. However, these changes can vary developmentally with age, and importantly, may be amplified by previous adverse environmental exposures early in life, possibly via the programming of cellular-aging processes [2].

Several theoretical perspectives address *the developmental effects of early-life stress*, including the Developmental Origin of Health and Disease (DOHaD) Model [3], the Allostatic Load Model [4], and Predictive Adaptive Response frameworks [5–7]. All share the view that early-life adversity "programs" physiology and behavior to promote survival and/or reproduction, but that such developmental processes carry a cost or have trade-offs in later life involving increased morbidity and reduced longevity. Also important to consider are *evolutionary theories of aging*, including the Mutation Accumulation Theory [8], the Antagonistic Pleiotropy Theory [9], the Disposable Soma Theory [10], and the recent Reproductive-Cell Cycle Theory [11]. These, like the aforementioned perspectives, highlight trade-offs between growth and the ultimate goal of evolution, reproductive success, at the expense of longevity later in life.

The following empirical observations would seem consistent with this claim: (1) perinatal and childhood adversity plays an etiological role in the programming of late-life disease, resulting in increased morbidity and reduced longevity [2,12]; (2) increased fertility coincides with reduced longevity in birds and mammals [13], as well as in primates [14], although this association has not gone unchallenged in the human case [15–17]. From an evolutionary life-history perspective, organisms facing risks that could reduce their chances of surviving to reproductive age should, if possible, accelerate their development and thereby increase their prospects of passing on genes to future generations before becoming unable to do so due to an early death [7,18]. Ultimately, the organism trades-off longer-term health costs involved in accelerating development for increased probability of reproducing before dying. Thus, accelerated aging does not so much represent a disease process, but rather the consequence of a developmental adaptation crafted by natural selection.

Should this analysis prove accurate, questions arise regarding underlying mechanisms linking developmental influences with accelerated aging processes. Recent evidence suggests that telomere erosion may function as one important cellular mediator

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linking early-life stress with later-life morbidity and early mortality [19–21]. And this is because telomere regulation appears receptive and malleable in response to environmental inputs [22], requires energy for its maintenance [23], and is predictive of health [24,25] and early mortality [26]. Several highly energetically costly biochemical processes are implicated in regulating telomeres, including, among others, mitochondrial function, oxidative stress and inflammation [27].

With that in mind, reproduction is considered a highly costly process, one linked to increased levels of oxidative stress and glucocorticoids during pregnancy [28,29], as well as energy demands during lactation [30,31]. Notably, oxidative stress is itself related to reproductive trade-offs [32,33] and aging [34,35], and is considered a main factor influencing the rate of telomere erosion [36]. Thus, theory and evidence raise the possibility that the very developmentally induced accelerated aging processes involving early-life adversity and reproduction may operate at the cellular level via accelerated erosion of telomere length (TL). Moreover, epigenetic programming suggests that the reproduction-related aging process can be *intensified* by stress exposure in early life, mediated by biological embedding mechanisms.

The hypothesis

Here, we borrow a term used in cancer research that describes accumulation of mutations—that is, 'hits' – to the cell's DNA [37], and broadly apply it to human cellular aging. Specifically, we offer a mechanistic analysis of our hypothesized two-hit developmental model of accelerated aging via accelerated telomere erosion. We first provide empirical evidence of the effects of early-life adversity (i.e., prenatal, postnatal and early childhood) on cellular aging processes (i.e., telomere erosion) in support of the first hypothesized "hit" of our model. Thereafter, we discuss the cost of reproduction and its effect on cellular aging in support of our second hypothesized "hit". We then highlight biological embedding mechanisms of early-life adversity and early reproduction that might link these two developmental frameworks to induce accelerate aging via telomere erosion. Before drawing conclusions, we point out limitations of our argument. Finally, we discuss our hypothesized two-hit model of accelerated aging—emphasizing the interaction between early-life stress and early reproduction – based on the mechanistic integration of these two frameworks – and discuss implications for aging research. Fig. 1 schematically illustrates the framework to be developed.

Supporting evidence and evaluation of the hypothesis

We advance our hypothesized two-hit model based on two seemingly independent bodies of research, one highlighting early-life stress and the other reproduction.

Hit one

Early life adversity, then, functions as the first hit in the two-hit model of accelerated aging being developed herein. DOHaD-related research indicates that adverse conditions during prenatal development, resulting, for example, in low birth-weight predict increased risk of cardiovascular disease [38], cognitive problems [39] and early mortality [12]. Such adverse developmental effects are not limited to the pre-/perinatal period, as evidence also indicates that poor family environments early in life are associated with compromised metabolic and immune functioning [40], and adult health more generally [41]. Further, childhood maltreatment, a severe form of toxic stress for young children, is associated with mental and physical health problems [42–44]. Also meriting attention is evidence linking cumulative risk and higher allostatic load among rural children [45] and adolescences [46].

Such early-life-adversity effects on health in later life invite consideration of underlying mediating mechanisms. Recently, the length of telomeres has been posited as a factor regulating aging processes that could mediate such early-adversity effects [47]. Telomeres are DNA-protein repeats at the end of chromosomes that act as a 'cap' to protect chromosomes from deterioration [20]. Telomeres shorten with each cell division and are considered a hallmark for cellular aging [19]. While TL can be maintained in certain cell types by telomerase, most somatic cells lack sufficient telomerase and, as a consequence, telomeres progressively shorten with each cell division [48,49].

Notably, not only is there ever increasing evidence linking age-related TL with a broad range of risk factors that predict disease morbidity and early mortality, such as adult mental disorders and unhealthy behaviors (e.g., smoking, substance use, poor sleep and diet) [21], but the same is true of research chronicling effects of early-life adversity, including prenatal stress and maltreatment, on TL [27,50–54]. The fact that telomeres prove sensitive to adversity and predictive of health, as well as related to known poor-health risk factors, has resulted in them being regarded as a "biological clock" for studying accumulated cellular aging throughout the life course. According to such a medical model, telomere erosion reflects "wear and tear" which eventually compromises well-being, thus proving predictive of increased morbidity and reduced longevity. Here we challenge this prevailing view, as have others [55,56], by casting telomere erosion, a conserved cellular mechanism [57], in evolutionary perspective in order to explain developmental trade-offs in later life involving increased senescence and reduced longevity.

Hit two

While the evidence just summarized is consistent with the claim that early-life adversity programs the organism's physiology to promote survival at the expense of increased morbidity and reduced longevity through faster erosion of telomeres, a separate body of research addresses trades-offs between reproductive success and longevity in later life. The work underscores the second hit of the two-hit model under consideration.

The Disposable Soma Theory suggests that the developing organism, under limited resources, will shift energy allocation to reproductive activities while reducing energy distribution to non-reproductive aspects of somatic maintenance [10]. Thus, even though accelerated development may prove detrimental to health and even longevity in the longer term, such costs are regarded as ones which natural selection would discount, according to life-history theory, given the primacy placed on reproductive success [55,58–60]. Consistent with such a life-history perspective is long-standing evidence that earlier timing of reproduction and shorter lifespans are related across taxa [61], including birds and mammals [13], as well as primates [14] and humans [62,63], although, as noted earlier, inconsistencies exist in the latter case [15–17]. Such data become especially noteworthy if the biological processes involved in linking reproduction and lifespan play a role in regulating developmental rate, reproduction and aging, which is exactly what we are predicting. As telomere length and erosion appear to be adaptive, there is reason to expect they may mediate trade-offs between developmental life-history processes and longevity [64]. Intriguingly, several animal models provide support for this line of thinking [65–70]. In addition, then, to early-life-adversity effects on telomere regulation, the energetically costly process of reproduction can further impact the rate of aging via accelerated telomere erosion, thereby supplying the second hit of our model.

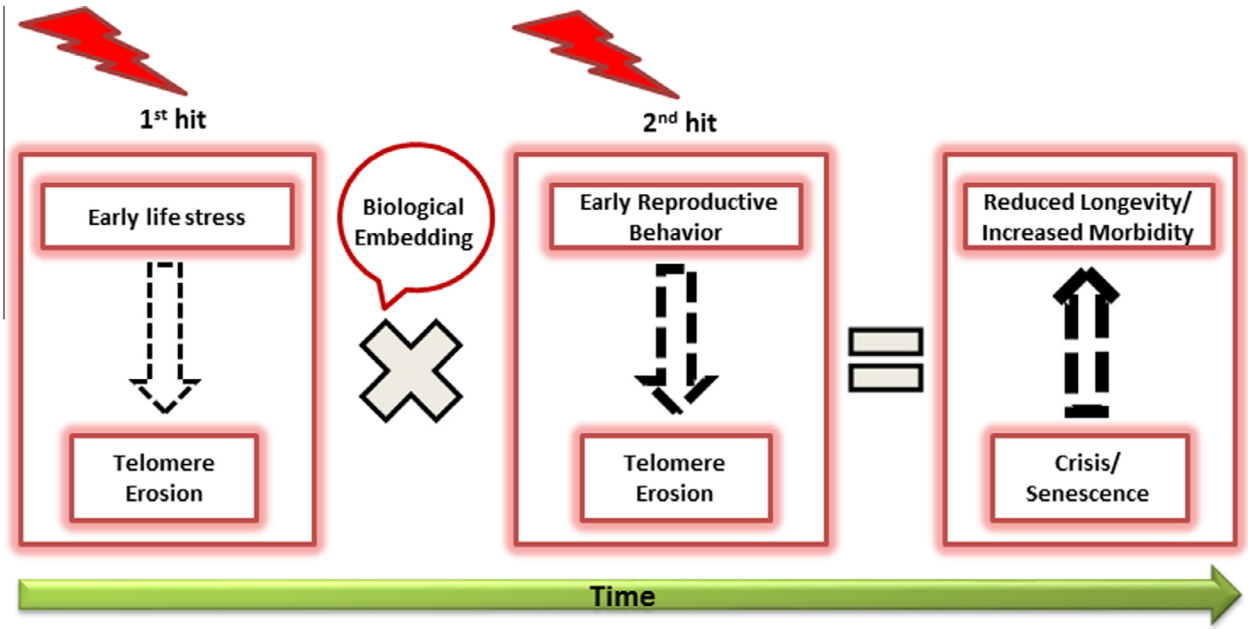

Fig. 1. Two-hit developmental model of accelerated aging. Overall model highlighting early-life adversity and early reproduction, via a process of telomere erosion, mediated by biological embedding mechanisms.

Biological embedding mechanisms of early life adversity and early reproduction

Considering the stress-telomere-erosion process central to this report, several mechanistic factors appear influential, including telomerase activity, glucocorticoids, mitochondrial regulation, inflammation and oxidative stress. As schematically illustrated in Fig. 2, these processes are not mutually exclusive and likely operate interactively, being influenced by one another and by other factors as well. Although the mechanistic regulation of TL is not entirely clear [27], empirical evidence suggests that chronic stress-induced secretion of cortisol down-regulates the activity of

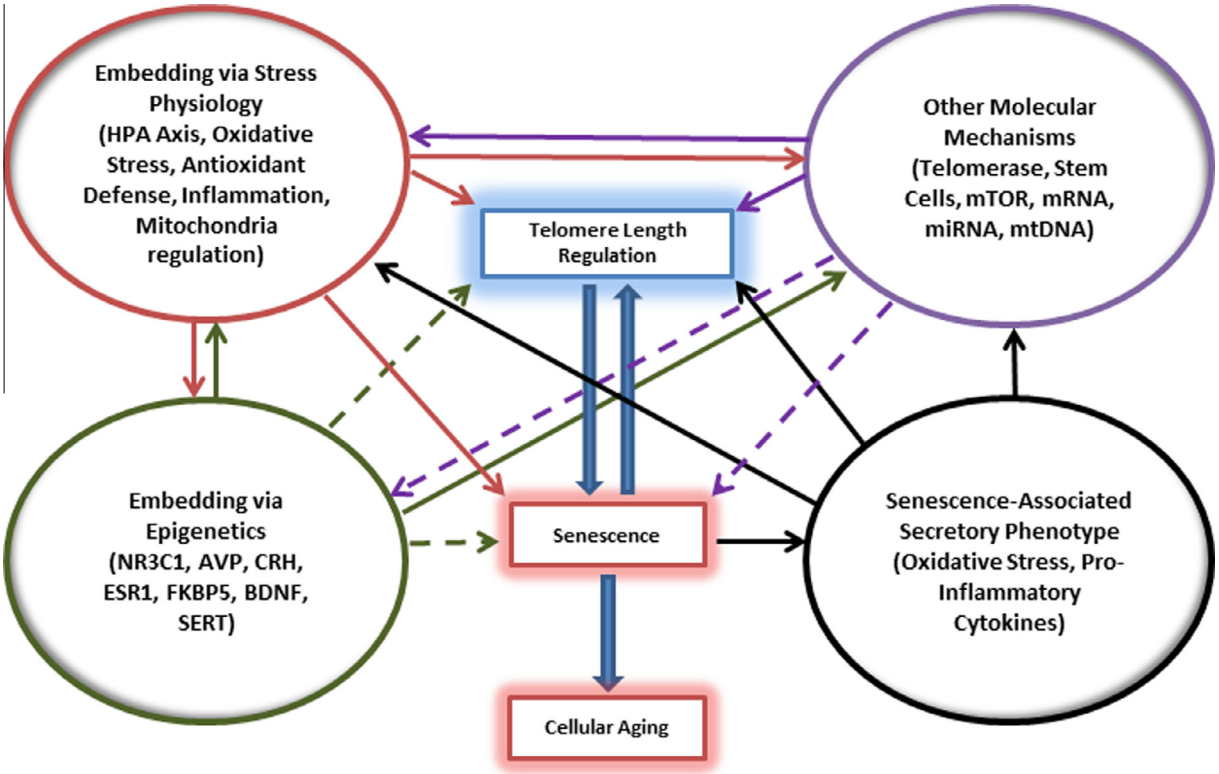

Fig. 2. Telomere length regulation. Schematic representation of telomere length regulation, senescence and cellular aging. Solid lines indicate direct effects, supported by empirical evidence. Dashed lines indicate hypothetical indirect effects, likely through other molecular mediators.

telomerase in lymphocyte cells, while increasing oxidative stress through mitochondrial dysregulation, which in turn leads to more rapid erosion of telomeres and, eventually, cellular senescence [71–73].

With regard to *glucocorticoids*, several studies of humans document significant associations between stress-related hypothalamus–pituitary–adrenal (HPA) axis indices and shorter TL [74–76], including research in children [77,78]. When it comes to *inflammation*, increased proliferation of immune cells in response to stress result in more telomere erosion [79], and a history of childhood adversity, by itself a strong predictor of elevated inflammation [80], is associated with shorter TL in white blood cells [81]. Notably, the inflammation-telomere-erosion process appears to be reciprocal rather than unidirectional. Telomere-induced senescence results in increased secretion of pro-inflammatory factors – such as interleukins 6 and 8 – known as the senescence-associated secretory phenotype (SASP) [82]. Thus, increased senescence rate, as a result of increased telomere erosion rate, increases the level of pro-inflammatory markers. Over time, chronic levels of inflammatory markers, as a result of early adversity, can damage tissues, promote tumor progression and accelerate aging [82].

The role of *mitochondrial regulation*, and the resulting increase in *oxidative stress* levels, appears to be a critical pathway by which early-life stress can impact telomere erosion and, thereby, accelerate aging. Evidence to support this claim is as follows: First, telomere dysfunction is associated with impaired mitochondrial biogenesis and function, likely through transcriptional regulators involved in energy metabolism [23]. Second, experimental research demonstrates that oxidative stress increases telomere erosion under conditions of high reactive oxygen species (ROS) [36]. Third, mitochondrial dysfunction is itself associated with increased ROS levels [83]. Fourth, oxidative stress levels are enhanced in the presence of glucocorticoids [71], most notably in the brain and in younger individuals [84]. Fifth, higher mitochondrial DNA copy numbers, as well as shorter telomeres, co-occur in individuals with a history of childhood maltreatment [85]. Finally, ROS production is also increased in senescent cells, providing more fuel for cellular damage and telomere erosion [86], and can further impair the self-renew ability of hematopoietic stem cells [87].

Also critical to consider with regard to early-life adversity and programming of biological systems is the role of *epigenetic regulation* [2,88]. Research suggests that the DNA methylation signature is responsive to environmental exposures, including the social environment [89–91]. Although mechanistic links with regard to telomere regulation are unclear, empirical evidence exist for epigenetic modification of genes in response to early-life adversity affecting HPA regulation, including arginine vasopressin [92], FK506 binding protein 5 (*FKBP5*) [93], brain-derived neurotrophic factor (*BDNF*) [94], and glucocorticoid receptor (*NR3C1*) [95]. The latter gene has been investigated the most and provides some of the mechanistic foundation of the biological-embedding processes. The proposed mechanism is thought to operate via methylation-mediated decrease in glucocorticoid receptor gene expression, most notably in the hippocampus, which reduces hippocampal sensitivity to suppress the HPA axis through negative feedback [90,96]. The methylation-mediated decrease in glucocorticoid receptor gene expression during sensitive developmental periods, and the links with increased HPA responses to stress, suggest a plausible embedding process which can further impact, and perhaps amplify, the accelerated erosion of telomeres. In sum, then, we contend that early life adversity programs biological systems which influence the rate of telomere erosion via glucocorticoids, inflammation, mitochondrial regulation, oxidative stress and epigenetic processes.

Turning to the second hit of our two-hit model of accelerated aging, it is critical to appreciate that reproduction is a costly process, involving energy expenditure, increased demand of nutrients during pregnancy, as well as physical changes in organs and tissues to carry out post-reproductive activities, specifically lactation in mammals. These direct costs are accompanied by a myriad of physiological changes including elevated stress hormones, compromised immune system and elevated oxidative-stress levels [31,97,98]. Notably, all these physiological changes are implicated in telomere regulation, thus suggesting a conserved mechanism linking early-life adversity *and* reproduction at the expense of TL and longevity.

Other systemic factors implicated in regulating metabolism, growth and survival can provide further support for the trade-off view of reduced longevity. Insulin signaling, for example, can sense the energetic demands and divert energy allocation to reproductive activities [97]. The mammalian target of rapamycin (mTOR) signaling pathway is an additional target of intense investigation [99]. The mTOR protein regulates cell growth, proliferation and survival by sensing systemic and energetic demands via insulin and growth factors [100]. Notably, mTOR signaling is linked to two processes that are integral to our two-hit model of increased senescence and reduced longevity; regulation of pubertal development and aging. Decreased mTOR signaling through rapamycin inhibitors delays puberty and extends lifespan in mice [101,102]. In light of the argument being advanced herein, it seems particularly noteworthy that early-life adversity is itself associated with earlier sexual maturation in females [103]. Thus, some of the biological processes under consideration seem to be involved in regulating sexual maturation [104], as well as reproduction and aging. Moreover, mTOR signaling also regulates mitochondrial metabolism and biogenesis as shown in studies utilizing rapamycin inhibitors, resulting in lower oxygen consumption by the mitochondrion [105]. Further studies reveal the modulating effect of mTOR on hematopoietic stem cell function and self-renewal ability, a process which is accompanied by elevated levels of ROS [106]. Taken together, we predict mTOR signaling to play a critical role in trade-offs between early development/reproduction and aging.

As mentioned above, oxidative stress is also implicated in trade-offs between reproduction and aging processes. Several studies of pregnant women document a marked increase in oxidative-stress levels during gestation [28,107]. Notable is evidence that such increased oxidative stress can reduce infant birth-weight and lower gestational age, conditions which are themselves associated with reduced longevity [108,109]. Furthermore, as early-life adversity can program biological systems in humans and nonhuman animals, more compromised organisms may experience higher levels of oxidative stress or reduced capacity to regulate protective factors such as antioxidant defense during gestation. Regulation of these activities by genes related to physiological plasticity are of considerable interest. Thus, adversity-related epigenetic modifications can provide mechanistic insight into the complex interaction between nature and nurture that regulates the rate of aging, as well as reproductive strategies [89,90]. Hence, if reproductive activities in mammals are linked at the genomic level to the rate of aging, this would suggest that both exposure to adversity, as well as reproductive investment, are important, interacting and mutually amplifying factors in regulating rate of development via a process of epigenetic modification.

Discussion

As should now be evident, the theoretical proposition central to this paper is that what have been regarded as two separate models of accelerated development, resulting from (1) exposure

to early-life adversity and (2) reproductive effort, may reflect an integrated two-hit developmental process fostering increased senescence and reduced longevity via accelerated telomere erosion. This trade-off of accelerated development in order to reproduce before dying at the expense of somatic maintenance may be an adaption of the organism, consistent with life-history theory, in the service of evolutionary fitness goals [7,58]. This line of thinking is supported by the fact that adversity-induced programming, likely through epigenetic modifications, can alter an organism's behavior and physiological systems in order to prioritize energy allocation for growth, reproduction and survival, rather than repair.

In other words, stressful exposures in early life (i.e., prenatal, postnatal and early childhood) can shift susceptible individuals onto a course of accelerated development. When faced with reproductive activities in later life, this programming can *intensify* fitness costs by producing higher levels of oxidative stress and glucocorticoids, compromise the immune system and dysregulate energetic demands at the cellular level, processes which can further accelerate the erosion of telomeres, and hence senescence (i.e., a second 'hit' of reduced longevity). Thus, not only does adversity accelerate telomere erosion but so do reproductive activities, at least in females—and many of the same physiological and genomic processes may be involved in each, though much remains to be illuminated about the mechanisms highlighted herein. Of importance is that these accelerated-aging processes are likely not restricted to reproduction per se, and may carry over to post-reproductive activities such as lactation [30]. Indeed, experimental research in rodents indicates that the energetic demands of lactation outweigh the energetic costs of pregnancy [31].

It should be appreciated, however, that such a proposal does not necessarily imply that telomere erosion functionally mediates developmental processes leading to reduced longevity. Indeed, even if such a causal process would appear to be the case in a statistical analysis of observational data, it would not necessarily indicate that telomere erosion causally affects reduced longevity; after all, the two constructs—telomere erosion and longevity—could be statistically related because both are affected by the same or related underlying biological processes, including increased senescence and many already highlighted. Telomere length may rather function as a 'sponge', absorbing both positive and negative life experiences, and thus, may be an indicator of overall fitness rather than a causal factor in disease processes. This, of course, is an empirical question.

Experimental work would be ideally positioned to evaluate the hypothesis of a two-hit model of accelerated aging via telomere erosion. It should be noted, however, that these tests could be evaluated mainly in (wild-) animal models [110], and considering the long lifespan perspective and ethical limitations with regard to humans. Thus, evolutionary ecologists conducting experimental research can manipulate environmental conditions in early life, as well as reproductive activities, while measuring TL and other biological factors throughout the lifespan. An example for such experimental manipulation is seen in Haussmann et al. [111], where corticosterone was injected into eggs of domestic chickens, mimicking embryonic exposure to maternal stress; this resulted in juveniles' increased stress response, increased levels of oxidative stress and shorter telomeres [111].

Should our theoretical framework of two hits accelerating aging prove accurate, several considerations and limitations should be acknowledged. First, although high parity in humans is the primary metric to test trade-offs between reproduction and longevity, there is a mixed evidence as to the effects of women bearing 2–4 children, suggesting perhaps a *U*-shaped relationship with significant effect for high parity, compared with 1 child or $\geqslant$5 children [112]. Second, as is evident in both nonhuman and human data, the effect of reproduction on aging processes may be especially evident at a young age [63,70,113–115]; thus age at first reproduction may be a critical factor in evaluating the two-hit model of increased senescence and reduced longevity. Studies evaluating the effect of early-life abuse and teenage pregnancy should be well-positioned to test the hypothesis presented here [116]. Third, bearing in mind the cost of reproduction, our analysis is restricted to females and thus, it is unclear whether it can be generalized to males. Notwithstanding, theory and evidence suggest that the cost of reproduction will be greater for women than men [117]. Fourth, while telomere erosion is proposed to mediate such life-history trade-off-incurring costs for longevity, telomere regulation is complex and influenced by many factors, including ones that can promote telomere maintenance or lengthening. An example is estrogen that can enhance the activity of telomerase in specific tissues [118]. Thus, as estrogen levels are increased during gestation, certain tissues may be protected from the otherwise costly effect on TL. Fifth, oxidative stress is also influenced by many factors, for example, the protein subunit of telomerase which can shuttle from the nucleus to the mitochondria upon oxidative stress to protect mitochondrial function and decrease oxidative stress [119,120], may also have tissue-specific effects [35], and can further be mitigated by antioxidants [98]. Thus, future research would benefit by examining the ratio of oxidative stress to antioxidants markers, and their combined role in regulating telomere erosion and senescence. Sixth, it is important to consider that heterogeneity of TL at birth may mask some of the effect of early development and reproduction on reduced longevity. In fact, the two main determinants of TL at birth, heritability and the paternal-age-at-conception effect [121], may suggest a 3- or perhaps even a 3.5-hit model of accelerated aging when taken into account. Finally, it must be appreciated that increasing evidence indicates that individuals differ in their susceptibility to the effects of early-life adversity (and support/enrichment) [122–124], with initial evidence even indicating that this is so with respect to TL [125]. This raises the possibility that for temperamental, physiological and/or genetic reasons some individuals will evince the reduced longevity effects considered herein more than others.

Conclusions

We advanced a mechanistic analysis of a two-hit developmental model of increased senescence and reduced longevity through (a) early-life adversity *and* (b) early reproduction, via a process of telomere erosion, mediated by biological embedding mechanisms likely involving mitochondrial regulation, oxidative stress, glucocorticoids, mTOR signaling, inflammation and epigenetic programming. Should this analysis prove accurate, vis-à-vis the mediational role of telomere erosion, several translational implications are suggested. Intervention studies that aim at slowing down aging processes with health-related modifiable factors (i.e., healthy diet, exercise, mindfulness, social support etc.) may seek to focus on high-risk groups and/or intervene during post-reproduction. Monitoring oxidative stress levels during pregnancy and supplements of antioxidants may further assist in protection against telomere erosion and aging processes.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Kirkwood TB, Austad SN. Why do we age? Nature 2000;408:233–8.
[2] Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med 2008;359:61–73.
[3] Barker DJ. The origins of the developmental origins theory. J Intern Med 2007;261:412–7.
[4] McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann NY Acad Sci 1998;840:33–44.
[5] Gluckman PD, Hanson MA, Spencer HG. Predictive adaptive responses and human evolution. Trends Ecol Evol 2005;20:527–33.
[6] Bateson P, Gluckman P, Hanson M. The biology of developmental plasticity and the predictive adaptive response hypothesis. J Physiol 2014;592:2357–68.
[7] Belsky J, Steinberg L, Draper P. Childhood experience, interpersonal development, and reproductive strategy: and evolutionary theory of socialization. Child Dev 1991;62:647–70.
[8] Medawar B. An unsolved problem of biology. College; 1952.
[9] Williams GC. Pleiotropy, natural-selection, and the evolution of senescence. Evolution 1957;11:398–411.
[10] Kirkwood TB. Evolution of ageing. Nature 1977;270:301–4.
[11] Atwood CS, Bowen RL. The reproductive-cell cycle theory of aging: an update. Exp Gerontol 2011;46:100–7.
[12] Swamy GK, Ostbye T, Skjaerven R. Association of preterm birth with long-term survival, reproduction, and next-generation preterm birth. JAMA 2008;299:1429–36.
[13] Lindstrom J. Early development and fitness in birds and mammals. Trends Ecol Evol 1999;14:343–8.
[14] Blomquist GE. Trade-off between age of first reproduction and survival in a female primate. Biol Lett 2009;5:339–42.
[15] Gavrilov LA, Gavrilova NS. Is there a reproductive cost for human longevity? J Anti-Aging Med 1999;2:121–3.
[16] Le Bourg É. Does reproduction decrease longevity in human beings? Ageing Res Rev 2007;6:141–9.
[17] Barha CK, Hanna CW, Salvante KG, et al. Number of children and telomere length in women: a prospective, longitudinal evaluation. PloS One 2016;11:e0146424.
[18] Chisholm JS, Ellison PT, Evans J, et al. Death, hope, and sex: life-history theory and the development of reproductive strategies [and comments and reply]. Curr Anthropol 1993:1–24.
[19] Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell 2013;153:1194–217.
[20] Blackburn EH. Telomere states and cell fates. Nature 2000;408:53–6.
[21] Shalev I, Entringer S, Wadhwa PD, et al. Stress and telomere biology: a lifespan perspective. Psychoneuroendocrinology 2013;38:1835–42.
[22] Puterman E, Epel E. An intricate dance: life experience, multisystem resiliency, and rate of telomere decline throughout the lifespan. Soc Pers Psychol Compass 2012;6:807–25.
[23] Sahin E, Colla S, Liesa M, et al. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature 2011;470:359–65.
[24] Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P. Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. BMJ 2014;349:g4227.
[25] Ma HX, Zhou ZY, Wei S, et al. Shortened telomere length is associated with increased risk of cancer: a meta-analysis. PLoS One 2011;6.
[26] Rode L, Nordestgaard BG, Bojesen SE. Peripheral blood leukocyte telomere length and mortality among 64 637 individuals from the general population. J Natl Cancer Inst 2015;107. djv074.
[27] Shalev I. Early life stress and telomere length: investigating the connection and possible mechanisms: a critical survey of the evidence base, research methodology and basic biology. Bioessays 2012;34:943–52.
[28] Toescu V, Nuttall SL, Martin U, Kendall MJ, Dunne F. Oxidative stress and normal pregnancy. Clin Endocrinol 2002;57:609–13.
[29] Burke CW, Roulet F. Increased exposure of tissues to cortisol in late pregnancy. Br Med J 1970;1:657–9.
[30] Clutton-Brock TH, Albon SD, Guinness FE. Fitness costs of gestation and lactation in wild mammals. Nature 1989;337:260–2.
[31] Speakman JR. The physiological costs of reproduction in small mammals. Philos Trans R Soc London Ser B 2008;363:375–98.
[32] Monaghan P, Metcalfe NB, Torres R. Oxidative stress as a mediator of life history trade-offs: mechanisms, measurements and interpretation. Ecol Lett 2009;12:75–92.
[33] Ziomkiewicz A, Sancilio A, Galbarczyk A, Klimek M, Jasienska G, Bribiescas RG. Evidence for the cost of reproduction in humans: high lifetime reproductive effort is associated with greater oxidative stress in post-menopausal women. PLoS One 2016;11.
[34] Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature 2000;408:239–47.
[35] Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007;39:44–84.
[36] von Zglinicki T. Oxidative stress shortens telomeres. Trends Biochem Sci 2002;27:339–44.
[37] Knudson AG. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci 1971;68:820–3.
[38] Barker DJP. The fetal origins of coronary heart disease. Acta Paediatr 1997 (Suppl. 422):78–82.
[39] Broekman BFP, Chan Y-H, Chong Y-S, et al. The influence of birth size on intelligence in healthy children. Pediatrics 2009;123:e1011–1016.
[40] Miller GE, Chen E, Fok AK, et al. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc Natl Acad Sci USA 2009;106:14716–21.
[41] Melchior M, Moffitt TE, Milne BJ, Poulton R, Caspi A. Why do children from socioeconomically disadvantaged families suffer from poor health when they reach adulthood? A life-course study. Am J Epidemiol 2007;166:966–74.
[42] Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry 2001;49:1023–39.
[43] Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol Bull 2011;137:959–97.
[44] Cicchetti D, Toth SL. A developmental psychopathology perspective on child abuse and neglect. J Am Acad Child Adolesc Psychiatry 1995;34:541–65.
[45] Evans GW. A multimethodological analysis of cumulative risk and allostatic load among rural children. Dev Psychol 2003;39:924–33.
[46] Theall KP, Drury SS, Shirtcliff EA. Cumulative neighborhood risk of psychosocial stress and allostatic load in adolescents. Am J Epidemiol 2012;176(Suppl. 7):S164–174.
[47] Haussmann MF, Marchetto NM. Telomeres: linking stress and survival, ecology and evolution. Curr Zool 2010;56:714–27.
[48] Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Exp Cell Res 1961;25:585–621.
[49] Olovnikov AM. Principle of marginotomy in template synthesis of polynucleotides. Dokl Akad Nauk SSSR 1971;201:1496–9.
[50] Shalev I, Moffitt TE, Sugden K, et al. Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study. Mol Psychiatry 2013;18:576–81.
[51] Entringer S, Epel ES, Lin J, et al. Maternal psychosocial stress during pregnancy is associated with newborn leukocyte telomere length. Am J Obstet Gynecol 2013;208.
[52] Shalev I, Caspi A, Ambler A, et al. Perinatal complications and aging indicators by midlife. Pediatrics 2014;134:e1315–1323.
[53] Drury SS, Theall K, Gleason MM, et al. Telomere length and early severe social deprivation: linking early adversity and cellular aging. Mol Psychiatry 2012;17:719–27.
[54] Marchetto NM, Glynn RA, Ferry ML, et al. Prenatal stress and newborn telomere length. Am J Obstet Gynecol 2016.
[55] Ellis BJ, Del Giudice M. Beyond allostatic load: rethinking the role of stress in regulating human development. Dev Psychopathol 2014;26:1–20.
[56] Monaghan P. Telomeres and life histories: the long and the short of it. Ann N Y Acad Sci 2010;1206:130–42.
[57] Meyne J, Ratliff RL, Moyzis RK. Conservation of the human telomere sequence (TTAGGG)n among vertebrates. Proc Natl Acad Sci USA 1989;86:7049–53.
[58] Belsky J et al. Toward an evo-devo theory of reproductive strategy, health, and longevity: commentary on Rickard. Perspect Psychol Sci 2014;9:16–8.
[59] Rickard IJ, Frankenhuis WE, Nettle D. Why are childhood family factors associated with timing of maturation? A role for internal prediction. Perspect Psychol Sci 2014;9:3–15.
[60] Kaplan HS, Gangestad SW. Life history theory and evolutionary psychology. Handb Evol Psychol 2005:68–95.
[61] Ricklefs RE. Life-history connections to rates of aging in terrestrial vertebrates. Proc Natl Acad Sci 2010;107:10314–9.
[62] Westendorp RGJ, Kirkwood TBL. Human longevity at the cost of reproductive success. Nature 1998;396:743–6.
[63] Tabatabaie V, Atzmon G, Rajpathak SN, Freeman R, Barzilai N, Crandall J. Exceptional longevity is associated with decreased reproduction. Aging-Us 2011;3:1202–5.
[64] Dantzer B, Fletcher QE. Telomeres shorten more slowly in slow-aging wild animals than in fast-aging ones. Exp Gerontol 2015;71:38–47.
[65] Kotrschal A, Ilmonen P, Penn DJ. Stress impacts telomere dynamics. Biol Lett 2007;3:128–30.
[66] Gao J, Munch SB. Does reproductive investment decrease telomere length in *Menidia menidia*? PLoS One 2015;10.
[67] Heidinger BJ, Blount JD, Boner W, Griffiths K, Metcalfe NB, Monaghan P. Telomere length in early life predicts lifespan. Proc Natl Acad Sci USA 2012;109:1743–8.
[68] Pauliny A, Wagner RH, Augustin J, Szep T, Blomqvist D. Age-independent telomere length predicts fitness in two bird species. Mol Ecol 2006;15:1681–7.
[69] Geiger S, Le Vaillant M, Lebard T, et al. Catching-up but telomere loss: half-opening the black box of growth and ageing trade-off in wild king penguin chicks. Mol Ecol 2012;21:1500–10.
[70] Bauch C, Becker PH, Verhulst S. Telomere length reflects phenotypic quality and costs of reproduction in a long-lived seabird. Proc Biol Sci 2013;280:20122540.
[71] Behl C, Lezoualc'h F, Trapp T, Widmann M, Skutella T, Holsboer F. Glucocorticoids enhance oxidative stress-induced cell death in hippocampal neurons in vitro. Endocrinology 1997;138:101–6.

[72] Choi J, Fauce SR, Effros RB. Reduced telomerase activity in human T lymphocytes exposed to cortisol. Brain Behav Immun 2008;22:600–5.
[73] Picard M, Juster RP, McEwen BS. Mitochondrial allostatic load puts the 'gluc' back in glucocorticoids. Nat Rev Endocrinol 2014;10:303–10.
[74] Epel ES, Lin J, Wilhelm FH, et al. Cell aging in relation to stress arousal and cardiovascular disease risk factors. Psychoneuroendocrinology 2006;31:277–87.
[75] Tomiyama AJ, O'Donovan A, Lin J, et al. Does cellular aging relate to patterns of allostasis? An examination of basal and stress reactive HPA axis activity and telomere length. Physiol Behav 2012;106:40–5.
[76] Révész D, Verhoeven JE, Milaneschi Y, de Geus EJ, Wolkowitz OM, Penninx BW. Dysregulated physiological stress systems and accelerated cellular aging. Neurobiol Aging 2014;35:1422–30.
[77] Kroenke CH, Epel E, Adler N, et al. Autonomic and adrenocortical reactivity and buccal cell telomere length in kindergarten children. Psychosom Med 2011;73:533–40.
[78] Gotlib IH, LeMoult J, Colich NL, et al. Telomere length and cortisol reactivity in children of depressed mothers. Mol Psychiatry 2015;20:615–20.
[79] Jurk D, Wilson C, Passos JF, et al. Chronic inflammation induces telomere dysfunction and accelerates ageing in mice. Nat Commun 2014;2:4172.
[80] Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci 2007;104:1319–24.
[81] Kiecolt-Glaser JK, Gouin J-P, Weng N-P, Malarkey WB, Beversdorf DQ, Glaser R. Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. Psychosom Med 2011;73:16.
[82] Coppe JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol 2010;5:99–118.
[83] Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 2006;443:787–95.
[84] Costantini D, Marasco V, Moller AP. A meta-analysis of glucocorticoids as modulators of oxidative stress in vertebrates. J Comp Physiol B 2011;181:447–56.
[85] Tyrka AR, Parade SH, Price LH, et al. Alterations of mitochondrial DNA copy number and telomere length with early adversity and psychopathology. Biol Psychiatry 2015.
[86] Passos JF, Nelson G, Wang C, et al. Feedback between p21 and reactive oxygen production is necessary for cell senescence. Mol Syst Biol 2010;6:347.
[87] Sahin E, Depinho RA. Linking functional decline of telomeres, mitochondria and stem cells during ageing. Nature 2010;464:520–8.
[88] Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. Annu. Rev. Nutr. 2007;27:363–88.
[89] Weaver ICG, Cervoni N, Champagne FA, et al. Epigenetic programming by maternal behavior. Nat Neurosci 2004;7:847–54.
[90] McGowan PO, Sasaki A, D'Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 2009;12:342–8.
[91] Szyf M. The early life social environment and DNA methylation DNA methylation mediating the long-term impact of social environments early in life. Epigenetics 2011;6:971–8.
[92] Murgatroyd C, Patchev AV, Wu Y, et al. Dynamic DNA methylation programs persistent adverse effects of early-life stress. Nat Neurosci 2009;12:1559–66.
[93] Klengel T, Mehta D, Anacker C, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat Neurosci 2013;16:33–41.
[94] Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting epigenetic influence of early-life adversity on the BDNF gene. Biol Psychiatry 2009;65:760–9.
[95] Meaney MJ, Szyf M, Seckl JR. Epigenetic mechanisms of perinatal programming of hypothalamic-pituitary-adrenal function and health. Trends Mol Med 2007;13:269–77.
[96] Welberg L, Seckl J, Holmes M. Prenatal glucocorticoid programming of brain corticosteroid receptors and corticotrophin-releasing hormone: possible implications for behaviour. Neuroscience 2001;104:71–9.
[97] Harshman LG, Zera AJ. The cost of reproduction: the devil in the details. Trends Ecol Evol 2007;22:80–6.
[98] Speakman JR, Garratt M. Oxidative stress as a cost of reproduction: beyond the simplistic trade-off model. Bioessays 2014;36:93–106.
[99] Weichhart T. Mammalian target of rapamycin: a signaling kinase for every aspect of cellular life. Methods Mol Biol 2012;821:1–14.
[100] Laplante M, Sabatini DM. MTOR signaling at a glance. J Cell Sci 2009;122:3589–94.
[101] Harrison DE, Strong R, Sharp ZD, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature 2009;460:392–5.
[102] Roa J, Garcia-Galiano D, Varela L, et al. The mammalian target of rapamycin as novel central regulator of puberty onset via modulation of hypothalamic Kiss1 system. Endocrinology 2009;150:5016–26.
[103] Belsky J, Ruttle PL, Boyce WT, Armstrong JM, Essex MJ. Early adversity, elevated stress physiology, accelerated sexual maturation, and poor health in females. Dev Psychol 2015;51:816–22.
[104] Belsky J. The development of human reproductive strategies: progress and prospects. Curr Dir Psychol Sci 2012;21:310–6.
[105] Schieke SM, Phillips D, Mccoy JP, et al. The mammalian target of rapamycin (mTOR) pathway regulates mitochondrial oxygen consumption and oxidative capacity. J Biol Chem 2006;281:27643–52.
[106] Chen C, Liu Y, Liu R, et al. TSC-mTOR maintains quiescence and function of hematopoietic stem cells by repressing mitochondrial biogenesis and reactive oxygen species. J Exp Med 2008;205:2397–408.
[107] Hung TH, Lo LM, Chiu TH, et al. A longitudinal study of oxidative stress and antioxidant status in women with uncomplicated pregnancies throughout gestation. Reprod Sci 2010;17:401–9.
[108] Kim YJ, Hong YC, Lee KH, et al. Oxidative stress in pregnant women and birth weight reduction. Reprod Toxicol 2005;19:487–92.
[109] Peter Stein T, Scholl TO, Schluter MD, et al. Oxidative stress early in pregnancy and pregnancy outcome. Free Radical Res 2008;42:841–8.
[110] Manning EL, Crossland J, Dewey MJ, Van Zant G. Influences of inbreeding and genetics on telomere length in mice. Mamm Genome 2002;13:234–8.
[111] Haussmann MF, Longenecker AS, Marchetto NM, Juliano SA, Bowden RM. Embryonic exposure to corticosterone modifies the juvenile stress response, oxidative stress and telomere length. Proc Biol Sci 2012;279:1447–56.
[112] Dior UR, Hochner H, Friedlander Y, et al. Association between number of children and mortality of mothers: results of a 37-year follow-up study. Ann Epidemiol 2013;23:13–8.
[113] Doblhammer G. Reproductive history and mortality later in life: a comparative study of England and Wales and Austria. Popul Stud 2000;54:169–76.
[114] Lemaitre JF, Berger V, Bonenfant C, et al. Early-late life trade-offs and the evolution of ageing in the wild. Proc Biol Sci 2015;282:20150209.
[115] Perls TT, Alpert L, Fretts RC. Middle-aged mothers live longer. Nature 1997;389:133.
[116] Boyer D, Fine D. Sexual abuse as a factor in adolescent pregnancy and child maltreatment. Fam Plann Perspect 1992;24. 4-&.
[117] Penn DJ, Smith KR. Differential fitness costs of reproduction between the sexes. Proc Natl Acad Sci USA 2007;104:553–8.
[118] Bayne S, Jones MEE, Ll H, Liu JP. Potential roles for estrogen regulation of telomerase activity in aging. Ann N Y Acad Sci 2007;1114:48–55.
[119] Sharma NK, Reyes A, Green P, et al. Human telomerase acts as a hTR-independent reverse transcriptase in mitochondria. Nucleic Acid Res 2012;40:712–25.
[120] Singhapol C, Pal D, Czapiewski R, Porika M, Nelson G, Saretzki GC. Mitochondrial telomerase protects cancer cells from nuclear DNA damage and apoptosis. PLoS One 2013;8.
[121] Broer L, Codd V, Nyholt DR, et al. Meta-analysis of telomere length in 19,713 subjects reveals high heritability, stronger maternal inheritance and a paternal age effect. Eur J Hum Genet 2013;21:1163–8.
[122] Belsky J, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. Psychol Bull 2009;135:885–908.
[123] Belsky J, Pluess M. Beyond risk, resilience, and dysregulation: phenotypic plasticity and human development. Dev Psychopathol 2013;25:1243–61.
[124] Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, van Ijzendoorn MH. Differential susceptibility to the environment: an evolutionary–neurodevelopmental theory. Dev Psychopathol 2011;23:7–28.
[125] Mitchell C, Hobcraft J, McLanahan SS, et al. Social disadvantage, genetic sensitivity, and children's telomere length. Proc Natl Acad Sci USA 2014;111:5944–9.