

## 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.

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### 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 accelerated 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].

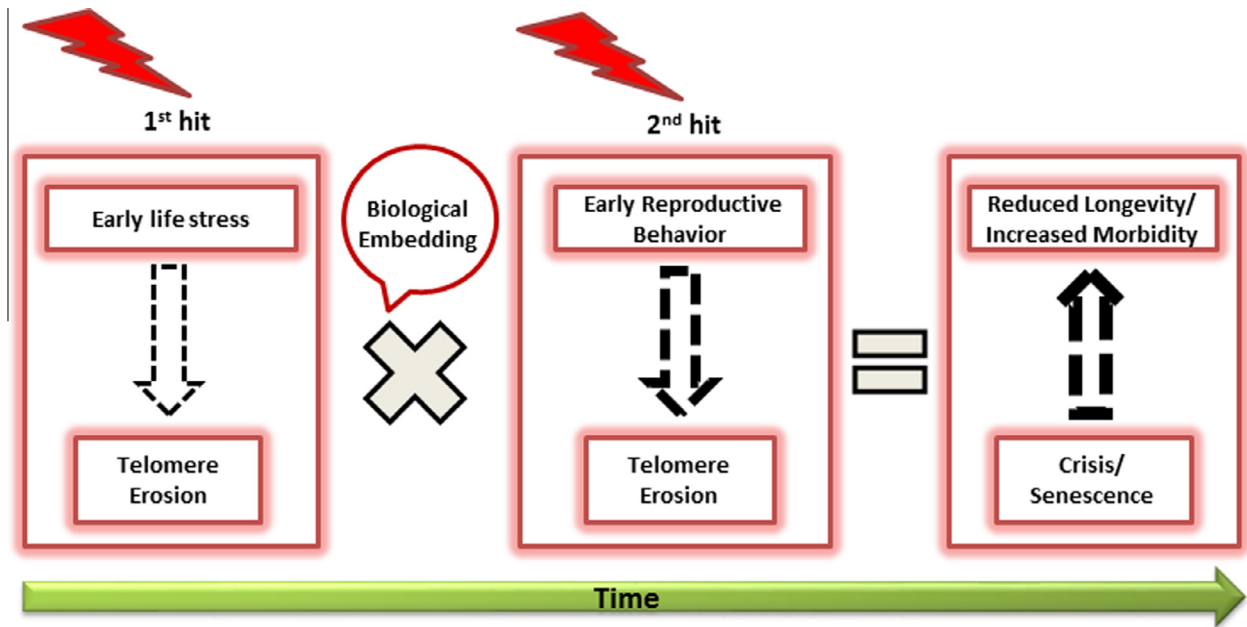
Such early-life-adversity effects on health in later life invite consideration of underlying mediating mechanisms. Recently, the length of telomeres has been posited as a factor regulating aging processes that could mediate such early-adversity effects [47]. Telomeres are DNA-protein repeats at the end 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 trade-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.

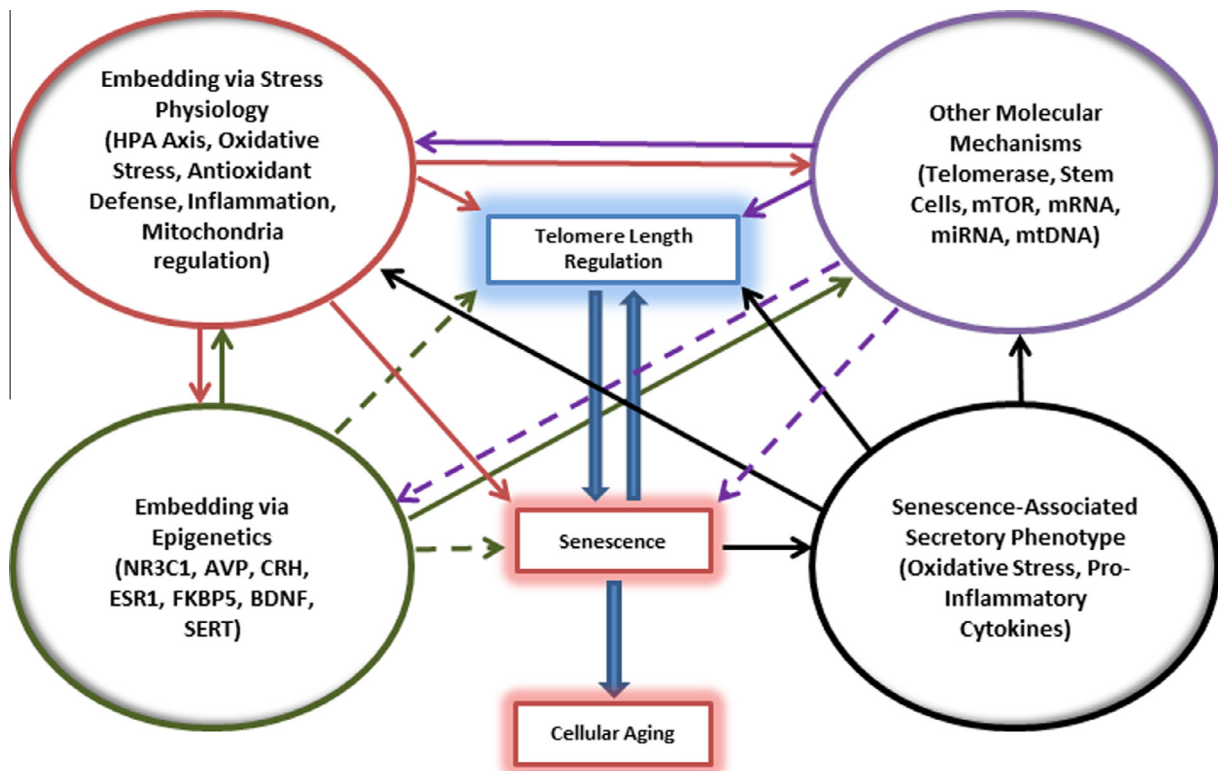


**Fig. 1.** Two-hit developmental model of accelerated aging. Overall model highlighting early-life adversity and early reproduction, via a process of telomere erosion, mediated by biological embedding mechanisms.

**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 adaptation 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  $\geq 5$  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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