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PROBLEMS & PARADIGMS

Prospects & Overviews

How does early-life adversity shape telomere dynamics during adulthood? Problems and paradigms

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Abstract

Although early-life adversity has been associated with negative consequences during adulthood, growing evidence shows that such adversity can also lead to subsequent stress resilience and positive fitness outcomes. Telomere dynamics are relevant in this context because of the link with developmental conditions and longevity. However, few studies have assessed whether the effects of early-life adversity on developmental telomere dynamics may relate to adult telomere dynamics. We propose that the potential links between early-life adversity and adult telomere dynamics could be driven by developmental constraints (the Constraint hypothesis), by the nature/severity of developmental adversity (the Resilience hypothesis), or by developmental-mediated changes in individual life-history strategies (the Pace of Life hypothesis). We discuss these non-mutually exclusive hypotheses, explore future research directions, and propose specific studies to test these hypotheses. Our article aims to expand our understanding of the evolutionary role of developmental conditions on adult telomere dynamics, stress resilience and ageing.

KEYWORDS
adult telomere dynamics, constraint hypothesis, pace of life hypothesis, resilience hypothesis, telomerase, telomere length

INTRODUCTION

Early-life adversity and fitness

Conditions experienced during early development can have profound effects on physiology, behavior, and health that can persist long into the future, within and over multiple generations. Earlier studies in humans highlight that different forms of early-life stress, are typically associated with impaired cognition and higher propensity for psychological/mood, cardiovascular and metabolic disorders into adulthood.[1,2] The term "stress" here broadly refers to the activation of the molecular, physiological, and behavioral stress response systems and we use the term early-life stress to indicate different kinds of adversities, including, but not limited to, nutritional restrictions, limited parental resources, social competition, predation pressures, pollutants, or hormones.[3,4] The clinical findings in this context greatly contributed to the foundation of the "*Developmental Origins of Health and Disease hypothesis*" in which early-life adversity has a central role in altering performance and ageing trajectories, most often with negative long-lasting consequences.[5,6] More recently, however, various theoretical models and empirical studies carried out in diverse species formulated plausible scenarios in support of adaptive operational changes that would improve fitness outputs of individuals even if developing under challenging circumstances.[7–9] These changes might lead to organisms better able to cope with subsequent adversities, or give rise to suboptimal phenotypes which might still have the best fitness advantage given the prevailing circumstances—"the best of a bad job" as defined in.[8] However, we still know very little about the main biological factors and mechanisms shaping the negative or positive organismal outcomes linked to early-life experience. In this opinion article, we highlight the potential importance of telomere dynamics as a mediator of the impact of early-life adversity on adult

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performance. Here, we specifically propose the novel hypothesis that early-life adversity may affect adult telomere dynamics, and therefore adult performance, through its effect on the ontogeny of multiple organismal systems that are linked to lifestyle, and stress resilience.

Telomere dynamics, a relevant marker of biological age and adult performance

An important route whereby the effects of early-life adversity might alter adult performance and fitness outputs is via changes in telomeres.[10–12] Telomeres are highly conserved nucleo-protein complexes found at the end of each eukaryotic chromosome arm and consist of tandem repeats of the non-coding guanine (G) enriched DNA sequence TTAGGG.[13] Telomeres play a key role in genome stability and integrity as they act as "protective caps" shielding genes from loss of coding sequences during cell division and preventing end-to-end fusion of chromosomes.[14] As a result of incomplete DNA replication (i.e., the "end replication problem") part of telomeric DNA sequences are lost at each cell division.[15] Once telomeres have shortened beyond a critical length, the cell loses its ability to replicate and enters a senescent or non-dividing state and this leads to apoptosis.[16] Other factors also contribute to further losses of telomeric sequences. Due to the high guanine content, telomeres are particularly vulnerable to oxidative damage, which is a major determinant of telomere loss from studies in vitro,[17] and probably in vivo.[18] Different mechanisms exist to maintain or restore telomere length. One of the best known restorative mechanisms involves the enzyme telomerase.[19] The restorative abilities of cells are however limited as telomerase appears down-regulated in most differentiated somatic cells,[20] however we still have limited knowledge of the functioning of this enzyme in vivo.[21]

Research across various species shows that telomere length is regulated by dynamic restoration and loss processes involving cell replication,[22] the influence of endocrine axes,[23] oxidative stress,[18] and telomerase activity.[24] In vivo experiments in several studied organisms show that mean telomere length tends to progressively decline with age, and this decline is especially pronounced during early development.[23,25] Telomere length and/or the rate of telomere change over time (i.e., telomere dynamics) have been associated with fitness proxies as shorter telomeres and/or greater rates of telomere attrition have been related to reduced lifespan, though most of the evidence is based on cross-sectional samples.[25–28] Exposure to stressors in growing individuals associated with increased exposure to glucocorticoid hormones, such as reduced food availability and maternal care have been shown to foster developmental telomere shortening.[22,29–32] Importantly, such effects often correlate with survival or recruitment probability over the juvenile life stages.[29,33,34] We also have good evidence indicating that adult telomere dynamics may be an even better marker of adult performance than absolute telomere length. In adults, there is often a large inter-individual variability in telomere dynamics and this variability has been linked with the occurrences of environmental challenges (reviewed in[35,36]) or physiological stress exposure (reviewed in,[23] including infection,[37] low-quality habitat,[38] harsh weather,[39] or pollution[40]). Similarly to that demonstrated in developing organisms (studies cited above), a rapid rate of telomere attrition in adult individuals has been associated with lower survival (e.g.,[27,41–45]), with behavioral and physiological markers of lower individual quality (i.e., foraging behavior, glucocorticoid hormones, breeding success,[46,47] and even with a higher risk of population collapse in wild vertebrates[48]).

Current gap: What is the link between early-life adversity and adult telomere dynamics?

First, while we have relatively good evidence for a strong legacy from early-life stress exposure to developmental telomere dynamics (examples in humans:[31,32]), the extent to which such effects persist and relate to rates of telomere change through adulthood remains poorly understood (Figure 1). Second, while it is well established that early-life adversity has long-lasting effects on stress reactivity, emotion regulation, and life history trade-offs, we still know very little about the relative contribution of these long-lasting changes on adult telomere dynamics (Figure 1).Third, while it is generally assumed that early-life adversity has negative long-lasting health and fitness consequences, we still have a limited knowledge about the exact nature of the relationship between various levels of severity of early-life adversity and its long-lasting consequences on telomeres. This is because most studies are based on cross-sectional designs and the relatively fewer longitudinal studies mostly assessed the effects of early-life adversity on adult telomere length at a single time point rather than across multiple adult life stages. A lifetime perspective of the effects of stress exposure is necessary as it accounts for biological embedding of early-life experience, and for vulnerability and resiliency factors that can change over the life course, thus potentially altering the extent to which lifetime stress exposure alters fitness outcomes.[36,49,50] Here, we focus on two central, and yet largely unexplored questions: What are the links between early-life adversity and telomere dynamics into adulthood at the individual level? How are these links mediated by the effects of early-life adversity on lifestyle, behavior, and physiology? Below, we discuss mechanistic plausibility of three non-mutually exclusive hypotheses on the potential evolutionary role of early-life stress on telomere dynamics at adulthood. Our hypotheses build on known theories about the organizational role of early-life adversity on adult physiology, cognition, and behavior. Finally, we conclude by exploring future research directions that would be important to undertake and propose specific studies needed to test these hypotheses.

HYPOTHESES ON ULTIMATE CONSEQUENCE OF EARLY-LIFE ADVERSITY ON ADULTHOOD TELOMERE LENGTH

Constraint hypothesis

A common theme in early-life stress research is that premature exposure to harsh conditions, in the form of nutritional and adverse social

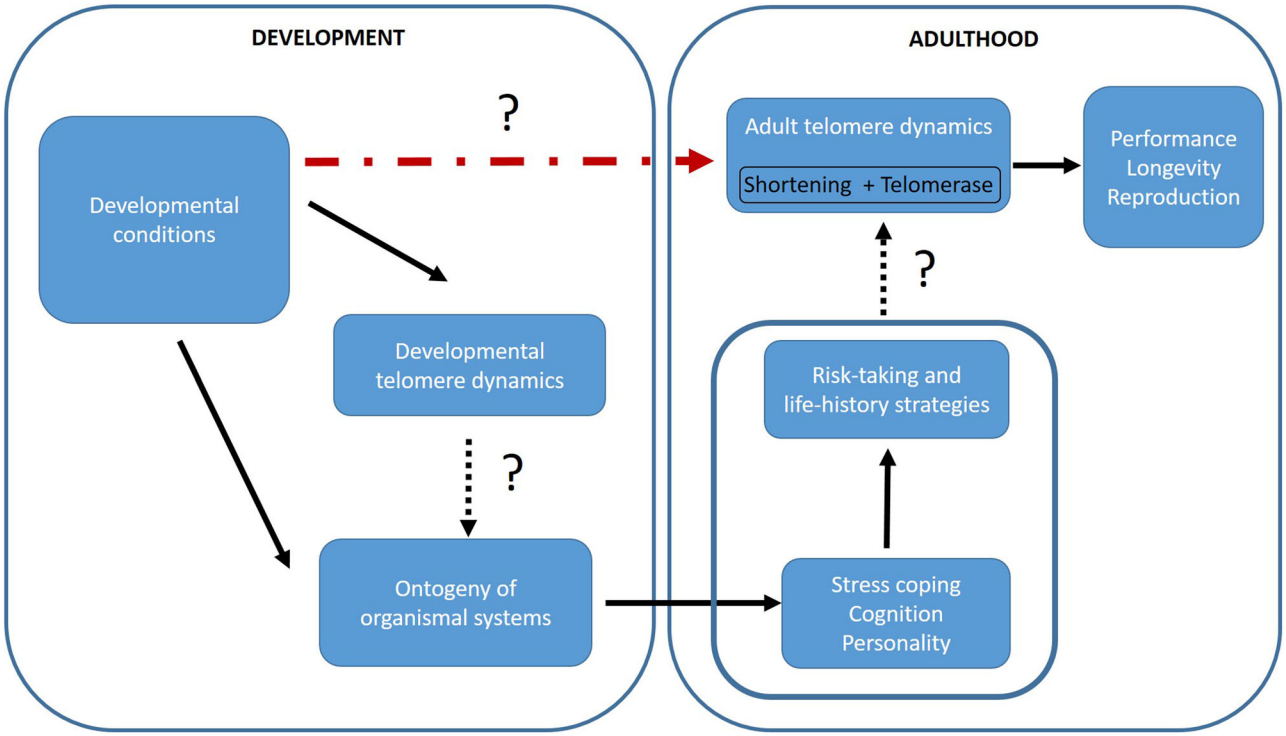

FIGURE 1 Schema illustrating the hypothesized links between developmental conditions and adulthood telomere dynamics (dashed arrows) on the basis of the available literature (black arrows). We lack experimental/manipulative data to elucidate the link between developmental conditions and changes in telomere length over the adult life stages (larger red dashed arrow). Changes in telomere length during early-life (developmental telomere dynamics) as a consequence of developmental cues may shape the ontogeny of organismal systems and then orientate an individual phenotype towards a specific stress-coping strategy and/or pace of life. Such phenotypic effects may contribute to explain the link between developmental conditions and adult telomere dynamics, and possibly organismal outcomes

experiences, is directly related to poorer organismal outcomes whatever the adult conditions.[51–53] The Constraint hypothesis follows the so-called "Silver Spoon" model (reviewed in[54]) whereby individuals experiencing adverse environmental circumstances will be able to invest less into growth, cognitive, and neurodevelopment, resulting in accelerated telomere attrition during adulthood, and ultimately in reduced survival probabilities and lifetime reproductive success. There are three concepts central to the Constraint hypothesis. First is that there are trade-offs to be faced in early-life when resources are scarce.[51,55] Individuals experiencing harsh conditions may be constrained to share the available resources between investments into somatic maintenance or into growth and development. Second, trade-offs must result in setbacks that will have consequences into adulthood. Finally, the damage incurred in early-life cannot be remedied before adulthood via catch-up growth or delayed somatic repair.[56,57] The general assumption of the Constraint hypothesis is that early-life adversity leads to inevitable developmental impairments that would lead to permanent cellular damage and result in reduced fitness outcomes. As telomere length reflects the physiological consequences of within-individual experiences (e.g.,[46,58]), increased constraints or a lower ability to cope with constraints, would lead to increased telomere shortening during adulthood (Figure 2A). Under this assumption, the Constraint hypothesis predicts direct links between adverse developmental conditions and adult telomere dynamics.

The concept finds support in many human clinical studies.[59] An overview of clinical psychology research[60] identified growing evidence that early-life stress impacts later life telomere length and that this could be a mechanism for psychiatric disease states in later-life. Interestingly, a recent study showed that risky family environments are associated with heightened negative emotions, and subsequently with shorter telomeres during adulthood,[61] supporting therefore the idea that early-life adversity may impact adult telomere length through its effect on the development of cognitive and emotional processes.[62] Ridout and colleagues[63] extended this further to more general health issues, with a meta-analysis concluding that early-life adversity may have long-lasting physiological consequences contributing to disease risk and biological ageing. The meta-analysis in literature is,[63] however, mostly based on cross-sectional studies, which makes it difficult to establish a direct/causal link between the three critical components: early-life adversity, somatic damage, and adult telomere dynamics. Importantly, recently published longitudinal studies provide evidence that goes in contrast with the expected link between early-life adversity and increased rates of adult telomere shortening (see paragraph "Resilience hypothesis" below).

In non-human literature various studies demonstrate that exposure to a variety of environmental stressors during growth often leads to reduced juvenile telomere length (e.g.,[64–67]; but see[33,68]). Linking this evidence of reduced juvenile telomere length to compromised

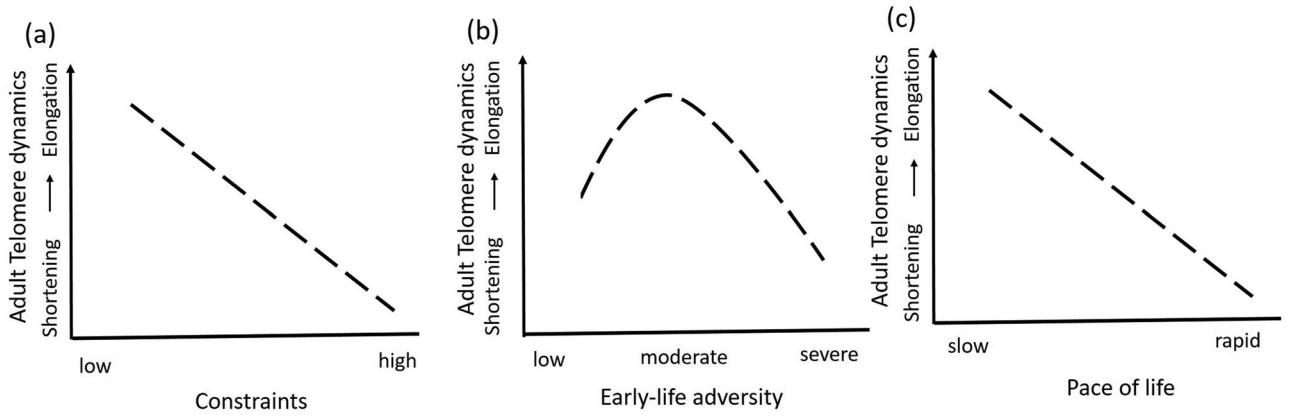

FIGURE 2 Predicted main associations between early-life adversity and adulthood telomere dynamics. In the (A) Constraint hypothesis, the association is driven by the amount of developmental constraints with increased rate of adult telomere shortening at increasing levels of susceptibility to constraints; in the (B) Resilience hypothesis the link is driven by the severity of early-life adversity exposure with adults that experienced mild/moderate stressors showing reduced rate of telomere loss relative to adults that experienced either low or severe stressors, in the (C) Pace of Life hypothesis the association is driven by changes in investment trade-offs under the assumption that early-life adversity accelerates the pace of life leading to high investment in reproduction and low investment in soma

adult telomere dynamics is often limited by study duration. More complete longitudinal studies are however emerging providing some support to such associations. A study of European badgers,[69] showed that the relationship between early-life telomere length and lifespan was associated with early-life cohort differences. However, the latter work was based on a correlative study design and did not manipulate early-life conditions. To our knowledge, only a single study provides convincing support for the Constraint hypothesis. Nettle and colleagues[70] were able to clearly outline, in European starlings, the link between early-life adversity, accelerated telomere attrition in juveniles and increased inflammation in adulthood, an immune mechanism known to induce telomere shortening.[37,71] Nevertheless, it remains largely untested whether developmental telomere length actually relates to adulthood telomere dynamics in early-life stress-exposed phenotypes.

Resilience hypothesis

Emerging evidence highlights that certain forms of mild developmental stressors can actually promote stress coping behaviors and have positive rather than negative effects on fitness-related proxies.[72,73] The "Stress Inoculation Model", almost exclusively employed in psychoneurobiology research, states that early-life adversities that are not overwhelming but just challenging enough to stimulate cognitive and emotional processing improve stress coping strategies into adulthood.[74,75] The model implies that the effects of early-life stress on organism function vary following an inverted *U*-shaped reaction norm on the basis of the intensity and/or duration of the challenge. It is important to remark that the gradient in stress exposure severity could be generated by various eco-physiologically relevant parameters related to social competition, food supply, temperature, predation, pollutants, or stress hormones. This concept is related to that of "Hormesis"—a phenomenon to explain anti-ageing effects produced by exposure to various mild stressors (see review in literature [76] on its eco-evolutionary relevance). However, while the "Stress Inoculation Model" is necessarily bound to early-life programming effects, hormetic responses can emerge at any time throughout the individual's life course.

The Resilience hypothesis extrapolates from the Stress Inoculation Model and the Hormesis theory. It aims to functionally link the beneficial "inoculation-like" effects of mild-to-moderate stressors on emotional and cognitive processes with changes in adulthood telomere dynamics and potentially on fitness outcomes. The basic prediction of the Resilience hypothesis is that individuals developing under mildly challenging circumstances will show reduced rate of adult telomere shortening compared to individuals developing under either low or severe stress exposure (Figure 2B). As a consequence, it is only severe stressors that would lead to irreversible cellular damage, contributing to accelerated mortality risk or ageing rates (supporting the previously described Constraint hypothesis) while mild stressors would, on the contrary, decrease mortality risk or slow ageing processes as a consequence of increased repair of endogenous damage.

The plausibility of the Resilience hypothesis is supported by at least three sets of indirect empirical evidence. First, a substantial amount of work in rodent models shows that mildly challenging neonatal experiences (e.g., brief periods of maternal separation or moderate increases in foraging demands) reduces hypothalamic-pituitary-adrenal axis (HPA axis) responses to stressors into adulthood, while severe neonatal challenges generally increase it.[77,78] Low stress reactivity could signify higher resilience due to increased ability to recover from acute challenges by attenuating maximal glucocorticoid responsiveness or by quickly returning to baseline glucocorticoids.[79] In wild barn swallows, adult telomere dynamics covaried with corticosterone stress responses to a standardized acute restraint protocol, with individuals showing a faster recovery to baseline also having reduced rates

of adult telomere loss.[80] Second, short-term developmental nutritional and social stressors can lead to long-lasting changes in adult stress coping behaviors, thus influencing an individual's exposure to risks.[73] Despite some of these changes undoubtedly leading to behavioral deficits, their potential adaptive role might depend on the individual's degree of flexibility to adapt to varying social landscapes into adulthood.[81] In a social bird, the white-browed sparrow-weaver, dominant breeders with shorter telomeres showed lower rates of telomere attrition than dominants with longer telomeres.[82] It may thus be plausible that certain early-life stress-induced behavioral phenotypes might display long-term somatic integrity strategies that could mitigate, rather than accelerate, subsequent telomere loss in adulthood. The fact that the rate of developmental telomere attrition is linked with regulation of emotional reactivity into adulthood[83–85] further supports this possibility. Third, evidence is accumulating showing that the link between stress exposure and the telomeric system is likely to be stressor type-, duration-, and dose-dependent.[63,86] For example, a study in laboratory rats show that exposure to stressors of intermediate durations can lead to rapid and marked increases (rather than decreases) in telomerase activity.[87] In the yellow-legged gull[33] a physiologically moderate increase of embryonic glucocorticoids (corticosterone) also up-regulated telomerase activity soon after hatching and this was correlated with telomere elongation; however, very high pre-natal glucocorticoid exposure was shown to increase developmental telomere loss in the domestic chicken.[88] In further support of curvilinear relationships between early-life stress exposure and telomeres, there are recent longitudinal studies in humans and nonhuman primates. By separating acute/short-term adversities from chronic/long-term adversities over childhood and mid-adulthood, Mayer et al.[50] demonstrated that only chronic stressors during childhood (age up to 18 years old) predicted greater telomere loss over the 2 years period in mid-adulthood. Ridout et al.[89] reported longer telomeres in children (age: 3–5 years) that experienced moderate-severe levels of childhood maltreatment in the prior 6 months; and, similarly, maternal variable foraging demands in bonnet macaques (i.e., a validated early-life maternal manipulation resulting in anxiety-like symptoms in offspring) led to longer adult telomere length.[9] Altogether these studies support the idea that exposure to relatively moderate and/or brief levels of early-life stress may lead to compensatory changes in the stress system through inoculation-like effects that could promote increases in resilience factors, including up-regulated telomerase activity, and thus reduced adult telomere shortening, or possibly, even adult telomere elongation.

However, other than the severity, duration, and exact nature of early-life adversity, the link between developmental stress exposure, subsequent resilience, and adult telomere dynamics could be more complex and depend on various other factors, including age-specific developmental effects and the timing of follow-up measurements of adult telomere length (see[90,91] for a discussion on these aspects). For instance, the association between early-life adversity and later-life telomere length weakens with progressing age since exposure,[63] suggesting a critical role for subsequent adult life events in mitigating, or potentially even reversing the effects of early-life adversity on telomere length at earlier ages. In addition, the emergence of a resilient phenotype could also depend on functional interactions between stressor severity and the degree of matching between the early-and late-life environments,[92] thus potentially influencing changes in telomere dynamics across adult life.

Pace of life hypothesis

There is now large evidence that developmental conditions can affect resource allocation processes towards competing life-history traits later in life,[51,53] and as a consequence, early-life conditions can orientate the phenotype towards specific life-history strategies[54] with potential, but currently unknown, consequences on telomere dynamics during adulthood. This phenotypic plasticity is closely linked with "the Pace of Life" theory, which suggests that individuals adopt a specific pace of life along a fast to slow continuum.[93,94] A slow pace of life is associated with a delayed maturity, a low reproductive investment, and a long lifespan while a fast pace of life is associated with a rapid maturity, a high reproductive investment, and a short lifespan.

A large amount of theoretical, empirical and experimental work suggests that this plasticity in the pace of life may be adaptive (e.g.,[95,96]), especially if it allows individuals to match their life-history strategy either to the environmental conditions that are likely to be encountered during adulthood (the external predictive adaptive response [ePAR][97]), or to their expected somatic state during adulthood (the internal predictive adaptive response [iPAR][97]). In both cases, theory predicts that early-life adversity may be associated with the adoption of a fast pace of life as this should be beneficial under harsh environmental conditions that may compromise longevity, or in low-quality individuals that are unlikely to have a long lifespan.[54,97]

The "Pace of Life theory" logically supports the idea that early-life adversity should be associated with an accelerated rate of telomere attrition during adulthood (hereafter called "the Pace of Life hypothesis", Figure 2c), mainly because early-life adversity is thought to result not only in a higher reproductive investment later in life but also to a lower allocation of resources to maintenance, and lower longevity.[98] Specifically, the logic behind "the Pace of Life hypothesis" comes from the links that may exist between telomere dynamics and several interconnected phenotypic determinants of the pace of life (i.e., behavior, physiology[93,99]). Firstly, a fast pace of life has been associated with several behavioral and personality traits that could trigger a rapid rate of telomere attrition in adults, such as risk-taking behavior, boldness and aggressiveness.[100] Secondly, a fast pace of life requires a high energy workload and it is therefore often associated with increased glucocorticoids, which often also accelerate telomere attrition and reduce telomerase activity.[23,101] Thirdly, a fast pace of life has been associated with increased metabolic rates and energy expenditures that may induce higher oxidative stress, which is one of the main causes of telomere attrition.[18,102] Finally, a fast pace of life is associated with a lower investment towards immunity, and

therefore with a higher probability of multiple infections, which can increase the rate of telomere shortening.[37,71] In addition, the rationale of "the Pace of Life hypothesis" is also supported by the association between adult telomere dynamics, survival and reproduction as high reproductive investment can trigger an accelerated rate of telomere attrition.[103] Moreover, several studies have found that a rapid rate of telomere attrition during adulthood is associated with a higher risk of mortality,[41,44,45,104] which is also a consequence of a fast pace of life.

Interestingly, findings from a few experimental studies suggest that the link between early-life adversity and adult telomere dynamics could be less straightforward than stipulated in the "Pace of Life hypothesis". Indeed, early-life adversity might apparently have opposite effects on the pace of life depending on its severity[105] and its variability.[106] Thus, several studies have also shown that early-life adversity could trigger a slow pace rather than a fast pace of life in some species or under specific developmental constraints.[107] In addition, it has also been convincingly demonstrated that there may be an interactive effect of early-life adversity and environmental conditions encountered during adulthood on the pace of life of organisms.[108] This suggests that the influence of early-life adversity on adult telomere dynamics is likely to be mitigated or exacerbated by the severity and the type of early life adversity, by the variability of early-life conditions, and by the environmental conditions that are encountered during adulthood, as stipulated in the non-mutually exclusive Resilience hypothesis.

PERSPECTIVE AND FUTURE DIRECTIONS

Need for studies monitoring telomere length through the whole lifespan

Although a few correlative and cross-sectional studies have provided support for some of these three hypotheses (e.g.,[50,63] see paragraphs above), it is clear that we currently have limited experimental/manipulative data available to explicitly test them. Such data are however important not only to determine the potential impact of developmental conditions on ageing processes, cellular/molecular damages, and performance later in life, but also to understand to what extent this impact can be mediated by telomere dynamics. As mentioned above, there is clear evidence that developmental conditions can affect developmental telomere dynamics.[22,23,31,32,109,110] However, it remains so far unclear whether and how developmental conditions and early life-adversity influence the operation of the telomeric system through adulthood in vivo and how this links to life-history evolution. There is strong support for a positive relationship between offspring telomere length and adult performance, involving key proxies of fitness (e.g.,[25,111,112]), and it is also true that adult telomere dynamics has been convincingly related to adult survival and performance.[47,104,113,114] We thus require studies attempting to tease apart the relative importance of developmental telomere dynamics and adult telomere dynamics for adult performance. How do developmental telomere dynamics relate to later adult telomere dynamics? What is the role of the organizational effects of early-life stress on physiology and behavior in the regulation of adult telomere dynamics? Is the influence of early-life adversity on adult performance driven by its impact on developmental telomere dynamics, its impact on adult telomere dynamics or, more likely, by a mix of both? Carefully designed longitudinal long-term experiments will be needed to answer these questions.

Need to manipulate the severity of developmental adversity in an appropriate ecological setting

Understanding the extent to which the severity of early-life stress exposure matters in the biological embedding equation, and how vulnerability and resiliency factors relate to adult telomere dynamics is a necessary step forward to test our three hypotheses. Despite there being some information about how varying levels of early-adversity might be associated with health status and adult telomere length (e.g.,[9,50,63]), most of these studies are limited to a single point measurement of telomere length during adulthood. We see the need for studies simulating ecologically relevant gradients of adversity to test for functional links between the severity of developmental challenges and within-individual changes in telomere dynamics and repair mechanisms, not only in juveniles but also in ageing individuals. Several studies have successfully manipulated developmental conditions to examine their influence on developmental telomere dynamics or performance (references above). However, despite few exceptions,[9,50,88] most of these experimental studies have compared one type of stressor with a control group, and they have not compared different stressor types and different degrees of stress exposure. Although this would require a larger sample size, it can certainly be achieved in both oviparous and viviparous vertebrates, for instance via experimentally manipulating the degree of nutritional constraints of developing offspring either directly (by modifying the type or abundance of food) or indirectly, by manipulating breeding effort, parental care, or sibling competition. This could also be achieved through direct experimental manipulations of other biotic and abiotic variables, such as exposure to predators, ambient temperature, or pollutants. Finally, to better understand the proximate mechanisms involved in the potential impact of early-life adversity on adult telomere dynamics, it will be relevant to manipulate key determinants of telomere attrition, such as hormones (glucocorticoids), the balance between oxidative damage and antioxidants, telomere repair mechanisms (see next paragraph), and to examine their long-lasting impact on physiological and molecular markers of stress, including adult telomere dynamics. Finally, performing such manipulations at different developmental time windows (e.g., prenatal *vs.* post-natal) could also be pertinent in terms of the severity of adversity as the long-lasting/irreversible nature of the effects generally diminishes with the developmental age in which the challenge occurs ([63,115]).

The importance of including telomerase measurement to test the three hypotheses

Telomere repair mechanisms are likely to be critical players in the framework of coping with the long-term effects of early stressors and in modulating the damage throughout later life. In that respect, the activity of telomerase certainly deserves a specific attention when aiming to test the three hypotheses we put forward as it is likely to be a prime candidate to follow for potential interplays with stress responses.[116] Telomerase is known to be regulated at different levels across tissue types and developmental stages.[24] Its demonstrated role in elongating telomeres provides an obvious mechanism for recovering from cellular damage after early-life adversity, and the ability for it to be up- and down-regulated at different stages offers the tantalizing prospect that it can be invoked on an "as needed" basis.[117] Crucial to this however, are the costs that may be associated with telomerase activation. There is growing evidence that telomere repair induces high energy costs and this will be an important determinant for whether it can be used as a buffer against detrimental early-life effects.[118] The measurement of telomerase activity is now within reach for most experimental settings[116] and we suggest that its inclusion is vital for future ecological and experimental studies aiming to test the impact of early-life adversity on adult telomere dynamics.

CONCLUSION

The three hypotheses presented in this opinion piece should not be considered in isolation and as opposing each other. The numerous examples that we present throughout this article strongly suggest that the relevance of each hypothesis will be highly condition dependent. There is little doubt that long-term extreme and chronic stressors are likely to impair brain development, to affect the ontogeny of key organismal systems, and lead to irreversible somatic damage in most organisms.[4,119] In this context, the Constraint hypothesis and, at least to some extent, the Pace of Life hypothesis probably provide the most fitting models to predict scenarios through which developmental adversity may be linked to adult telomere dynamics. However, we have little data to date to make specific predictions about associated outcomes of moderate/short-term stressors, and about their relative contribution in fostering resiliency factors throughout the life course. These kinds of stressors are likely to be the most relevant in ecological contexts, and more broadly, in healthy ageing populations. We would expect that the Resilience hypothesis may provide a better framework to explain why certain forms of mild adversities, such as brief neonatal handling or moderate dosing of glucocorticoid hormone, can have long-lasting positive effects and to predict the role of telomere maintenance and repair processes in the evolution of stress coping mechanisms and stress resilience. Another related aspect often overlooked in experimental planning, concerns the large inter-individual variability in the phenotypic responses to early-life adversity.[4] As a consequence, similar or even the same particular early-life event could have major long-lasting effects in the ontogeny of organismal systems in one individual and have negligible effect in another and this could also change the way through which early-life experiences are linked to adult telomere dynamics. This statement probably also holds true when comparing different species, meaning that it may be difficult to generalize the results from one species to another. This is especially true because different types of early-life adversity may not entail the same costs, and therefore, the same phenotypic responses for all species. These contrasted responses may for example depend on the species-specific life-history strategies (e.g., long-lived *vs.* short lived) and social systems (e.g., gregarious *vs.* solitary). In that context, future studies should test these three hypotheses in the light of the ecology of the study species. Combining experimental studies in laboratory models and epidemiological studies in wild vertebrates and humans appears crucial to properly test these hypotheses. This will shed some light on the impact of developmental conditions on lifelong ageing processes and fitness outcomes, and on the evolution of developmental plasticity.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were generated or analyzed in this study.

CONFLICT OF INTEREST

The author declares no conflict of interests.

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