PNAS COMMENTARY

Telomeres as a sentinel of population decline in the context of global warming

Jean-François Lemaître[a,1,2], Jean-Michel Gaillard[a,1], and Eric Gilson[b,c,1]

For almost a century, telomeres have been increasingly studied in biological and biomedical sciences with the ultimate hope that changes in telomere DNA length (abbreviated as TL) might offer a promising avenue for limiting biological aging and protecting against diverse age-specific mortality risk, especially cancer (1). From a molecular point of view, telomeres are complex nucleoprotein structures that avoid chromosome extremities to be recognized as accidental double-stranded DNA breaks, thereby avoiding unwanted DNA recombination and DNA damage checkpoint activation (1). In a large range of organisms, including all vertebrates, telomeres are formed by an array of TTAGGG DNA repeats specifically associated with a noncoding RNA named TERRA and a protein protective complex named shelterin. The duplication of telomeric DNA is not completed by the conventional replication machinery and therefore relies on a specialized reverse transcriptase named telomerase. In the somatic cells of several vertebrates, the expression of telomerase is repressed, thus preventing the full replenishment of telomeric DNA during the cell cycle. Therefore, over cellular divisions, telomere DNA length decreases, until critically short TL triggers proaging effects (e.g., cellular senescence) (2) and ultimately impairs survival prospects (1). In addition to this developmentally controlled telomerase down-regulation, TL shortening can result from exposure to a wide range of environmental stressors (e.g., social adversity, environmental harshness) through still elusive processes involving stress hormones and oxidative stress (1).

In the last two decades, numerous studies have quantified TL dynamics (i.e., changes in TL during lifetime) in the wild. They revealed that the decline in TL in somatic cells constitutes the rule rather than the exception (3) and that short TLs are, in several species, associated with a higher mortality risk (4). Despite this pattern of TL decline throughout life largely documented in the living world, empirical studies have pointed out a striking variability in telomere dynamics, both within and across species. Identifying the ecoevolutionary causes and consequences of individual variation in TL has recently become a popular topic (5). In that context, the study by Dupoué et al. (6) among populations of lizards subjected to a continuum of environmental harshness pushes the field forward by shedding an exciting light on the ecological relevance of TL.

Telomere DNA Length: From a Biological Marker of Aging to an Early Warning Signal of Population Decline?

Global warming threatens biodiversity, especially for ectotherms that are more responsive to increases in temperature (7). As a consequence, individuals facing elevated temperatures grow faster and reach larger size, leading them to start reproducing earlier at the expense of a shorter lifespan, as previously observed in common lizards (*Zootoca vivipara*) (8). Such changes may be associated with and/or driven by physiological changes. The study by Dupoué et al. (6) provides clear support that, in lizards, mean individual TL (measured by qPCR) shifts toward low values when going from sustainable populations under cool minimum temperature to declining populations under warm minimum temperature. Quite strikingly, the same pattern of variation in TL was retrieved at all female life stages (offspring, yearling, and adult females). From these findings, the authors proposed the "aging loop hypothesis" stating that the detrimental effects of climate warming on TL are passed from the mothers to the offspring who will thus carry short telomeres straight from birth. This transgenerational accumulation of the climatic burden on the telomere dynamic progressively leads populations to include biologically older individuals. Overall, this study suggests that TL is not only a biological marker of aging but depicts overall individual performance and can provide, thereby, a potential "early warning signal" of population collapse (*sensu* ref. 9).

Lizards from Threatened Populations Born Old

An intriguing result of this study is the observation that the telomeres of newborns from declining populations already have shortened TLs. Although one cannot rule out a defect in telomere reset during embryogenesis (10), either due to the heat wave or to a deficient maternal physiology, the authors (6) propose the interesting hypothesis that short telomeres are transmitted at conception. If so, the impact of climate change could be maternally inherited, as supported by the high inheritance of TL reported in Dupoué et al.'s study. Several mechanisms can be considered, from abnormal maintenance of telomeres during gametogenesis to epigenetic transmission (11), for example, by the noncoding RNA TERRA or, as recently shown in the nematode, by signaling damaged somatic cells to germ cells (12). If, indeed, the critically short TL trait is caused by global

Author affiliations: [a]Université de Lyon, Université Lyon 1, CNRS, Laboratoire de Biométrie et Biologie Evolutive UMR5558, F-69622 Villeurbanne, France; [b] Institute for Research on Cancer and Ageing, Nice (IRCAN), Université Côte d'Azur, CNRS, INSERM, Nice, 06107 France; and [c]Department of Medical Genetics, Centre Hospitalier Universitaire (CHU), 06000 Nice, France

Author contributions: J.-F.L., J.-M.G., and E.G. wrote the paper.

The authors declare no competing interest.

[1]J.-F.L., J.-M.G., and E.G. contributed equally to this work.

See companion article, "Lizards from warm and declining populations are born with extremely short telomeres," 10.1073/pnas.2201371119.

[2]To whom correspondence may be addressed. Email: jean-francois.lemaitre@univ-lyon1.fr.

Published August 10, 2022.

warming, the endangered lizards could be considered as the equivalent of patients suffering from "hereditary telomere syndromes," rare genetic diseases caused by germline mutations in telomere maintenance genes leading to premature aging and death, such as dyskeratyosis congenita (1). In common lizards, the mortality cost of carrying shorter TLs in individuals living in declining populations appears extremely high, as only 7% of the offspring born in these environments will reach sexual maturity (6). Thus, this timely article lends credence to the idea of proaging effects of climate change, a matter of paramount importance, since the general rise in temperatures is expected to lead to mass species extinction and increased human mortality (13).

Toward a New Generation of Physiological Indicators of Population Decline

Overall, this study (6) adds to the growing body of evidence that global warming leads to populations with, on average, shorter telomeres. Additionally, the authors provide evidence that abnormally short TLs are an inherited sign of impending population extinction. Therefore, they propose that TL could be a valuable biomarker of extinction risk. In this perspective, it is now necessary to understand the causes and consequences of TL shortening from birth onward in response to climate warming and how to use telomere biology in conservation policies.

However, while using mean individual telomere length to assess the conservation status of a population, as done here, is tempting, the threshold relationship between TL and population status identified by Dupoué et al. (6) indicates that the signal is only efficient when the population has started to decline, which might not allow conservationists to rely only on TL erosion per se. For instance, while many, if not all, ecological studies measure the average amount of telomeric DNA, it is now well documented that the proaging effects of short TLs rely on the presence of a few extremely short TLs (14). Thus, designing cost-effective, high-throughput assays to measure the shortest telomere frequency could be a more sensitive tool to integrate into future animal conservation policies and human health investigations. In addition, coupling TL with other biomarkers of an individual's biological age could be a promising way to refine the ecological value of such an indicator, if it allows detection of population collapses in advance (Fig. 1). To reach such objectives, ecologists should incorporate recent advances from biogerontological sciences.

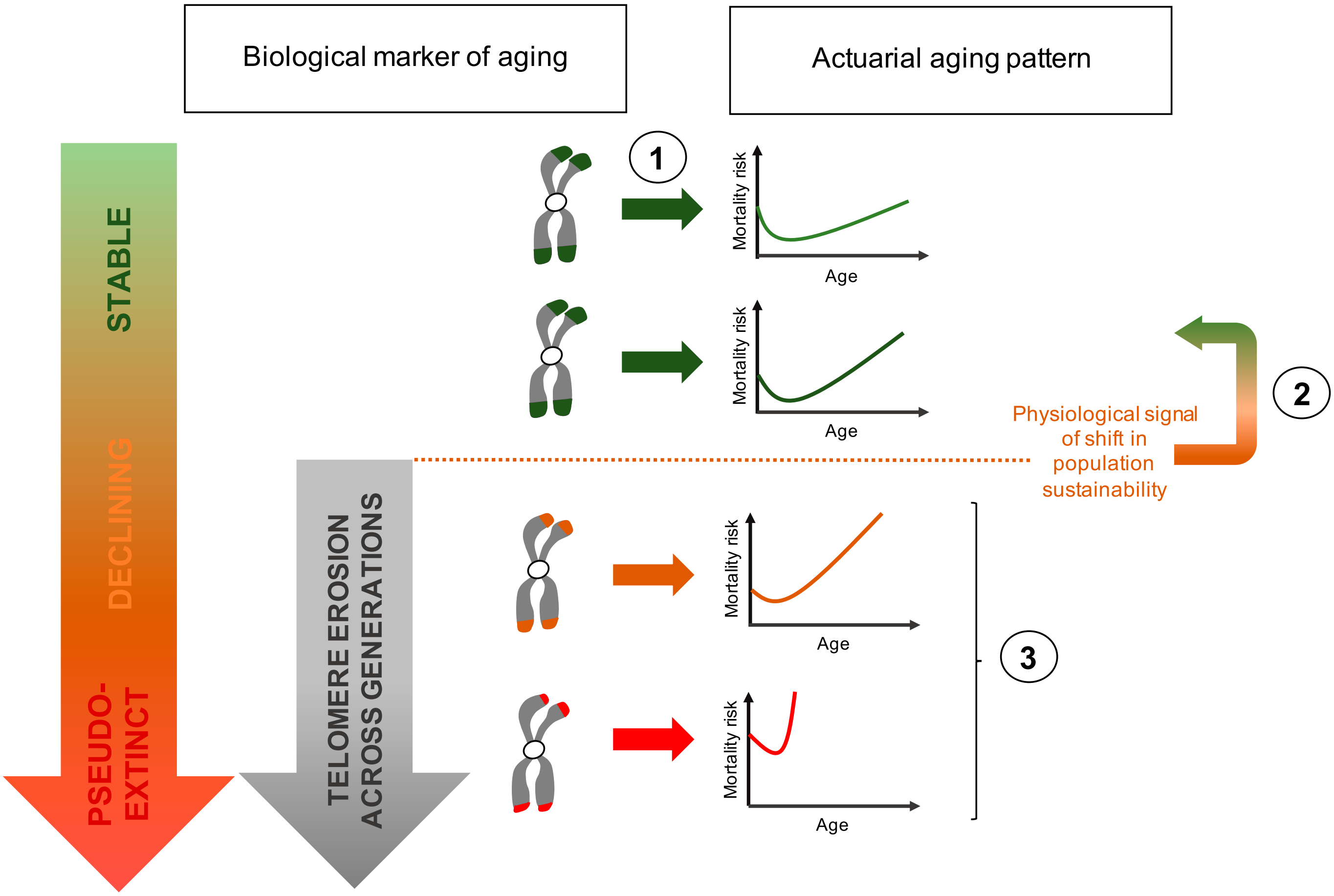

Fig. 1. Biological marker of aging as a tool to predict population demographic status: the case of TL. Natural populations can be placed along a gradient from stable to pseudoextinct populations. Based on the finding from Dupoué et al. (6), TL can serve as a tool to detect threatened populations as soon as they start to decline. Once TL reaches a critical threshold, telomeres indicate a shift in population sustainability. On this figure, we have emphasized three aspects that deserve further consideration: (1) Whether telomere length is "only" a marker of aging (not tested in Dupoué et al.'s study) and/or acts as a driver of population demographic status remains to be elucidated. (2) TL should be coupled with other phenotypic and demographic traits and biological markers of aging to obtain a set of composite indicators that might indicate a shift in population sustainability before the population is actually declining. For instance, generation time would be a complementary tool to predict the changes from a slightly increasing to a stable population. (3) Whether short TL is responsible for elevated baseline mortality, an earlier age at the onset of actuarial aging, and/or a steeper rate of aging, which, in return, will impact population dynamics, is still to be answered.

 https://doi.org/10.1073/pnas.2211349119

For instance, metrics of biological age derived from composite epigenetic clocks incorporating epigenetic age with several other physiological traits have been found to predict mortality risk accurately in humans (15). Given the increasing use of epigenetic clocks and other fine-scale physiological measurements such as TL in ecology, notably, in some endangered species (e.g., ref. 16), the development of such composite markers, along with other phenotypic traits such as body size (17), should definitely be added to the set of early warning signals that characterize shifts from sustainability to decline in populations in the wild. For instance, in the studied lizard, increased body size and higher reproductive participation of yearlings both appear to offer relevant signals of phenotypic changes before population declines.

Back to Demographic Aging

As mentioned above, the study by Dupoué et al. (6) brings evidence that TL provides reliable information on population sustainability. However, while short TL from birth is associated with a higher mortality risk, we still do not know how this can predict the overall mortality trajectory over the life course (Fig. 1). Indeed, most vertebrates (including reptiles) display actuarial aging (18)—an increase of mortality risk with age. Future demographic studies are thus required to assess whether declining populations with short TLs show a decrease in baseline mortality, an earlier age at the onset of actuarial aging, and/or a steeper rate of actuarial aging. Such a full consideration of age-specific demographic data remains mandatory to identify the key life history and demographic parameters for conservation purposes (19). In addition, such longitudinal studies could shed new light on the still elusive mechanisms linking TL shortening to actuarial senescence patterns (Fig. 1).

Finally, fine-scale demographic data are also required to evaluate whether the increase of life history speed under harsh environmental conditions is costly in terms of fitness. This is particularly important as an accelerated life history is not necessarily detrimental, because it allows increasing mean individual fitness for a given number of offspring produced during a lifetime. In such a case, the acceleration of the life cycle in response to warming is adaptive and allows individuals to keep similar fitness under warmer environments (e.g., see ref. 20 for recent evidence in the long-lived Bechstein's bat [*Myotis bechsteinii*]). However, the adaptive value of accelerated life cycles is constrained sooner or later by seasonality and growth constraints. While the generation time of lizards might decrease from a bit more than 2 y to be less than 2 y in warm environments, getting populations with a generation time of 1 y is simply not possible for this species. This means that generation time, per se, might also provide a suitable early warning signal with an expected threshold relationship with demographic performance (i.e., a decrease of generation time from growing to stable populations and then a plateau). In that context, a combination of TL and generation time might offer a way to accurately monitor demographic changes along the entire continuum going from growing to quasi-extinct populations.

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