INTRODUCTION

Over the last two decades, the question of how variation in telomere length and telomere dynamics (i.e., shortening or lengthening of telomeres) is related to life-history traits, survival and Darwinian fitness in animal populations has received considerable attention.

This is evident not only by the large number of empirical studies, but also by the increasing number of proposed hypotheses and reviews related to “telomere ecology and evolution” (e.g., Monaghan, 2010; Eisenberg, 2011; Gomes et al., 2011; Monaghan, 2014; Sudyka, 2019; see also Monaghan et al., 2018 for a special issue focusing on understanding diversity in telomere dynamics).

Abstract

Research on telomeres in the fields of ecology and evolution has been rapidly expanding over the last two decades. This has resulted in the formulation of a multitude of, often name-given, hypotheses related to the associations between telomeres and life-history traits or fitness-facilitating processes (and the mechanisms underlying them).

However, the differences (or similarities) between the various hypotheses, which can originate from different research fields, are often not obvious. Our aim here is therefore to give an overview of the hypotheses that are of interest in ecology and evolution and to provide two frameworks that help discriminate among them. We group the hypotheses (i) based on their association with different research questions, and (ii) using a hierarchical approach that builds on the assumptions they make, such as about causality of telomere length/shortening and/or the proposed functional consequences of telomere shortening on organism performance. Both our frameworks show that there exist parallel lines of thoughts in different research fields. Moreover, they also clearly illustrate that there are in many cases competing hypotheses within clusters, and that some of these even have contradictory assumptions and/or predictions. We also touch upon two topics in telomere research that would benefit from further conceptualization. This review should help researchers, both those familiar with and those new to the subject, to identify future avenues of research.

KEYWORDS

cancer surveillance, critical threshold in telomere length life history strategies, senescence and ageing, telomere elongation, telomere maintenance costs, telomere shortening, telomere signalling life history
The structure and cellular function of telomeres have been described and discussed in detail elsewhere (de Lange et al., 2006; Monaghan, 2010; Shay & Wright, 2019 and references therein). Here, we just briefly reiterate some aspects that are important for understanding the concepts in this review. Telomeres are repetitive, noncoding DNA sequences that cap and protect the ends of chromosomes (e.g., reviewed in Blackburn, 2005). Due to the “end replication problem”, telomeres shorten with each cell division (Lansdorp, 2005). In addition, oxidative stress (caused by highly reactive chemical molecules produced during, e.g., high metabolism and immune activation) can accelerate telomere shortening (von Zglinicki, 2001, 2002; Hodes et al., 2002; but see Boonekamp et al., 2017; Reichert & Stier, 2017 for a review of this effect in vivo). When progressive erosion makes telomeres reach a critically short length, the chromosomes risk degradation or fusing and the cell therefore commits apoptosis (Lange et al., 2006). Telomeric repeats can be maintained, or even increased in length due to activation of telomerase, a reverse transcriptase that elongates telomeres (Lange et al., 2006) or by recombination, referred to as ALT—alternative lengthening of telomeres (Cesare & Reddel, 2010; Henson et al., 2002). In humans and large placental mammals (>1 kg) telomerase is active in cells of the germline and in infants/subadults, whereas most somatic cells in adults normally express little or no telomerase production (e.g. Cong et al., 2002; Gomes et al., 2011; Weng, 2006). This has been interpreted as an adaptation to minimize the risk of tumour development in organisms with high metabolic and cell turnover rates (e.g. Holt et al., 1996; Young, 2018), or a resource trade-off where higher maintenance of the germline vs. soma is more beneficial (Kirkwood, 1977; Kirkwood & Austad, 2000). However, in smaller mammals and other nonmammalian species, telomerase production can vary considerably across tissue and taxa, and many species can have upregulated telomerase production later in life or show lifelong telomerase activity (Ingles et al., 2016; Olsson et al., 2018). However, note that telomerase activity in these species may not necessarily be related to telomere elongation as telomerase also has other functions such as regulation of chromatin states, DNA damage responses, and gene expression or reprogramming of pluripotent stem cells (Cong & Shay, 2008).

That telomeres play a critical role in cellular ageing is well established (Shay & Wright, 2019). However, what role telomeres play in life-history trade-offs, disease and longevity in wild animal populations is less clear. Many studies have found (positive) correlations between Darwinian fitness traits and telomere length, but how these correlations come about and how they are maintained is still under investigation. For example, selection has been found to act on telomere length/shortening through fitness-determining factors such as survival or longevity (e.g. Asghar et al., 2015a; Barrett & Richardson, 2011; Eastwood et al., 2019; Fairlie et al., 2016; Flanary & Kletetschka, 2005; Heidinger et al., 2012; Seeker et al., 2020; Willbourn et al., 2018). Moreover, there are many environmental or stress-related factors such as growth (Monaghan & Ozanne, 2018a and references therein), physiological health (Asghar et al., 2015a; Ilmonen et al., 2008; Le Vaillant et al., 2015), stress (Epel et al., 2004; Kotrschal et al., 2007; Monaghan, 2014) or reproductive effort (Asghar et al., 2015a; Bauch et al., 2013; Sudyka et al., 2014) that have been shown to be associated with telomere length or shortening. However, for some fitness-related traits such as reproductive output, a considerable number of studies fail to report any association with telomere length/shortening (Sudyka, 2019 and references therein). The wide range of reported associations (or nonassociations) together with the high variability in telomere regulation patterns observed across taxa has spurred the formulation of a multitude of hypotheses (many of them name-given, Figures 1 and 2). The hypotheses focus on different aspects such as the existence and direction of causality of telomere length/shortening, the role of intermediate or confounding factors (e.g., poor physiological condition), or specific mechanisms (e.g., signal mediators) through which telomeres may impact on Darwinian fitness. However, many of them are complementary or overlapping and their similarities or subtle discrepancies can be confusing. Also, different hypotheses seem to either dominate or be neglected in different subsets of the field. An overview of the different hypotheses and how they relate to each other is therefore helpful, to identify similarities and differences as well as to locate conceptual gaps.

In this review, we have compiled the name-given telomere hypotheses related to ecology and evolution to give an overview of the current directions in the field. Name-given hypotheses can be relatively easily identified and are likely to reflect main research directions, as they are coined when reviewing the state of a field, when conceptualizing an idea or when there has been accumulating evidence for certain associations. We present two groupings of hypotheses, one based on (i) how the hypotheses are connected to different research questions, and another based on (ii) the assumed role of telomeres in life-history evolution. In the first grouping, we briefly describe the hypotheses and discuss them in the context they have been proposed; that is, we discuss them in relation to the other hypotheses within a research question. In the second grouping, we instead sort the hypotheses using a hierarchical classification based on whether they do or do not assume that telomere length/shortening has a causal effect on fitness-related factors, if they propose functional consequences of telomere shortening on organism performance, etc. By applying the latter hierarchical classification, we also allow for comparisons of hypotheses across different research questions/areas. Both approaches are intended to help distinguish and highlight similar and separating features and, thus, to facilitate coherent evaluation of multiple related (competing) hypotheses. It should also make it easier to establish which hypotheses (or sets of hypotheses) that relate to a specific level of organization (cellular, organism or species level) and which hypotheses solely apply to certain life stages (as opposed to hypotheses that are relevant for the whole lifespan of an individual). In addition to sorting the hypotheses, we also briefly discuss some research directions for which we did not identify a name-given hypothesis, which may either be targets of current research or have the potential to be future avenues for research.
2 | IDENTIFICATION AND GROUPING OF THE HYPOTHESES

To get a broad overview over the literature, we first scanned in detailed key articles, reviews and special issues on telomere biology published in ecology and evolution journals, and also used these articles to find other publications that seemed likely to contain discussions of ideas and hypotheses relevant for the purpose of this review. To search for name-given hypotheses in an even broader set of journals and adjacent research fields, and at the same time check how many hypotheses we had located by our primary scanning of what we considered the most relevant literature, we also used the Web of Science (WoS) database of September 2, 2021 to search the published literature. We used the search string “(telomer*) AND (loss or shorten* OR length OR dynamics) AND (hypothes* OR model*)” and restricted the search to the WoS categories evolutionary biology, ecology, zoology, plant sciences and biology. This yielded in total 328 articles, and for all these we screened abstracts and, if they appeared relevant, we also screened full articles for eligibility. In the abstract screening, articles were considered relevant if they contained “explicitly named” hypotheses in which telomeres were linked to some aspect of ecology and evolution, for example life history and parental effects or were related in some way to Darwinian fitness. If an article was considered relevant for full-text screening, we also searched for hypotheses or models that may have been mentioned in the introduction or discussion, but not given an explicit name in the title or abstract. Full-text screening in a few cases led to additional articles (often at the interface between medicine and biology) that were also checked for eligibility. We acknowledge the possibility that the above search strategy may exclude specific hypotheses that do not use words covered by the strings “hypothesis” or “model” in the title, abstract or keywords. However, given that our main focus is on name-given hypotheses that either are established in the literature or are discussed in detail when named the first time, we think that it is unlikely that we missed any important hypothesis relevant for ecology and evolution by our search strategy. Moreover,
all of the hypotheses/articles that we had previously identified were included in the WoS search output list, suggesting that our search string was broad enough to obtain good coverage of the field.

Our screening resulted in a total of 23 name-given hypotheses. We subsequently grouped the hypotheses according to two different sets of criteria: the first grouping sorts the name-given hypotheses based on the research question to which they are linked. Thus, this classification is helpful to get an overview of the proposed hypotheses within a particular research field, as well as the whole range of research questions prevalent in telomere ecology and evolution research. For each hypothesis, we first identified the main research question. We then listed all the research questions and identified common topics into which we grouped the different questions. In this way, we narrowed down the grouping into the following four larger questions (Figure 2): (1) What is the role of telomeres in ageing? (2) Are telomeres a predictor/marker of individual quality or integrated somatic damage? (3) Is telomere length/shortening involved in the regulation of life-history strategies? (4) What are the potential physiological currencies/constraints that shape telomere-mediated life-history trade-offs? Note that some of the hypotheses may have been so broadly formulated that they encompass more than one of these contexts, and in these cases the same hypothesis may occur under more than one research question. We discuss this in more detail in the grouping section below.

The second grouping is based on the assumptions hypotheses make regarding the causality of telomeres in evolutionary processes and in the regulation and development of (physiological and/or behavioural) traits that can affect Darwinian fitness-determining factors. This grouping is hierarchical and independent of the specific research area context in which the hypothesis was originally formulated, instead highlighting similar lines of thought. Moreover, another aim of this review was to inspire new lines of thought in this research field, and we believe that a hierarchical framework could be very useful in this process. The hierarchical classification contains 25 hypotheses, including two hypotheses that we added and which concern aspects that need further conceptualization (Figure 3, Box 1). To improve readability in the hierarchical grouping, we use the term “model” primarily for clusters of hypotheses and the term “hypothesis” mainly in relation to the specific hypothesis stated in the original article. Elsewhere, if not specified, we consider the terms “model” and “hypothesis” as synonymous.

Finally, note that not all hypotheses that are listed here state explicitly whether they concern telomere length, telomere shortening rate or both. To facilitate sorting, we assumed in these cases that they refer to both and therefore write this as telomere length/shortening. However, we caution the reader that even though telomere length and telomere shortening may often be correlated, the association may not be linear across life stages and, hence, they may not always be interchangeable. For example, it might be argued that variation in telomere length across individuals may be determined primarily by genetics and early-life environment (Benetos et al., 2013; but see Dugdale & Richardson, 2018), whereas variation in telomere shortening seems to reflect to a greater extent the effects of intrinsic and extrinsic stressors (Boonekamp et al., 2014; Chatelain et al., 2020; Seeker et al., 2020). Arguably, this distinction is too simplistic and the relevance of telomere length vs. telomere shortening as traits linked to life history or other fitness-facilitating processes is still under debate (see, e.g., Seeker et al., 2020).

GROUPING I: RESEARCH QUESTIONS IN TELOMERE ECOLOGY AND EVOLUTION

In this section, we briefly describe each of the hypotheses and discuss them within the context of the associated research question (see Figure 2 for a graphical presentation of this grouping). However, it is beyond the aim of this paper to thoroughly describe each hypothesis and readers should therefore refer to the original work for more details.

3.1 | What is the role of telomeres in ageing?

Ageing is defined as an age-related decline of biological functions; that is, the “progressive loss of function accompanied by decreasing fertility and increasing mortality with advancing age” (Kirkwood & Austad, 2000). The question of whether telomeres causally mediate the ageing process and therefore determine lifespan is perhaps the oldest and most controversial one. The “telomere hypothesis of cellular ageing” (Autexier & Greider, 1996; Harley et al., 1992), which states that in the absence of telomerase activity, telomeres shorten with each cell division until a critical point (the so-called “Hayflick limit”) is reached after which cells stop dividing is now well established (Shay & Wright, 2019). The hypothesis of cellular ageing also postulated a potential causal role of telomeres in ageing, namely that telomere shortening at the cellular level might contribute to age-related degeneration of organism function. This postulation is, however, still debated. While there is relatively good support for an association between short telomere length and increased mortality risk in humans and other vertebrates (Boonekamp et al., 2013; Wilbourn et al., 2018) and, at least in humans, an inverse association between telomere length and the risk of age-related diseases (Blasco, 2005; Haycock et al., 2014; Zhao et al., 2013), the causal involvement of telomeres in ageing has been questioned (Simons, 2015). This uncertainty about the causal involvement of telomeres in ageing is also reflected by the fact that there are multiple competing hypotheses regarding telomeres and ageing. The “non-causal biomarker hypothesis” (Young, 2018; see also Boonekamp et al., 2014; Simons, 2015) reflects the concept that telomere length is not a determinant of lifespan. Instead, it is a molecular marker that can predict life expectancy and disease risk for “currently unknown mechanistic reasons” (cf. Simons, 2015). This notion contrasts with two other main views about the role of telomeres in ageing. The first of those two views is reflected by the “telomeric brink hypothesis” (Aviv et al., 2015; Tricola et al., 2018) and the “fetal programming of
telomere biology hypothesis” (Entringer et al., 2012, 2018). Both suggest that telomere length during early life (i.e., at birth or during early development) presets lifespan (or health span) of the organism irrespective of the exposure to factors affecting telomere dynamics later in life. The “telomeric brink hypothesis” in particular states that telomeres shorten at more or less equivalent rates across individuals in somatic tissues after birth (Aviv et al., 2015). The second view is reflected by the “accumulating costs hypothesis” (Hasselquist & Tobler, 2021), which proposes that telomere dynamics later in life contribute significantly to differences in lifespan. This hypothesis assumes that telomere shortening is directly affected by disease and stress episodes and therefore is dynamic and changeable over time. Individual differences in telomere shortening rates are therefore not viewed as solely due to individual differences in early life telomere length, but also as a consequence of adverse experiences later in life. At present, none of the above three views can be refuted. There are a considerable number of (longitudinal) studies that link telomere length/shortening to lifespan (see Introduction), suggesting that the validity of telomeres as a marker of ageing is plausible (Asghar et al., 2015a; Barrett et al., 2013; Froy et al., 2021; Heidinger et al., 2012; Heidinger et al., 2021; Lieshout et al., 2019; Seeker et al., 2020; see also next section below). However, whether telomeres shorten in a dynamic way or at a constant rate over life is currently not clear (e.g., Nettle & Bateson, 2017). Several longitudinal studies support the assumption that the shortening rate is consistent across years (Benetos et al., 2013; Bichet et al., 2020; Daniali et al., 2013; Ehrlenbach et al., 2009) and recent long-term studies on cattle, common terns (Sterna hirundo) and soay sheep (Ovis aris) suggest that environmental effects on telomere shortening rate may be small (Froy et al., 2021; Seeker et al., 2018; Vedder et al., 2021). However, other longitudinal studies find low repeatability of individual telomere length between years (Foley et al., 2020; Lieshout et al., 2021) and suggest that stochastic events such as infection episodes and stressful conditions can influence telomere dynamics (Asghar et al., 2015a; Bateson, 2016 and references therein). Also note that some of the uncertainty related to rate of telomere shortening and the within-individual repeatability may be related to methodological issues (see, e.g., Kärkkäinen et al., 2021 for a discussion on this aspect).

While the four hypotheses mentioned above concern telomeres and ageing of the individual organism, two other hypotheses that have been explicitly name-given concern the “ageing” of species. Both hypotheses discuss the idea that there is potential telomere shortening across generations so that telomeres become progressively shorter as the species/lineage ages. The “species clock hypothesis” (or “telomeric sync model of speciation”; Stindl, 2004, 2014) proposes that telomere shortening is a species-specific, inherent mechanism that could lead to global destabilization of a population. A tiny decrease in telomere length per generation may eventually (over long time spans) result in critically short telomeres in the genomes of all individuals of a species and, thus, genome instability effects that accrue at the species level. The hypothesis proposes that this could lead to extinction of old species (and the creation of new ones) due
to genome instability processes and fusion of chromosomes. The "telomere-resetting hypothesis" also assumes a decrease in telomere length with each generation, but proposes that telomere length can be "reset" and thus avoid extinction of the lineage (species). It was framed in the context of survival and persistence of lineages of asexual organisms (Loxdale & Lushai, 2003; Lushai & Loxdale, 2007) and proposes that lineage "longevity" is associated with the integrity of telomere function. During asexual reproduction, lineage-specific average telomere length is shortened with each generation, driving the organism group towards the telomeric brink. Telomere length and function can be "reset" by sexual reproduction (which involves ALT through recombination). Hence, through this mechanism, lineages may persist over (evolutionary) time. At present, there is no clear evidence regarding whether telomere length indeed decreases over (many) generations in different organisms. Holohan et al. (2015) show that there is a decrease in initial/birth leucocyte telomere length across several generations in three human populations, but the decline is attributed to environmental influences rather than to an inherent mechanism. Furthermore, there is no evidence that clones show a transgenerational decline in telomere length. Monti et al. (2011) found no decline in telomere length in aphid strains held in the laboratory for 40 years. Similarly, Wakayama et al. (2000) found no decline in lymphocyte telomere length in mouse clones over six generations. However, it is possible that the species-specific inherent decreases in telomere length are too small to be detected over the time periods (and number of generations) used in the two latter studies and, hence, further studies are needed to critically test the hypothesis proposed by Stindl (2004, 2014).

3.2 Are telomeres a marker of individual quality and/or health?

We found nine name-given hypotheses that concern the role of telomeres as indicators of individual quality or the state of current somatic damage (reflecting previous adverse events such as stress or disease episodes). We group these hypotheses together under the heading "individual quality" here defined as reflecting life-long individual performance (e.g., as measured by lifetime reproductive success). Individual quality is likely to be closely associated with the capacity to cope with and/or repair somatic damage. An increasing number of studies have found a positive relationship between proxies of Darwinian fitness and telomere length or telomere shortening. For example, longer telomeres are associated with earlier arrival at the breeding grounds (Bauch et al., 2013; Le Vaillant et al., 2015), increased reproductive performance (Sudyka, 2019 and references therein), stronger immune function (Le Vaillant et al., 2015) and lower stress hormone levels (Angelier et al., 2019; Lemaitre et al., 2021). Based on this type of results, the suggestion that long telomeres are associated with better life-long performance has recently been dubbed the "telomere-individual quality hypothesis" (Angelier et al., 2019; or simply the "quality hypothesis" by Heidinger et al., 2021). Telomere length is seen as a marker of individual quality where a lower rate of telomere shortening may, for example, reflect a better ability to cope with environmental stress or achieve a higher reproductive performance (Angelier et al., 2019; Sudyka, 2019). Moreover, studies reporting associations between telomere length/shortening and secondary sexual traits (e.g. Girardeau et al., 2016; Taff and Freeman-Gallant, 2017; Watson et al., 2017) often discuss their results in a framework that fits the telomere individual quality hypothesis. For example, a positive relationship between telomere length and the size of a sexual ornament may suggest that the expression of the sexual signal is dependent on physiological health. An extension of the "telomere individual quality hypothesis" is the "telomere-parental quality hypothesis" (coined by Viblanc et al., 2020) under which telomere length reflects parental quality (i.e., the ability to raise a large number of high-quality offspring with high survival rates). Two other name-given hypotheses that link telomeres to individual quality are the "selection hypothesis" and the "elongation hypothesis" (Haussmann & Mauck, 2008). The "selection hypothesis" assumes that individuals with shorter telomeres are of lower quality, and it therefore predicts that they disappear from the population at a younger age. The "elongation hypothesis", on the other hand, proposes that only high-quality individuals (with excess of resources) could afford to invest in telomere maintenance (and cope with an increased risk of cancer, which has been associated with activation of telomerase and, thus, telomere elongation; see below).

Several hypotheses have been name-given that concern the role of telomeres as a marker of current health and past (adverse) experiences, namely the "non-causal biomarker hypothesis" and the "accumulating costs hypothesis" (which also relate to research within the field of ageing, see above). A third hypothesis that relates to human health is the "weathering hypothesis" (Geronimus et al., 2015). This was originally framed to explain disparities in health and life expectancy between women of different ethnicities, and it proposed that exposure to and coping with chronic social stress will have a cumulative negative effect on disease susceptibility and ageing (Geronimus, 1992; Geronimus et al., 2010). It was later refined to include aspects of telomere biology (Geronimus et al., 2015). Under the "weathering hypothesis" telomere length is an indicator of (population) weathering (i.e., a cumulative measure of exposure to biological stress responses). A similar rationale has been used to suggest that telomeres can be used as a marker of animal health (Bateson, 2016). The review by Bateson (2016) discusses the potential of telomeres as a biomarker that is sensitive to the cumulative effects of negative (and positive) experience in a dose-dependent manner, and it also gives a comprehensive overview of the different stressors that have been shown to affect telomere length/shortening. The idea that telomere length reflects organism weathering is supported by a recent meta-analysis which shows that exposure to stressors such as pathogen infection, competition or reproductive effort is associated with shorter telomere length or higher telomere shortening rate (Chatelain et al., 2020).

Finally, Bateson and Nettle (2018) coined the "causation hypothesis" and the "selective adoption – third factor hypothesis" when reviewing the association between telomeres and behaviour. The causation
hypothesis suggests that telomere length/shortening reflects past behaviour that has induced changes in the somatic state (health) of the organism (e.g., through the behavioural response to a stressor). The "selective adoption – third variable hypothesis", on the other hand, suggests that the association between telomere length and behaviour comes about through another (unknown) factor/state that affects behaviour and concomitantly also telomere shortening. Bateson and Nettle (2018) use the example of early life adversity (the third factor) that presets post-birth telomere shortening rate and the behavioural phenotype. Hence, under this scenario telomere length/shortening reflects previous experiences that impact on somatic health (and behaviour). Moreover, both telomere length and behaviour are indicative of early life conditions, and this aligns with the hypotheses discussed under the ageing models above (i.e., the "telomeric brink hypothesis" and the "fetal programming of telomere hypothesis").

3.3 | Is telomere length/shortening involved in the regulation of life-history strategies?

Telomere length/shortening has been suggested to determine or shape individual life-history trajectories. This idea is inferred in the "fetal programming of telomere hypothesis" (Entringer et al., 2012; 2018) and the "telomeric brink hypothesis" (Aviv et al., 2015; Tricola et al., 2018) (both of which also are relevant for the ageing research field, see above). These hypotheses suggest that early life telomere length/shortening "programmes" individual life-history trajectories and that differences in telomere length between individuals remain relatively constant after birth. For example, environmental conditions affecting the mother’s physiological state and stress level during the prenatal (pregnancy) period could affect offspring early-life telomere length/dynamics and thereby have long-lasting effects on offspring physiology, disease susceptibility and ageing. While the "telomeric brink hypothesis" does not assume any adaptive adjustment of early-life telomere length in response to, for example, the environment, the "fetal programming of telomere hypothesis" emphasizes the importance of both the early environment and maternal effects, assuming both as passive as well as active adjustment of offspring telomere length by the mother. The "paternal effects hypothesis" coined by Eisenberg (2011), on the other hand, also predicts an adaptive modulation of offspring physiology, but in this case through age-specific inheritance of paternal telomere length. Telomeres are suggested to be life-history markers that determine how much the offspring should invest in somatic maintenance (Eisenberg & Kuzawa, 2018). Paternal age at conception affects telomere length of sperm which, in turn, determines offspring telomere length. Longer sperm telomeres, for example, may be a signal of longer life expectancy and, thus, preset the offspring for these conditions. More recently, several hypotheses have been proposed that suggest regulation of individual life history through telomeres also during adulthood. The "life-history regulation hypothesis" (Young, 2018), the "selective adoption – reverse causation hypothesis" (Bateson & Nettle, 2018), the "metabolic telomere attrition hypothesis" (Casagrande & Hau, 2019) and the "telomere messenger hypothesis" (Giraudeau et al., 2019; or "pace-of-life hypothesis", Heidinger et al., 2021) all assume that telomere length/shortening can mediate life history or behavioural strategies during different life stages. Prevailing environmental conditions may be converted into a "telomeric signal" (i.e., a change in telomere length or shortening rate) that can affect an individual’s physiological state and, in turn, lead to adjustments in life-history strategy/pace-of-life. The "telomere messenger hypothesis" suggests a combination of early life programming which resets life history (see above) and later life adjustment depending on environmental influences (e.g., pathogens). Although the hypotheses regarding the dynamic regulation of life histories in response to telomere length/shortening are relatively new, there is some support for the mechanisms through which such a regulation may occur. For example, telomeres may mediate life-history strategies through a regulatory effect on gene expression (Bateson & Nettle, 2018; Young, 2018 and references therein). Other mechanisms may be energy trade-offs or a trade-off between somatic maintenance and disease avoidance (see next section).

3.4 | What are the potential physiological currencies/constraints that shape telomere-mediated life-history trade-offs?

The physiological mechanisms underlying evolutionary trade-offs remain elusive and controversial and are therefore a major research target in evolutionary ecology (e.g., Flatt & Heyland, 2011). Studies on a wide range of taxa show that there is large variation in telomere length/shortening, both between individuals in a population and between species (e.g., Gomes et al., 2011; Ingles et al., 2016; Olsson et al., 2018; Spurgin et al., 2018; Lieshout et al., 2019; but see Ehrenbach et al., 2009; Benetos et al., 2013; Daniali et al., 2013; Bichet et al., 2020 for studies reporting consistent shortening rate across years). However, given the potential benefits of long telomeres (e.g., suggested extended lifespan and higher fitness, see above), this begs the question why not all individuals/species are born with and retain long telomeres, or, in other words, which are the factors and mechanisms that regulate telomere maintenance?

There are at present three name-given hypotheses suggesting that one mechanism may be a resource/energy trade-off between investing in telomere length maintenance and other energy-demanding functions: the "costly maintenance hypothesis" (Young, 2018), the "thrifty telomere hypothesis" (Eisenberg, 2011) and the "metabolic telomere attrition hypothesis" (Casagrande & Hau, 2019). All three hypotheses assume that organisms must tolerate some telomere shortening in order to invest in other fitness-improving functions (i.e., allowing telomere shortening might be an optimal strategy under certain circumstances). However, they differ with respect to the importance of energetic costs. The "costly maintenance hypothesis" assumes that resource (energy) costs to maintain telomere length are presumably negligible in relation to the maintenance and regulation costs of the whole genome, and it is suggested that other costs imposed
by “physical” constraints may be more relevant (Young, 2018). This contrasts with the other two hypotheses, which both assume that resource/energetic costs to maintain telomere length are large enough to be a key explanation for the observed variation in telomere length/shortening between individuals. The “thrifty telomere hypothesis” predicts “that the costs of longer telomeres are mainly in increasing energy/resource expenditures” (Eisenberg, 2011). It is based on the assumption that (rapid) cell proliferation, which occurs as a consequence of somatic maintenance (e.g., during activation of the adaptive immune system), is energetically costly and therefore must be traded-off against other energy-demanding functions such as reproduction. The idea is that telomeres may function as regulators of cell turnover rate and thereby limit energy expenditure (e.g., short telomeres may be a “signal” that restrain adaptive immunity to save energy), especially when there are nutritional constraints or there is a high frequency of adverse experiences (e.g., oxidative stress episodes). Finally, the “metabolic telomere attrition hypothesis” suggests that changes in telomere length are strongly dependent on competing energetic requirements (Casagrande & Hau, 2019). The hypothesis proposes that when organisms face periods of high energy demands (e.g., particularly during periods of elevated stress), resources are actively diverted away from telomere maintenance (and telomere shortening is then progressing) to other more essential physiological functions, prioritizing immediate survival (Casagrande & Hau, 2019). Also note that in the latter two hypotheses, longer telomeres could also reflect a higher resilience towards resource (energy) shortages. Whether resource/energy trade-offs are important factors that govern maintenance of telomere length across different taxa is not yet clear. There are many correlative studies supporting the idea that telomeres shorten at a higher pace during energy-demanding periods, such as growth phases, and that long telomeres are linked to a favourable nutritional/energetic state (reviewed in Casagrande & Hau, 2019; Monaghan & Ozanne, 2018b). Recent experimental studies also suggest that energetic trade-offs may at least contribute to variation in telomere maintenance. For example, studies on edible dormice (Glis glis) show that hibernation reduces telomere length, but that this effect can be reversed through food supplementation or increased periods of energy mobilization during hibernation (arousals) (Hoelzl et al., 2016; Nowack et al., 2019). Casagrande et al. (2020) recently showed that glucocorticoid-induced telomere shortening in great tit (Parus major) nestlings was associated with higher mitochondrial metabolic rate, which in turn was related to decreased mitochondrial efficiency, thus supporting the “metabolic telomere attrition hypothesis”. However, the idea of a dynamic regulation of the cellular energy balance through telomere length and, thus, the mediation of energy trade-offs is somewhat at odds with the notion that telomere shortening may be relatively constant between individuals (e.g., see “telomeric brink hypothesis” above) and that, at least in some study systems, (adverse) environmental effects on telomere shortening rate seem to be small (Froy et al., 2021; Seeker et al., 2018; Vedder et al., 2021). Finally, as pointed out by others (van Noordwijk & de Jong, 1986; Vedder et al., 2017), absence of covariance between life-history traits may also be caused by individual heterogeneity in resource availability; that is, trade-offs can be masked if between-individual variation in resource acquisition is small compared to that of resource allocation (the “big house, big car” syndrome). To resolve this and reveal the potential trade-offs, carefully designed experiments are needed. Hence, this is clearly an area for further research.

Another cost of maintaining telomere length that was suggested several decades ago is the increased risk of cancer that might be associated with telomere maintenance or elongation. Two name-given hypotheses capture the idea of a trade-off between cellular senescence (telomere maintenance) and cancer risk: the “telomere-telomerase hypothesis of ageing and cancer” (Holt et al., 1996; see also Shay et al., 1995; de Lange & Jacks, 1999; Shay, 2016) and the “cancer surveillance hypothesis” (Young, 2018). The “telomere-telomerase hypothesis of ageing and cancer” was originally formulated based on the observation that in humans, telomerase is usually suppressed in somatic cells (thus, permitting cellular senescence), but often expressed in tumours (thus, allowing immortalization) (Kim et al., 1994; Shay, 2016). Both these hypotheses suggest that telomere length works as a cellular tracker that monitors cell proliferation rate and cellular damage. The idea behind both these cancer-related hypotheses is that a critical (short) telomere length reflects proliferation rate or DNA damage that is indicative of cancer and, thus, this will trigger cell death and remove malicious cells. Many studies have explored telomere shortening and telomerase expression in the context of a cancer protection mechanism (reviewed in Shay, 2016; Young, 2018). The trade-off between cancer protection and telomere maintenance (i.e., replicative senescence) is probably the result of cancer being a selective force over evolutionary history (e.g., Young, 2018). For example, it has been suggested that telomere shortening (and suppression of telomerase) in mammals has evolved in response to homeothermy, to compensate for the increased mutational load (and thereby increased cancer risk) associated with higher body temperatures (Gomes et al., 2011; see also Olsson et al., 2018 for a discussion on telomerase activity in somatic tissue of ectotherms and its potential role for the evolution of cancer). However, knowledge about cancer prevalence in the wild is still limited, although it is clear that in some species it can have a significant negative impact on individual fitness (e.g., Madsen et al., 2017; McAloose & Newton, 2009). Thus, whether trade-offs between telomere maintenance and cancer risk can shape individual life histories remains an open question.

4 | GROUPING II: HIERARCHICAL CLUSTERING OF THE HYPOTHESES

Our hierarchical classification is independent of the specific research area context in which the hypothesis was originally formulated, and is intended to highlight similar lines of thoughts across fields as well as conceptual gaps. In the sections below, we explain the structure of the classification (as outlined in Figure 3 and Box 1). We start with the highest-level dichotomy (models making assumptions about telomere function vs. models that do not) and then continue with the
next-highest level. Where relevant, we also highlight how hypotheses may be related across the clusters we have identified.

### 4.1 Models making no assumption about the causality of telomeres (I.)

The first step in distinguishing between different hypotheses was to determine whether the authors proposing the hypothesis make any assumptions about causality. Many hypotheses make explicit or implicit assumptions about whether telomere length or shortening has direct causal effects on organism function and/or life-history traits. However, some hypotheses merely build on the fact that there is an association between telomere length/shortening and environmental factors or life-history traits. We have named the latter category “no-assumption models” (I., Figure 3, Box 1) as these hypotheses do not distinguish if associations are causal (i.e., telomere dynamics directly influence the associated trait) or merely correlative (i.e., telomere dynamics just reflect variation in the trait under consideration but do not exert any causative effect on it). We have identified four hypotheses that fall under this category (Figure 3, Box 1). The “telomere-individual quality hypothesis” (Angelier et al., 2019), the “telomere-parental quality hypothesis” (Viblanc et al., 2020), the “selection hypothesis” (Haussman and Mauck, 2008) and the “weathering hypothesis” all assume a positive association between telomere length and some measure of individual quality (see above). However, it remains unclear whether telomeres shorten faster because organisms are of lower quality (e.g., shortening is the consequence of poor condition) or if shorter telomeres contribute to lower quality (e.g., early-life telomere length predetermines individual quality), and, thus, there is not explicit inference of causality for these hypotheses.

While the four hypotheses under the category “no-assumption models” (I.) are important in highlighting the patterns between telomeres and fitness traits, which may allow us to make predictions about lifespan and health, they do not make assumptions about the direction of the relationship and/or the mechanisms that maintain these associations. This sets them apart from hypotheses that attribute a function to telomere length/shortening or those that refute any causal effects of telomeres on organism performance (arguing that any relationship is merely correlative). To understand if and how natural selection
BOX 1  Tabulated version of the hierarchical classification of the telomere hypotheses in ecology and evolution with shorthand explanations of the main differences between the clusters and with the relevant references assigned to each hypothesis

I NO ASSUMPTION MODELS: no specific assumptions are made about the effects of telomere dynamics on organism function (i.e., telomere shortening may be the cause or the consequence of organism state and function).

- Telomere individual quality hypothesis (Angelier et al., 2019)
- Telomere parental quality hypothesis (Viblanc et al., 2020)
- Selection hypothesis (Haussmann & Mauck, 2008)
- Weathering hypothesis (Geronimus et al., 2015)

II MODELS MAKING ASSUMPTIONS ABOUT TELOMERE FUNCTION: assumptions are made about how telomere dynamics affect organism function.

A MODELS ASSUMING NO EFFECTS OF TL/TS (NO CAUSALITY MODELS): assume that changes in telomere length or shortening (TL/TS) per se have no consequences for organism function/performance (health). There is no causality between TL/TS and (Darwinian) fitness.

- Noncausal biomarker hypothesis (Simmons, 2015; Young, 2018)
- Causation hypothesis (Bateson & Nettle, 2018)
- Selective adoption – third factor hypothesis (Bateson & Nettle, 2018)

B MODELS ASSUMING SPECIFIC EFFECTS OF TL/TS (CAUSALITY MODELS): assume that changes in TL/TS have direct consequences for organism function and individual performance. The models imply causality between TL/TS and (at least some aspect of) Darwinian fitness.

1. DISRUPTION OF FUNCTION MODELS: changes in TL/TS in some way disrupt organism functioning and are associated with an (at least potential) overall Darwinian fitness cost.

a. Maintenance cost models: maintaining (or elongating) telomere length demands non-negligible resources and thus entails costs.

   (i) Cost acceptance models: losing TL repeats are potentially costly in terms of risk of lowered Darwinian fitness. However, maintenance of TL entails too high physiological costs for the organism (at least in its current state/condition). Thus, TL can therefore not (presently) be maintained.

   - Costly maintenance hypothesis (Young, 2018)
   - Thrifty telomere hypothesis (Eisenberg, 2011)
   - Metabolic telomere attrition hypothesis (Casagrande & Hau, 2019)

   (ii) Cost compensation models: maintaining TL is (physiologically) costly, but not costly enough to outweigh the benefits of compensating these costs by investing in TL maintenance.

   - [Excess resource] Elongation hypothesis (Haussmann & Mauck, 2008)
   - Last resort elongation hypothesis (this review)

b. Critical threshold models: assume that telomeres remain (fully) functional until reaching a critical length after which ageing sets in with (rapid) cell death, decrease in organ function and impaired health. Telomere shortening has little or no effect on organism performance before the critical length (the telomeric brink) is reached.

   (i) Individual-level telomere shortening models: the critical threshold TL has consequences over an individual’s lifetime.

   - Telomeric brink hypothesis (Aviv et al., 2015; Tricola et al., 2018)
   - Accumulating costs hypothesis (Hasselquist & Tobler, 2021)

   (ii) Species-level telomere shortening models: the critical threshold TL has consequences across (many) generations of a species.

   - Species clock hypothesis (or telomeric sync model of speciation; Stindl, 2004, 2014)
   - Telomere resetting hypothesis (Lloyd & Lushai, 2003; Lushai & Loxdale, 2007)

2. ADAPTIVE REGULATION (SIGNALLING) MODELS: TL/TS are signals that facilitate adaptive regulation of organism function. Although telomere shortening per se may or may not be costly (in terms of a potential reduction in Darwinian fitness), monitoring the state of telomere shortening and signalling this to the soma will induce adaptive changes in behaviours/physiological functions/life-history strategy. This will help refine phenotypic plasticity processes, eventually leading to an overall net benefit in Darwinian fitness.

a. Static signal models: telomeres are primarily influenced by parental factors and/or early-life conditions (prenatal or early postnatal) and they are therefore relatively static markers that preset individual life histories. Between-individual differences in TL remain relatively constant after birth.
Parental programming models: parental stress or traits modulate offspring telomere length with long-term consequences for offspring life-history strategy.

(i) Maternal programming models
- Fetal programming of telomere biology hypothesis (Entringer et al., 2018)
- Paternal [age] effects hypothesis (Eisenberg, 2011)

(ii) Paternal programming models
- Maternal age effects hypothesis (this review, see also Asghar et al. 2015a,b)

b. Dynamic signal models: telomere length changes in relation to prevailing internal or external conditions and can therefore act as a signal which induces concomitant adaptive (physiological, behavioural or life history) responses. Between-individual differences in TL can vary significantly over time.

(i) Disease regulation models: TL/TS act as controllers of cellular health.
- Cancer surveillance hypothesis (Young, 2018)
- Telomere-telomerase hypothesis of ageing and cancer (Holt et al., 1996)

(ii) Life history regulation models: changes in TL/TS signal the internal state and can affect an individual’s life-history decisions.
- Life-history regulation hypothesis (Young, 2018, see also Eisenberg, 2011)
- Selective adoption – reverse causation hypothesis (Bateson & Nettle, 2018)
- Telomere messenger hypothesis (Giraudeau et al., 2019, see also Eisenberg, 2011)

influences telomere length/shortening it is, however, important to address whether and how telomeres may have an impact on organism function. This is emphasized in the following sections, which list the hypotheses that have considered functional consequences of telomere length/shortening on organism performance.

4.2 | Models making assumptions about telomere function (II.)

4.2.1 | No causality models (II.A)

Within the group of models making assumptions about telomere function (II), we separate the hypotheses that imply some degree of causality from those that explicitly refute any causal effect of telomere length/shortening on organism function and fitness. This is important for the next lower level of our classification in which we distinguish between hypotheses that propose a mechanism of how telomeres may influence organism function. We therefore group together hypotheses explicitly assuming that changes in telomere length or dynamics per se have no causative consequences for organism function (health) in the cluster “no causality models” (II.A). For these hypotheses, the association between telomeres and Darwinian fitness is correlational. This distinction is important because of the ongoing debate regarding the role of telomeres as a causal agent in ageing and other life-history processes (see above).

We group three hypotheses into the cluster denoted as “no causality models” (II.A, Figure 3, Box 1). These are “non-causal biomarker hypothesis” (Young, 2018; see also Simons, 2015), which assumes that telomere length is solely a marker that can predict life expectancy and disease risk; the “causation hypothesis”, which suggests that an association between behaviour and telomere length comes about through a direct effect of behaviour on telomere shortening and not vice versa (i.e., telomere shortening is a marker of behavioural alterations) (Bateson & Nettle, 2018); and the “selective adoption – third variable hypothesis”, which assumes that the association comes about through another (unknown) factor that directly affects behaviour, but concomitantly also affects telomere shortening (Bateson & Nettle, 2018). In the last hypothesis, telomere shortening per se is assumed not to be directly involved in the processes that (negatively) affect Darwinian fitness.

4.2.2 | Causality models (II.B)

Seventeen of the hypotheses we have identified either implicitly or explicitly assume that changes in telomere length/dynamics have direct consequences for organism function; that is, telomere length/dynamics have a causal effect on Darwinian fitness (rather than just correlated to another factor that is the actual causative agent). We grouped these models into the category “causality models” (II.B). We consider that the well-established “telomere hypothesis of cellular ageing” (Autexier & Greider, 1996; Harley et al., 1992) is basal to all causality hypotheses, and therefore not included in our hierarchical classification. Within the “causality models” cluster, we divide the hypotheses in two major subcategories: the “disruption of function models” (II.B.1) and the “adaptive regulation models” (II.B.2) (Figure 3 and Box 1). The main characteristic that leads us to categorize a hypothesis as a “disruption of function model” is the assumption that telomere shortening will have a negative, disruptive effect on organism function (both general performance or functioning of specific traits such as physiology or behaviour). This is assumed to result in an overall net fitness cost, such as shortened lifespan (due to accelerated ageing) and reduced lifetime reproductive success, for the
individual. According to the hypotheses in this category, organisms are limited in their abilities to mitigate telomere shortening and to alleviate the costs associated with it. In contrast, the "adaptive regulation models" assume that telomere length/shortening operate as "signals" that facilitate adaptive regulation of organism function. Although telomere shortening per se potentially has some negative effects on Darwinian fitness (e.g., for the same reasons as in the "disruption of function models"), the "adaptive regulation models" assume that there is an overall net fitness benefit of monitoring the state of the soma based on changes in telomere length, because it allows for adaptive phenotypic plasticity (i.e., adjustments of behaviour, physiology and/or life-history strategy).

Disruption of function models (II.B.1)—maintenance cost models

Within the category of "disruption of function models", we distinguish between two further subcategories: the "critical threshold models" and the "maintenance cost models" (Figure 3, Box 1). The "maintenance cost models" all share the assumption that maintenance of telomere length (i.e., reducing the rate of shortening or even inducing elongation) entails non-negligible costs (e.g., energetic costs). Hence, they assume a trade-off between investment in maintenance of telomere length and investment in other fitness-related traits, such as reproduction or immediate survival. Moreover, they assume that the maintenance costs arise continuously throughout life (i.e., any change in telomere length from birth until death of the organism will have consequences for organism function). Among the maintenance cost models, we further classified three of the five hypotheses as "cost acceptance models" (Figure 3, Box 1). By that we mean that the costs of maintenance outweigh the benefits; that is, the organism is accepting some degree of telomere loss, at least in its current state/condition, because the organism would have had to pay even larger costs to maintain a certain telomere length. In the "cost acceptance models" category, we include the "costly maintenance hypothesis" (Young, 2018), the "thrifty telomere hypothesis" (Eisenberg, 2011) and the "metabolic telomere attrition hypothesis" (Casagrande & Hau, 2019). These three hypotheses all assume that organisms must tolerate some telomere shortening in order to invest in other fitness-improving functions. However, they differ with respect to the type of physiological costs involved and when they occur during life (see Box 1). Maintenance costs may also have transgenerational effects (e.g., through a trade-off between investment in somatic cells and germline stem cells; Maklavok & Immler, 2016) and may, thus, influence offspring development and life trajectory. This appears to connect "maintenance cost models" to "parental programming models" (see below), although the latter cluster of hypotheses (II.B.2a models in Figure 3) focus on the effects of telomere length/shortening on offspring phenotype, rather than on how maintenance costs come about (as in I.B.1b models in Figure 3).

The second hypothesis in the "cost compensation models" cluster is an additional hypothesis that we outline here (and it is therefore not described above in Grouping I). The "last resort telomere elongation hypothesis" proposes that if there are costs of elongating telomeres (either short-term physiological costs such as energy, or long-term costs such as increased risk of cancer or some other disruptive effect on the soma), an organism will only elongate its telomeres when telomere length has become so short that it is close to the point when cells are becoming dysfunctional. Hence, the organism will venture telomere elongation as a last resort (i.e., a form of terminal investment), which may help it to survive until at least another breeding event. Hence, the "last resort elongation hypothesis" differs from the "[excess resources] elongation hypothesis" with respect to what induces the pattern of telomere elongation and, thus, also which type of individuals are expected to show elongation. For the "last resort elongation hypothesis", the prediction is that individuals with very short telomere length (e.g., old or lower quality individuals) show telomere elongation, whereas the "excess resources elongation hypothesis" predicts that it is individuals of high quality and/or high resource access that show telomere elongation.

Disruption of function models (II.B.1)—critical threshold models

The second subcategory under the disruption of function models we have termed the "critical threshold models". These models assume that telomere shortening has no functional consequences until a critical telomere length (also called the "telomeric brink"); Aviv et al., 2015) is reached. In contrast to the "maintenance cost models", which assume that investment in telomere maintenance needs to be traded off against other fitness functions continuously throughout life, the "critical threshold models" assume that organisms can accrue substantial telomere shortening without any immediate negative effects on Darwinian fitness. Instead, fitness effects will be more dramatic after the critical threshold is reached, because after this point rapid cell death, decrease in organ function and impaired health will set in. We further separate the "critical threshold models" into "individual-level telomere shortening models" and "species-level telomere shortening models" (Figure 3, Box 1). In the "individual-level telomere shortening models" (II.B.1.b.i), the proposed critical threshold for telomere length has consequences over an individual's lifespan. The "telomeric brink hypothesis" (Aviv et al., 2015; Tricola et al., 2018) suggests that it is essentially early-life telomere length that determines and, thus, predisposes an individual's lifespan. Thus, individuals with shorter early-life telomere length will reach the critical threshold at an earlier age, and
the "accumulating costs hypothesis" (Hasselquist & Tobler, 2021) also assumes that negative effects of telomere shortening do not become apparent until a critical threshold is reached. However, in contrast to the "telomeric brink hypothesis", the "accumulating costs hypothesis" proposes that the time it takes for an individual to reach the critical point in telomere length depends critically on the frequency and magnitude of disease/stress episodes experienced during the adult life stages (rather than solely on early-life telomere length) and that the rate of telomere shortening is relatively variable over an individual's own lifetime (Hasselquist & Tobler, 2021).

In contrast to the "individual-level telomere shortening models", the "species-level telomere shortening models" (Figure 3, Box 1 [II.B.1.b.ii]) assume that the critical threshold in telomere length has consequences across (many) generations. The "telomere re-setting hypothesis" (Loxdale & Lushai, 2003; Lushai & Loxdale, 2007) proposes that in facultatively asexual organisms, lineage-specific mean telomere length will become shorter with each subsequent generation eventually causing extinction if telomere length is not "reset" by sexual reproduction. In contrast to the "telomere resetting hypothesis", which refers to a specific group of organisms with facultative asexual reproduction, the "species clock hypothesis" (Stindl, 2004, 2014) proposes that telomere shortening is a species-specific, inherent mechanism that could lead to a telomeric brink for the species (see above in Grouping I for more details).

Adaptive regulation (or signalling) models (II.B.2)
The other large cluster of hypotheses within the "models assuming causality" group is what we term the "adaptive regulation (or signalling) models". The hypotheses that belong to this cluster assume that the process of telomere shortening may be negative, in terms of, for example, loss of cell functions and increased cell death, but also that there is a benefit in using telomere structure or shortening as a cellular signal/tracker for internal (physiological) and environmental state. The reason for this is that it may allow adaptive adjustment of an individual's behaviour and life-history strategy and, thus, induce a reduction in the potential "costs" imposed on the individual due to its current lifestyle. We further categorized hypotheses in the "adaptive regulation models" cluster into "static signal models" and "dynamic signal models" (Figure 3, Box 1), based on whether telomere length/shortening is seen as a "static" signal that is perceived early in life (e.g., during early development) inducing more or less permanent effects on physiology and/or behaviour (for the rest of the individual's life) (II.B.2a), or whether telomere length/shortening is viewed as a "continuous" signal that can alter life-history trajectories also later in life (II.B.2b).

Adaptive regulation models—Static signal models (II.B.2a)
As static signal (or parental programming) models, we consider hypotheses which assume that telomere length/shortening is primarily influenced by embryonic and early life conditions (prenatal or early postnatal). There is evidence that offspring telomere length can be affected by nongenetic (environmental) conditions that directly or indirectly (i.e., through parental behaviours and experiences, e.g., parental stress exposure during the prenatal period) affects the neonate, with long-lasting consequences for offspring life-history trajectory (e.g., Entringer et al., 2018; Monaghan & Ozanne, 2018). Thus, in the "static signal models" category of hypotheses, telomere length is assumed to preset the life-history trajectory of an individual already early in life and, hence, that between-individual differences in telomere length remain relatively constant after birth. We group three hypotheses among the "static signal models" and divide them further into "maternal programming" and "paternal programming" models. In all three cases, telomere length/shortening early in life are assumed to determine how much the offspring should invest in future somatic maintenance. The "fetal programming of telomere biology hypothesis" (Entringer et al., 2012, 2018) suggests that offspring telomere dynamics are "programmed" through environmental conditions affecting the mother's physiological state and stress level during the prenatal (pregnancy) and postnatal periods and that this will have long-lasting effects on the offspring phenotype (Entringer et al., 2012, 2018). Importantly, any changes in offspring telomere length mediated by conditions experienced by the mother during the pre- and postnatal periods are assumed to have causal effects on offspring life trajectory and fitness. The influence of the mother on offspring telomere length and dynamics can either be passive (caused by, e.g., maternal stress hormones that are transferred to the neonate) or active (adaptive maternal programming of offspring phenotype). In contrast, the "paternal effects hypothesis" (Eisenberg, 2011) proposes that permanent adaptive adjustment of offspring physiology is achieved through age-specific inheritance of paternal telomere length. We note that the "paternal effects hypothesis" is quite specific as it focuses solely on paternal age effects, and we therefore rename it the "paternal [age] effects hypothesis" in our hierarchical classification (Figure 3, Box 1). It should be contrasted with a "maternal age effects hypothesis" that assumes an effect of maternal age on offspring telomere length. It builds on studies that have found positive relationships between maternal age and offspring telomere length (Asghar et al., 2015a, b; Marasco et al., 2019). Such positive relationships between mother age and offspring telomere length may either reflect that older mothers generally are of higher quality and therefore able to produce high-quality offspring with longer telomeres, or that older mothers somehow realize that they are close to death and therefore make a terminal investment (Clutton-Brock, 1984; Part et al., 1992) by producing offspring with longer telomeres.

Overall, the hypotheses in the "static signal models" cluster propose that environmental conditions or parental programming in early life will set a relatively static telomere length trajectory in the offspring, resulting in deterministic consequences for offspring quality and/or life-history strategy. The idea that early-life telomere length determines the life-history trajectory of an individual is shared with the "telomeric brink hypothesis" (Aviv et al., 2015, see critical threshold models II.B.1). However, the latter hypothesis assumes that early-life telomere length is genetically determined and...
thus independent of the environmental and/or parental programming factors that the offspring is exposed to during the embryo and neonatal stages.

Adaptive regulation models—Dynamic signal models (II.B.2b)
The second cluster within the adaptive regulation (signalling) models are the "dynamic signal models". In contrast to the "static signal models" discussed above, telomere length is assumed to shorten in response to prevailing cell, organ or organism state or in response to environmental conditions. Telomere shortening is assumed to act as an intrinsic signal to the organism that can induce adaptive physiological, behavioural and life-history responses. In these hypotheses, the critical assumption is that the rate of telomere shortening is not constant after birth, and that the relative difference in telomere length between individuals therefore is assumed to vary significantly when measured at different points in time (i.e., individual telomere length trajectories can cross each other over time).

Changes in telomere length reflect (and thus "signal") changes in organism function (at the cellular, organ or soma level). We distinguish between two types of models proposing that telomere length/shortening is perceived as a dynamic signal: "disease regulation models", in which telomere shortening acts as a controller of cellular health, and "life-history regulation models", where telomere shortening acts as a signal of internal (somatic) state modulating life-history decisions (Figure 3, Box 1). Here, we list two explicitly named hypotheses under the "disease regulation models" (although there are probably more alternatives in the field of medicine), the "telomere-telomerase hypothesis of ageing and cancer" (Holt et al., 1996; see also Shay et al., 1995; de Lange & Jacks, 1999; Shay, 2016) and the "cancer surveillance hypothesis" (Young, 2018). Both these hypotheses view telomere length/shortening as an anticancer protection mechanism (see above), and have in common that they suggest that the benefit of cancer suppression earlier in life may outweigh the costs of age-related pathologies later in life (which is congruent with the antagonistic pleiotropy theory of ageing; Kirkwood & Rose, 1991; Williams, 1957).

The "disease regulation models" focus on controlling the internal health state of an organism, where telomere length helps to coordinate cellular responses to tumour growth. In contrast, the "life-history regulation models" propose that telomere length/shortening is strategically used as a cellular "signal" that enables adaptive adjustments of the behaviour and life history of an individual. The "life-history regulation hypothesis" (Young, 2018) and the "selective adoption - reverse causation hypothesis" (Batson & Nettle, 2018) both assume that telomere length/shortening is used as a physiological signal that helps the organism match its internal (physiological) state to an optimal life-history strategy. This idea is somewhat reminiscent of two hypotheses from the previously mentioned cluster of "disruption of function models" (II.B.1), in which both the "thrifty telomere hypothesis" (Eisenberg, 2011) and the "metabolic telomere attrition hypothesis" (Casagrande & Hau, 2019) suggest that telomere length could have a dynamic regulatory function on metabolic processes or immune function over life by signalling (cellular) energy debt, and thereby affect life-history trade-offs. However, in contrast to these latter two hypotheses, the "life-history regulation models" assume that telomere shortening has an overall positive effect on Darwinian fitness, irrespective of the mechanisms involved in the direct regulatory effects. This is because by monitoring telomere length and using this signal to make changes in behaviour and lifestyle, individuals will behave optimally given the current circumstances for the soma, thus providing net benefits in terms of Darwinian fitness.

A third hypothesis within the life-history regulation models is the "telomere messenger hypothesis" (Giraud et al., 2019). It is an extension of the two other hypotheses in this category as it assumes that changes in telomere length/shortening can also reflect fluctuations in the environment (i.e., not solely internal organismal changes). Under this hypothesis, organisms may use telomere length/shortening to actively adjust their behaviour and life-history decisions in relation to the environment. Furthermore, it also states that telomeres may act as a filter through which genetic correlations between parents and offspring are expressed, resulting in offspring being better adapted to the environment they are born into (see also discussion about paternal inheritance of telomere length in relation to age in Eisenberg, 2011; Eisenberg & Kuzawa, 2018). The "telomere messenger hypothesis" also shares the idea of adaptive intergenerational plasticity with the two parental programming hypotheses in the static signal models cluster (Eisenberg, 2011; Entringer et al., 2012, 2018). However, in contrast to the static signal models, the "telomere messenger hypothesis" assumes that life-history strategies are flexible and can be adjusted later in life (i.e., beyond the early life period).

5 | DISCUSSION AND SYNTHESIS

The aim of grouping the different name-given hypotheses was to provide frameworks within which the hypotheses can be compared so that differences and/or parallelisms can be highlighted. The reason for this is that the rapidly increasing number of name-given hypotheses can make it difficult to identify and refer to clusters of related hypotheses. Moreover, it is also clear from both our groupings that there exist parallel lines of thoughts in different research fields that researchers should be aware of.

It may be argued that the set of hypotheses presented in this review could be biased, as it reflects a particular way of presenting specific research findings (e.g., if naming hypothesis is more likely when trying to explain idiosyncratic results). However, we argue that the opposite is true. Researchers are more likely to give names to a hypothesis when reviewing the state of a field, when conceptualizing an idea or when there has been accumulating evidence for certain associations. This is true for all except two hypotheses in the first classification, the selection hypothesis and the elongation hypothesis, which discuss a specific research result for which there are no earlier corroborating studies (Haussman & Mauck 2008). Hence, what we present here should give a relatively unbiased picture of the current lines of research related to "telomeres in ecology..."
and evolution”. Consequently, these hypotheses are likely to be referenced by other researchers and to have an important influence on research related to telomeres in, for example, the fields of life history and ageing. What we have identified as “gaps” are areas of research where there is further potential for conceptualization and review, but where there are already a substantial number of studies. Our classifications might also be used to identify further conceptual gaps.

Our first grouping is more conventional, presenting each hypothesis in relation to its research context (i.e., it is based on research questions). It illustrates from which field a particular hypothesis has originated and provides a very brief overview of the current state of research. Moreover, it helps to identify controversies in the different fields, such as the different ideas about the rate of telomere shortening (constant vs. variable) and its potential impact on organism performance. In contrast, in the hierarchical grouping hypotheses we tried to sort hypotheses independent of research context. Hypotheses framed in different organism groups or research fields, but that share a similar context, can therefore end up in similar clusters (e.g., the critical threshold models) and this can illustrate associations and similarities between them that previously may not always have been obvious. In the following sections, we discuss the outcome of the hierarchical classification in more detail.

The first clustering in the hierarchical framework is not based on conceptual differences, but instead driven by a necessity to separate out models that make no assumptions about telomere function. The “no assumption models” cluster includes hypotheses that do not provide explicit assumptions and/or do not generate predictions about occurrence or direction of causality of telomere length/shortening. It is noteworthy that the hypotheses in the “no assumption models” cluster were not formulated due to lack of knowledge (i.e., in the early days when the “research field” of telomere ecology and evolution was emerging), because three of the four hypotheses have been formulated after 2014 (Figure 1). Instead, we believe that this reflects the fact that researchers working on telomeres in “ecology and evolution” have been cautious about the role of telomeres as a causal mediator of life-history trajectories (e.g., Bateson & Nettle, 2018; Monaghan et al., 2018; Young, 2018) and this no doubt owes to the difficulty of finding evidence for such a role. However, it might be useful to discuss “no assumption models” in a framework of causality/no causality to gain a better understanding how the reported associations come about. One could, for example, view the “individual quality hypothesis” in the context of “cost maintenance models” in which only individuals that can afford the costs of maintaining telomere length are high-quality individuals. This may lead to more specific predictions about variation in telomere length/shortening and, thus, facilitate testing.

The second dichotomy in our hierarchical classification is the one between models assuming causal effects of telomere dynamics on Darwinian fitness and models that do not assume such causal effects. Our classification illustrates that the question of whether telomere shortening has a causal impact on the life history and Darwinian fitness of an organism has been and remains one of the most critical questions in telomere biology. It is noteworthy, however, that most of the hypotheses in our classification assume that either a critical telomere length or (variation in) telomere shortening rate directly cause changes in life history and/or physiological factors (energy balance, growth, reproductive investment, senescence, survival, etc.) that directly or indirectly affect Darwinian fitness. Thus, one might interpret this as a tentative consensus that, at least on the conceptual level, telomeres have the potential to play a role as mediators of life history trade-offs. It is clear, however, that finding ways to experimentally manipulate telomere length or telomere repair mechanisms is key to move forward, and that this will be an important challenge for future research (see, e.g., Criscuolo et al., 2018).

The third main dichotomy which stands out in our hierarchical classification is the one between “disruption of function models” and “adaptive regulation models”. The difference between these two clusters is not always straightforward, especially because the costs envisioned to underly the different hypotheses may be similar (e.g., adaptive regulation models do not necessarily exclude energetic costs of maintaining telomere length). This is also reflected in the “metabolic telomere attrition hypothesis”, which besides pointing out energy limitations as a key to why telomere length erosion may disrupt body functions, also attributes telomeres a role as a “master regulator” of cell homeostasis (Casagrande & Hau, 2019). However, the main difference between the “disruption of function models” and the “adaptive regulation models” is that the former focus on the costs (both physiological and Darwinian fitness costs) entailed due to telomere shortening, whereas the latter focus primarily on the usefulness of telomere shortening (i.e., potential benefits that can be gained from an essentially unescapable process). We also note that the latter view, namely that telomere shortening rate may have a valuable function as a signal of current organism state and/or environmental conditions, is relatively recent. All the hypotheses concerning signalling (II.B.2 in the hierarchical grouping), except the cancer surveillance hypothesis, have been formulated within the last decade (Figure 1). They have therefore not yet been thoroughly tested as alternatives to the “disruption of function models”. Manipulating or disrupting the factors that are considered to be monitored by the telomeric signal may provide a fruitful avenue for future research.

Our classifications provide overviews but do not state which hypothesis may be more relevant or general than others. Although in our view none of the listed hypotheses can be completely refuted or proven to be right at this point in time, one might nevertheless question the inclusion of some hypotheses in our classifications as they may be considered less relevant. For example, the “[excess resources] elongation hypothesis” was originally formulated based on the finding that telomeres appeared to lengthen with age in a cross-sectional study on Leach’s storm petrel (Oceanodroma leucorhoa) (Haussmann & Mauck, 2008). The hypothesis was refuted in the same study in which it was proposed, based on the data available. However, we consider that the “[excess resources] elongation hypothesis”, like other hypotheses included here, propose interesting
concepts that may be important for current research and our future understanding of telomere dynamics and function in the context of ecology and evolution. It might well be that the elongation hypothesis deserves its merit. There are, for example, an increasing number of longitudinal studies that report telomere elongation with age in some individuals (e.g. Asghar et al., 2018; Canestrelli et al., 2021; Hoelzl, Smith, et al., 2016; Seeker et al., 2020; Spurgin et al., 2018; Vernasco et al., 2021). Thus, it is possible that telomere length/shortening are flexible traits that can vary over life in a more dynamic fashion than previously thought. This is an area which is in need of further conceptualization, and it is in this context we propose the "last resort telomere elongation hypothesis".

6 | CONCLUSIONS

The increasing number of name-given hypotheses during the past 5 years may suggest that concepts related to telomeres in ecology and evolution are becoming more "established", in line with the rapidly growing number of empirical and theoretical studies. Our review of hypotheses related to "telomere ecology and evolution" gives a brief overview of the current research directions and our classifications show that there is considerable overlap in lines of thought and theory, but also that there are various unresolved controversies. Hence, we anticipate a vibrant future for research on telomeres in the context of ecology and evolution, and we hope our review will stimulate future research and collaborations to further disentangle, verify or falsify the different hypotheses in the field.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

M. To. and D.H. conceived the original idea and formalized it with input from all authors. All authors helped to screen the literature for telomere hypotheses, summarize and group them into clusters. M. To. drafted the original manuscript. M. To. and D.H. revised the draft with substantial contributions from all authors.

DATA AVAILABILITY STATEMENT

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

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