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Decline in telomere length with increasing age across non-human vertebrates: a meta-analysis

Short title: Telomere attrition across non-human vertebrates

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23 **Abstract:**

24 The prediction that telomere length (TL) shortens with increasing age is a major element
25 in considering the role of telomeres as a key player in evolution. While telomere attrition is
26 found in humans both *in vitro* and *in vivo*, the increasing number of studies reporting diverse
27 age-specific patterns of TL challenges the hypothesis of a universal decline of TL with
28 increasing age. Here we performed a meta-analysis to estimate the relationship between TL and
29 age across 175 estimates encompassing 98 species of vertebrates. We found that, on average,
30 TL does decline with increasing age during adulthood. However, this decline was weak and
31 variable across vertebrate classes, and we also found evidence for a publication bias that might
32 weaken our current evidence of decreasing TL with increasing age. We found no evidence for
33 a faster decline in TL with increasing age when considering the juvenile stage (from birth to
34 age at first reproduction) compared to the adult stage. Heterogeneity in TL ageing rates was
35 explained by the method used to measure telomeres: detectable TL declines with increasing age
36 were found only among studies using TRF with in-gel hybridisation and qFISH methods, but
37 not in studies using qPCR and Southern blot-based TRF methods. While we confirmed that TL
38 declines with increasing age in most adult vertebrates, our results identify an influence of
39 telomere measurement methodology, which highlights the need to examine more thoroughly
40 the effect of the method of measurement on TL estimates.

41

42 **Keywords: Ageing, Telomere attrition, Life-history traits, Systematic review, Telomere**
43 **Restriction Fragment, qPCR**

44

45 **Introduction:**

46

47 Telomeres are composed of non-coding DNA sequences repeated in tandem (TTAGGG
48 in most animals) at the extremity of chromosomes in eukaryotes (Blackburn, 1991). Telomeres
49 prevent chromosomal fusions during mitosis and play an essential role in chromosomal
50 segregation during cell division (Aubert & Lansdorp, 2008). However, each time a cell
51 replicates, DNA polymerase is unable to fully replicate the 5'-3' strand (the so-called "end-
52 replication problem") leading to a loss of nucleotide sequences (Levy et al., 1992). This
53 telomere attrition has attracted a lot of attention because short telomeres can be responsible for
54 chromosomal fusions, and ultimately lead to replicative cell senescence and apoptosis.
55 Although telomere length (TL) declines with each mitotic cell cycle due to the end-replication

56 problem, oxidative damage on telomeric DNA is another mechanism involved in accelerated
57 telomere attrition (von Zglinicki et al., 2001; Reichert & Stier, 2017). Accumulation of
58 oxidative damage, known as oxidative stress, is favoured when the generation rate of reactive
59 oxygen species (ROS) exceeds the antioxidant machinery. ROS are highly reactive and cause
60 damage to nucleic acids, proteins and lipids. Because of their guanine rich structure, telomeres
61 are highly sensitive to oxidative damage (Kawanishi & Oikawa, 2006). Telomere erosion
62 patterns can be modulated by the activity of telomerase. This enzyme is a reverse transcriptase
63 that adds telomeric repeats and can potentially compensate telomere shortening (Sherratt et al.,
64 2004). In mammals, the activity of telomerase in most somatic cells is negatively linked to the
65 species body mass and is mostly expressed (at least in fibroblasts) in species weighing less than
66 2kg (Gomes et al., 2011) and in very proliferative tissue (e.g. antlers in cervids; Li, 2012). In
67 birds, high telomerase activity was found in bone marrow in two long-lived species but not in
68 two short-lived species (Hausmann et al., 2007). Telomerase activity was found in somatic
69 tissue in the limited number of fish, reptiles and amphibians studied to date (Gomes et al., 2010),
70 which suggests different telomere dynamics compared to birds and mammals. However,
71 available data remain scarce and little is known about telomerase activity in vertebrates and the
72 effect of this activity on age-related telomere dynamics.

73 Early research on telomere dynamics in humans found that TL consistently declines
74 with increasing age in cultured fibroblasts (Harley et al., 1990) and the research that has been
75 done on human's telomere dynamics since (Aubert et al., 2012; Lapham et al., 2015) has led to
76 the same conclusion. The shortening of telomere repeats is now considered as a marker of
77 ageing (López-Otín et al., 2013) and telomere length is known to predict subsequent morbidity
78 (Herrmann et al., 2018). In addition, shorter telomeres are linked to an increased mortality risk
79 in both humans and non-human vertebrates (Wang et al., 2018; Wilbourn et al., 2018).
80 Telomere length and dynamics have also been linked to growth (Monaghan & Ozanne, 2018)
81 and reproduction (Sudyka 2019), conferring them a possible key role in mediating life-history
82 trade-offs. Since the early 2000s, we have witnessed a burst of studies measuring TL in
83 laboratory animals and wild populations (Monaghan et al., 2018). Similarly to the patterns
84 observed in humans, most of these studies reported a decline in TL with increasing age (e.g.
85 Pauliny et al., 2006 in two species of birds, the dunlin (*Calidris alpina*) and the sand martin
86 (*Riparia riparia*), Beirne et al. 2014, in the badger (*Meles meles*)). However, other studies
87 reported no decline (e.g. Horn et al., 2011 in the kakapo, *Strigops habroptilus*; Lewin et al.,
88 2015 in the spotted hyena, *Crocuta crocuta*) or even an increase in TL with age (Hoelzl et al.,

89 2016 in the edible dormouse, *Glis glis*; Ujvari & Madsen, 2009 in the water python, *Liasis*
90 *fuscus*). Patterns of telomere attrition also vary within species, which suggest that
91 environmental conditions might to some extent also modulate telomere dynamics (Salmón et
92 al., 2016; Wilbourn et al., 2017). Various patterns (*i.e.* an increase, a decrease or no relationship
93 of TL with age) that has been reported across all classes of vertebrates calls into questions the
94 hypothesis that TL is a universal marker of ageing. Here, we use meta-analyses to test whether
95 or not the decline in TL with increasing age constitutes a general pattern in vertebrates. We also
96 aim to identify factors that could modulate the strength of the decline in TL with increasing
97 age, and determine whether these are ecological, biological or methodological.

98 One factor that might explain variation in the relationships reported between TL and
99 age among vertebrates is phylogeny. Indeed, telomerase is differentially expressed throughout
100 life across taxa and across species within taxa (Gomes et al., 2010; Olsson et al., 2018). Besides
101 telomerase expression, fish, reptiles and amphibians are indeterminate growers (in contrast with
102 birds and mammals), which might influence the relationship with age. Indeed, somatic growth
103 is linked to an increase in cell division and oxidative stress that will impair TL (Monaghan &
104 Ozanne, 2018). It is then expected that organisms that grow throughout their life should display
105 different age-specific patterns of TL than determinate growers.

106 Related to phylogeny, the decline in TL with increasing age might vary with the species-
107 specific life history. So far, studies have highlighted that telomere attrition rate negatively
108 correlates with maximum lifespan in birds (Dantzer & Fletcher, 2015; Tricola et al., 2018) and
109 more generally that telomere attrition rate is linked to the species position along the slow-fast
110 continuum of life histories (Dantzer & Fletcher, 2015), with fast-living species (*i.e.* short-lived
111 species that start to reproduce early and produce several offspring per year) displaying steeper
112 rates of telomere attrition than slow-living species (*i.e.* long-lived species that start to reproduce
113 late and produce one offspring or less per year). The difference in telomere attrition rate
114 between short- and long-lived species might be due to a difference in telomerase expression
115 between those species or a lower level of oxidative stress in long-lived species than in short-
116 lived ones (Tricola et al., 2018; Vágási et al., 2019). However, this relationship has not yet been
117 investigated in non-avian taxa, due to an evident lack of studies available. Besides the slow-fast
118 continuum, we should observe different patterns of telomere dynamics, at least in mammals, in
119 different-sized species because the activity of telomerase is higher in mammal species weighing
120 less than 1kg (Gomes et al., 2011).

121 In addition, because TL shortens with each mitotic cycle and cellular division may occur
122 at a faster rate during the growth period, this may lead to a steeper decline in TL during the
123 juvenile stage than during the adult stage (Monaghan & Ozanne, 2018). Substantial telomere
124 loss has been found during the embryonic and the nestling stages in three species of birds
125 (Boonekamp et al., 2014; Stier et al., 2020; Vedder et al., 2017) compared to adults. In addition,
126 greater telomere shortening throughout the juvenile stage compared to the adult stage has been
127 observed in some bird species (Hall et al., 2004; Pauliny et al., 2006) as well as in mammals
128 (Aubert et al., 2012; Fairlie et al., 2016; Frenck et al., 1998; Seeker et al., 2018). A human-
129 based mathematical model further suggests that the rapid telomere loss during the juvenile stage
130 (a four-fold difference between juvenile and adult stages, (Zeichner et al., 1999)) could be
131 explained by a higher turnover rate of peripheral mononuclear cells in children than in adults
132 (Sidorov et al., 2004). Hence, depending on the life stage analysed, the relationship between
133 TL and age may not be consistent.

134 The type of data collected might also influence the reported patterns. Indeed, because
135 short telomeres might be associated with a higher mortality risk (e.g. Bichet et al., 2020; Bize
136 et al., 2009; Wilbourn et al., 2018), the selective disappearance of individuals carrying short
137 telomeres could lead to underestimation of the age-specific decline in TL with increasing age
138 (see also Nussey et al., 2008 for a broader discussion of the importance of considering selective
139 disappearance in the context of senescence). Therefore, the analysis of age-specific TL data
140 collected from longitudinal studies, where known-aged individuals are regularly sampled
141 throughout their life, will provide a much more accurate pattern of the changes in TL with
142 increasing age.

143 Finally, the method used to measure TL is known to be a source of heterogeneity in TL
144 that potentially influences age-specific patterns. Currently, three methods are generally
145 employed (Nussey et al., 2014), which provide absolute or relative measures. The first
146 technique used is the telomere restriction fragment method (TRF), which involves the use of
147 restriction enzyme to digest the genomic DNA without cutting within the telomeric fragment.
148 Telomeric fragments are then separated by gel electrophoresis and probed with telomeric
149 sequences providing an absolute measure of the mean TL in a sample of cells (Harley et al.,
150 1990). Two different types of TRF have been developed: TRF with in-gel hybridization
151 (hereafter TRFI) and TRF followed by a southern blot (hereafter TRFS). In TRFI the probe
152 binds to the single-stranded overhang of the telomere and therefore only telomeres at
153 chromosome ends are measured. In contrast, DNA is denatured in TRFS and the probe binds

154 not only to terminal telomeres but also to interstitial telomeric sequences, which are telomere
155 repeats located all along chromosomes, that can vary in length both between and within species
156 (Foote et al., 2013). The second technique is the quantitative real time PCR method (qPCR) and
157 gives a relative measure of TL by amplifying telomeric fragments and a non-telomeric reference
158 gene that does not vary in copy number (Cawthon, 2002). As for TRFS, qPCR amplifies both
159 telomeres and interstitial telomeric sequences. Finally, the quantitative fluorescent in situ
160 hybridisation (qFISH) technique uses a specific fluorescent-conjugated telomere probe to
161 quantify average TL from tissues or isolated cells (Lansdorp et al., 1996). It is important to
162 mention that methodologies are not equally distributed across the phylogeny. Indeed, while
163 qFISH methodology is barely used in ecology, TRFI is mostly used in birds. In a previous meta-
164 analysis looking at sex differences in TL in humans (Gardner et al., 2014), TL was found to be
165 longer in women only in studies using the TRF (TRFS and TRFI pooled) method. In a meta-
166 analysis linking TL and mortality in vertebrates (Wilbourn et al., 2018), the negative
167 relationship between TL and mortality was stronger in studies using qPCR.

168 We performed a phylogenetically-controlled meta-analysis to examine the relationship
169 between TL and age in non-human vertebrate species. We predicted that telomere dynamics
170 with age should vary depending on the class of vertebrates due to differences in telomerase
171 expression. More precisely, we expected a stronger decline in species where telomerase
172 expression seems to be repressed (e.g. large mammals and short-lived birds). We also predicted
173 that TL declines on average with increasing age across vertebrates but with a steeper decline
174 during the juvenile than the adult stage. Based on both theoretical aspects and previous
175 empirical studies, we also predicted that the decline in TL should be more pronounced in short-
176 lived species, since the TL decline is fastest in short-lived species of birds. We also predicted
177 that the decline in TL with increasing age is more likely to be recorded in longitudinal studies
178 due to selective disappearance in transversal studies. All analyses were corrected for the method
179 used to measure telomeres and associated heterogeneity was calculated to assess whether the
180 method used influenced the detected association between telomere length and age.

181

182 **Material and methods:**

183 1) Literature search

184 The literature search was performed using the ISI Web of Science Database in December
185 2019 and updated in May 2021. Key words used in the Topic window for the search were

186 telom* not (clinic OR hospital). The keyword telom* was used instead of telomere to ensure
 187 studies on telomerase were included in the results. By using “not (Clinic OR hospital)” we also
 188 avoided a lot of articles from medical literature. We restricted our search to the following
 189 categories: “*Evolutionary biology*”, “*Marine Freshwater Biology*”, “*Multidisciplinary*
 190 *sciences*”, “*Geriatrics gerontology*”, “*Physiology*”, “*Zoology*”, “*Environmental sciences*”,
 191 “*Fisheries*”, “*Ecology*”, “*Agriculture dairy animal sciences*”, “*Veterinary sciences*”. We
 192 limited our search to articles providing TL estimates for known age individuals of vertebrate
 193 species. Since the main goal of our analysis focused on the non-manipulated decline of TL with
 194 increasing age we excluded studies of laboratory strains of mouse and rat as well as
 195 experimental studies (e.g. pathogen infection, diet experiment etc.). We found very few studies
 196 (i.e. 4 studies only in birds) that measured TL at different time point during the first month of
 197 life. Hence, we decided to include only studies that covered more than the first month of life in
 198 the juvenile stage to avoid this very limited number of studies that focus solely on the first
 199 month of life due to a manifest lack of data. When data were not available within the main text
 200 or supplementary materials, we requested the dataset directly from the authors. Thirty-two (out
 201 of 43) authors kindly provided their dataset. At the end of the literature survey, we ended up
 202 with 87 articles (See **Figure 1**).

203

204 2) Effect size calculation

205 To assess the relationship between TL and age, we calculated Fisher’s Z transformation of
 206 the correlation coefficient using the following procedure. We first fitted either a linear model
 207 between TL and age for transversal studies or a linear mixed-effects model (package *lme4*
 208 (Bates et al., 2020)) with individual identity as a random factor for longitudinal studies. We
 209 then computed the correlation coefficient:

$$210 \quad r = \frac{t * \left(1 + \frac{Ni}{No} * R\right) * \sqrt{1 - R}}{\sqrt{t^2 * \left(1 + \frac{Ni}{No} * R\right)^2 * (1 - R) + No - k}}$$

211 with t being the t-value of the linear regression, Ni being the number of individuals, No the
 212 number of observations, k the number of parameters including the intercept and R the intra-
 213 class correlation (Nakagawa & Cuthill, 2007). In the case of transversal studies (i.e. studies
 214 without repeated measurements), the formula become:

215
$$r = \frac{t}{\sqrt{t^2 + df}}$$

216 because in this case $R = 0$, $N_i/N_o = 1$ and the number of degree of freedom df is $N_o - k$.

217 We finally transformed the correlation coefficient to Fisher's Z :

218
$$Zr = \frac{1}{2} \log\left(\frac{1+r}{1-r}\right)$$

219 And we calculated the sampling variance associated:

220
$$Vz = \frac{1}{Ni - 3}$$

221

222 Zr was used over the correlation coefficient because Zr is normally distributed and thus
223 not bounded between -1 and 1 unlike the correlation coefficient. A negative effect means a
224 decrease of TL with increasing age, whereas a positive effect means an increase of TL with age.
225 Following the Cohen's rule of thumb (Cohen, 1977), absolute values of Zr of 0.25, 0.5 and 0.75
226 represent low, moderate and strong relationship, respectively

227 Fisher's z was calculated separately in juveniles and adults (*i.e.* before and after the species-
228 specific age at first reproduction, defined as the earliest age at which females give birth). We
229 also calculated Zr on data combining juveniles and adults ('all age-classes' dataset), which leads
230 to three distinct datasets.

231 3) Moderators included

232 To investigate the various factors that could explain the direction and the magnitude of the
233 relationship between TL and age, we included the following moderators as covariates in the
234 meta-analytic models:

- 235 - The age at first reproduction (hereafter AFR) of the species was used as a proxy of the
236 slow-fast continuum of life histories (Gaillard et al., 2005).
- 237 - The mean body mass of adult females for each species was included since body mass is
238 negatively correlated with telomerase expression in mammals (Gomes et al., 2011).
- 239 - The method of telomere measurement was included as a four-level factor: TRFI, TRFS,
240 qPCR and FISH.
- 241 - The type of study was included as a two-level factor ("Transversal" vs. "Longitudinal").

242 - The ratio of the age range covered by the data (hereafter lifespan coverage) corresponds
243 to the age range covered by the data divided by the maximum lifespan of the species.
244 With a wider lifespan coverage, we expected a more accurate estimate and so a higher
245 probability to detect a change in TL with age. However, this moderator was not tested
246 on the juvenile dataset because the age range was inevitably too low in this specific
247 case.

248 All species information (*i.e.* AFR, mean adult female body mass and maximum lifespan)
249 was retrieved in the literature (**See Supplementary material**).

250

251 4) Meta-analysis

252 The meta-analysis was performed using R (version 4.0.2) (R Core Development Team,
253 2020). Phylogenetically-corrected mixed effect models were run using the package *metafor*
254 (Viechtbauer, 2010). To assess phylogenetic relatedness, since there is no single pan-vertebrate
255 phylogeny, a phylogenetic tree was built using the website <http://www.timetree.org/> (Kumar et
256 al., 2017). A correlation matrix of phylogenetic relatedness among the species was then
257 extracted from the tree.

258 Random-effects meta-analytic models were performed with the effect sizes entered as
259 the dependent variable along with the sampling variance associated with each effect size
260 included in the model. The phylogeny (using the phylogenetic distance matrix), the population
261 and the species independently of the phylogeny were included as random factors. The same
262 model was used for each age class (juvenile, adult and ‘all age classes’ datasets) (See **Table 1**
263 for a summary of the data analysed). To quantify heterogeneity in our data accounting for
264 random factors, we estimated I^2 for each random factor (*i.e.* the percentage of the total variance
265 explained by each random factor) as well as I^2 total (*i.e.* the percentage of the total variance
266 explained by the between-study variance) following Nakagawa & Santos (2012).

267 First the overall association between TL and age was quantified using the intercept
268 model (*i.e.* null model). Next, we added the taxonomic class as a fixed effect to analyse the
269 heterogeneity between vertebrate classes. Finally, to explain the variability in the association,
270 we built a full model that included the moderators listed above as fixed effects for the dataset
271 on adults and on ‘all age classes’. For the dataset on juveniles, we tested the same moderators
272 but we removed the lifespan coverage. For all models, AFR and body mass were log-
273 transformed to improve normality. Since results from the ‘all age classes’ dataset were

274 qualitatively the same as results from the adult dataset, we decided, for the sake of clarity, to
275 present only the results on juveniles and on adults in the main text. Results on the ‘all age
276 classes’ dataset are therefore presented in **Supplementary (Table S1-S4 and Figure S1-S4)**.
277 To avoid the use of multiple correlated proxies of life-history (See **Supplementary, Table**
278 **S11**), AFR and body mass were included separately in the full model. Since results did not
279 change qualitatively whether we used AFR or body mass, we decided to present results using
280 only the AFR. In addition, the use of phylogenetically-controlled mixed models allowed us to
281 test the effect of different life history variables while accounting for the phylogenetic
282 relatedness among species. The sex of individuals might be a source of heterogeneity in
283 telomere dynamics as males and females of the same species might have a different relationship
284 between TL and age (Barrett & Richardson, 2011; but see Remot et al., 2020). However, due
285 to a high number of studies that did not report information regarding the sex of the individuals,
286 we analysed the effect of sex separately and these results are presented in supplementary section
287 (**See Supplementary, Table S5-S7**). For this complementary analysis, we built a new dataset
288 by calculating Zr for each sex separately.

289 Models with every possible combination of fixed effect were then compared using the
290 corrected Akaike Information Criterion (AICc) using the *MuMIn* package (Bartoń, 2019),
291 selecting the model with the lowest AIC value. When models were within two AICc units, the
292 simpler model was retained (Burnham & Anderson, 2002).

293 Orchard plots were used to visualize the results from both meta-analyses and meta-
294 regressions (Nakagawa et al., 2019). The orchard plot displays the estimate of the model and
295 its confidence interval. In addition, it also displays the prediction interval and the effect size of
296 each study allowing us to visualize precisely the heterogeneity in the data. Orchard plots were
297 drawn using the package *orchaRd* (Nakagawa et al., 2019).

298 5) Publication bias:

299 To test for possible publication bias, we used contour-enhanced funnel plots to represent
300 the precision of each study (*i.e.* the inverse of the standard error) against the estimate of the
301 study. When the data points are symmetrically distributed around the mean, this indicates an
302 absence of publication bias. In addition to funnel plots, we performed an Egger’s regression
303 (Egger et al., 1997), which is a linear regression of the mean of each study against their
304 precision. However, because means are not independent, we fitted the linear regression on the
305 residuals of the meta-analysis (which are independent) against its precision. In absence of

306 publication bias, the intercept of the regression should not differ from zero. To confirm and to
307 assess the influence of the publication bias, the trim and fill method was used (Viechtbauer,
308 2010). This method estimates the number of missing studies on one side of the funnel plot and
309 provides an adjustment of the meta-analysis mean according to those missing studies.

310

311 **Results:**

312 1) Meta-analyses in juveniles and in adults

313 In our meta-analyses, the relationship between TL and age was weak and negative. The
314 negative relationship was statistically significant in adults (estimate and 95% CI: -0.16, [-0.26:-
315 0.06]) but not in juveniles (estimate and 95% CI: -0.13, [-0.50:0.24]). However, estimates in
316 adults and in juveniles were not detectably different, as their confidence intervals overlapped;
317 **Table 2, Figure 2 and Figure 3).**

318 2) Heterogeneity analysis

319 The total heterogeneity was high and similar for juveniles (I^2 total = 84.06%) and adults
320 (I^2 total = 83.94%). In juveniles, the total heterogeneity was mainly due to the phylogeny (I^2
321 phylogeny = 54.51%) and the heterogeneity within populations (I^2 population = 29.55%).
322 However, the species independently of the phylogeny and the population explained the I^2 Total
323 in adults, and the phylogeny had little contribution to total heterogeneity (**Table 2**).

324 3) Meta-regression

325 We found a negative (but weak) association between TL and age in juvenile and adult
326 stages of all taxa (except for juvenile reptiles, likely due to the low number of effect sizes). In
327 mammals, estimates were similar between juvenile and adult stages but their 95% CI
328 overlapped zero (estimate and 95% CI = -0.04, [-0.24:0.17] and -0.09, [-0.26:0.08] for juveniles
329 and adults, respectively). In fish, estimates were moderate and statistically significant for
330 juveniles (estimate and 95% CI = -0.47, [-0.69:-0.26]) but low and not statistically significant
331 for adults (estimate and 95% CI = -0.14, [-0.42:0.15]). Finally, in birds, estimates were negative
332 and the 95% CI overlapped zero in juveniles but not in adults (estimate and 95% CI = -0.17, [-
333 0.36:0.01] and -0.22, [-0.36:-0.08]). For adult reptiles, estimates were very close to zero
334 (estimate and 95% CI = -0.08, [-0.38:0.22]) (**Figure 4**)

335 In the juvenile dataset, the model selected was the null model, meaning that none of our
336 moderators, independently of phylogeny, explained the heterogeneity in the relationships
337 between telomere length and age during this stage (**Table S8**). The selected model for adults
338 included the type of study and the method of TL measurement (**Table S9**). When tested
339 separately, the relationship was weak and negative in both Transversal and Longitudinal studies
340 but not statistically different (estimate \pm 95% CI = -0.20, [-0.31:-0.08] and -0.11, [-0.26:0.03]
341 for Transversal and Longitudinal studies, respectively). Regarding the effect of the method, the
342 association between TL and age was negative whatever the method considered. However, the
343 estimate was strongly negative for FISH (estimate and 95% CI = -0.73, [-1.18:-0.28]) and small
344 to moderate for TRFI (estimate and 95% CI = -0.30, [-0.49:-0.12]). The estimates for studies
345 using TRFS and qPCR were small and their 95% CI overlapped zero (estimate and 95% CI = -
346 0.23, [-0.49:0.03] and -0.07, [-0.16:0.03]; **Table 3, Figure 5**).

347 In the adult dataset, we performed the same meta-regression as above but this time using
348 data restricted to the methods that provided evidence for a decline in telomere length with
349 increasing age (i.e. TRFI and FISH). The model selected was the null model, meaning that none
350 of our variables could explain the decline of telomere length with increasing age (**Table S10**).

351 4) Publication bias analysis

352 There was no detectable publication bias for the juvenile dataset because the intercept
353 of the Egger's regression was not different from zero (Estimate \pm SE: 0.06 \pm 0.09) and the trim
354 and fill method did not detect any missing studies (**Figure 6**). However, we found a funnel plot
355 asymmetry in the adult dataset. The intercept of the Egger's regression was different from zero
356 (Estimate \pm SE: -0.39 \pm 0.07) and the trim and fill method detected 56 missing studies on the
357 right-hand side of the funnel plot (**Figure 6**). Those missing studies might change the estimate
358 of the meta-analysis mean (change in the meta-analysis mean = 0.13, SE = 0.04) leading to a
359 weaker relationship between TL and age (estimate after the trim and fill = -0.03).

360

361 **Discussion:**

362 Our meta-analysis based on 175 effect sizes and 98 species, encompassing birds,
363 mammals, fish and reptiles, revealed a negative relationship between TL and age in adults but
364 not in juveniles. However, the relationship was both weak and variable across taxonomic
365 classes, which suggests more complex telomere dynamics than a simple decline with increasing

366 age throughout life in vertebrates. Despite the high number and diversity of species analysed,
367 we were not able to include any amphibian species. Our dataset was also biased in favour of
368 birds that were over-represented (45 bird species and 81 effect sizes out of 98 species and 175
369 effect sizes) relative to the other taxonomic classes. Along with the taxonomic class effect, we
370 also found a strong effect of the method used to measure telomeres in adults. Indeed, the
371 relationship was statistically significant only when using TRFI and qFISH methodologies.

372 Contrary to our hypothesis, we found a similar decline in age-specific TL during the
373 whole juvenile and adult stage. Our results suggest that juveniles and adults do not differ in TL
374 attrition rates on average across our set of species. Two non-mutually exclusive hypotheses
375 could be made to explain this lack of difference in telomere dynamics among life stages. First,
376 we used the age at first reproduction as the cut-off age between juveniles and adults. However,
377 the period of most rapid growth (which corresponds to the period of highest cell division and
378 thus decline in TL) might not cover the entire period before the age at first reproduction in all
379 taxa (Monaghan & Ozanne, 2018). In birds, for instance, final body size is reached by fledgling
380 or shortly after while sexual maturation could be achieved several years later for long-lived
381 birds. This is well illustrated in the wandering albatross where chicks reached adult body size
382 at around 10 months old (Mabille, et al., 2004) but individuals only start to reproduce around 7
383 years old (Froy et al., 2013). While there is compelling evidence that telomeres shorten at a
384 faster rate during embryonic development (Stier et al., 2020) and nestling stage in some bird
385 species (Boonekamp et al., 2014; Vedder et al., 2017), we excluded those articles from our
386 analyses due to the lack of data available covering the first month of life. The lack of available
387 data on TL change over the earliest developmental stages could lead us to underestimate the
388 decline of telomere length in juveniles. Repeated sampling in very young individuals, especially
389 in taxa other than birds, is clearly needed to better understand early-life telomere dynamics and
390 the link between growth and telomere shortening. However, repeated sampling of very young
391 individuals in wild populations may be both ethically and logistically challenging. A second
392 explanation is that variation exists in the form of the relationship between TL and age, being
393 curvilinear in some species (Rollings et al., 2017; Ujvari et al., 2017) and bi-phasic (Aubert et
394 al., 2012; Hall et al., 2004) in others, so that different relationships cancel into noise and we
395 cannot pick up the expected difference between juveniles and adults. To perform our meta-
396 analyses, we made strong simplifying assumption (*i.e.* linearity of the relationship between TL
397 and age and a cut-off between juvenile and adult stages using the AFR) that researchers working

398 on single species do not have to make. In that respect, some relationships we estimated might
399 be at odds with what is reported in the literature.

400 Among the different moderators included in our analyses, we found that the method
401 used to measure telomeres influenced the mean effect size in adults. More precisely, we found
402 stronger negative relationships in studies using TRFI and qFISH methodologies, but weaker
403 and not statistically significant relationships in studies using TRFS and qPCR. Conversely, in
404 a previous meta-analysis linking TL and mortality risk in non-human vertebrates (Wilbourn et
405 al., 2018), the relationship was stronger in studies using qPCR. In another meta-analysis looking
406 for the association between stress exposure and TL (Chatelain et al., 2020), the association was
407 34% stronger when telomeres were measured with qPCR than TRF. The stronger association
408 in qPCR was explained by a possible publication bias in qPCR studies, which is supposed to be
409 higher than in TRF since qPCR is a cheaper and faster method than TRF. Chatelain et al. (2020)
410 also explained such discrepancies by the fact that mean TL might be more accurately estimated
411 using qPCR since TL distribution can be highly skewed and thus poorly reflected by average
412 value obtained using TRF. On the other hand, a meta-analysis of human studies found sex
413 differences only in articles using TRF (Gardner et al., 2014). The authors suggested that this
414 difference could arise from higher measurement error in qPCR than in TRF. To date, only one
415 published study compared estimates of TL using qPCR and TRFS on the same sample in
416 relation to age (Aviv et al., 2011). While the authors found a higher measurement error in qPCR
417 than in TRFS (6.45% against 1.74%), age accounted for 17.2% of the inter-individual variation
418 of TL measured with qPCR against 29% using TRFS. While the number of studies measuring
419 telomeres in wild vertebrates has increased dramatically in recent years, TRF, considered as a
420 'gold standard' (Nussey et al., 2014), is being used less and less in favour of qPCR because
421 qPCR requires less DNA and is easier to perform than TRF (Lai et al., 2018). However, qPCR
422 assay is known to have higher measurement error than TRF in humans (Aviv et al., 2011; Elbers
423 et al., 2014) and is subject to well-position effects in thermocyclers, which, when not controlled,
424 increase the overall measurement error (Eisenberg et al., 2015). In overall, qPCR require to be
425 highly optimized in order to increase the precision and the accuracy of telomere length
426 measurement (Eastwood et al, 2018; Lin et al., 2019). However, a higher measurement error in
427 qPCR than in TRF cannot explain the pattern we observe since in our analysis we detected an
428 effect of age using TRFI but not using qPCR nor TRFS. Another explanation for the
429 discrepancy between the methods used is that TRFI uses non-denatured DNA, contrary to TRFS
430 and qPCR. By denaturing the DNA, TRFS and qPCR measure, in addition to telomeres,

431 interstitial telomere sequences (ITS), which are telomeric repeats located inside the
432 chromosomes (Foote et al., 2013; Meyne et al., 1990). ITS are known to be shorter than
433 telomeres but should not shorten with increasing age (Foote et al., 2013). Accordingly,
434 methodologies that include ITS may underestimate the average TL in a sample of cells. In
435 addition, because ITS may also vary among individuals within a same species (Foote et al.,
436 2013), including ITS could also decrease the power to detect differences in TL over time.
437 However, this hypothesis could not explain the negative result we found in studies using qFISH,
438 since qFISH also include ITS in the estimation of TL. Overall, we cannot explain the effect of
439 TL measurement method we found in our meta-analyses. At present, only one meta-analysis in
440 the field of telomere dynamics makes the distinction between TRFI and TRFS (Remot et al.,
441 2020) and it is now necessary that forthcoming comparative and meta-analyses also make this
442 distinction. In addition, reasons given to explain such discrepancies between methodologies
443 remain hypothetical, and more research should focus on understanding how and why telomere
444 measurement methods differ in the results they produce. To address this question, we
445 recommend that further studies should focus on measuring TL in the same sample of known-
446 age individuals using different methodologies. Finally, while the qFISH is rarely used in non-
447 medical research (only 9 effect sizes in our dataset), the TRFI is almost exclusively used in
448 birds (32 effect sizes in birds, 1 in mammals and 2 in reptiles, **see Supplementary, Table S12**).
449 Hence, the effect of the method we found in our analyses and the fact that the methods used are
450 not balanced across taxonomic classes could explain why we detected a decline in TL with
451 advancing age in birds but not in mammals. In addition, because of the bias in methodologies,
452 we may have underestimated the overall decline in telomere length with increasing age. To
453 tease apart the effect of the phylogeny from the effect of the methodology, we recommend the
454 use of methodologies such as TRFI and qFISH in taxa other than birds.

455 We found no evidence for an effect of the age at first reproduction nor a difference
456 between the type of study (transversal vs. longitudinal) on the association between TL and age,
457 contrary to what we expected. Previous studies found that telomere rate of change was
458 positively linked with maximum lifespan in 19 species of bird (Tricola et al., 2018), and also
459 associated with the species pace of life (*i.e.* fast-living species lose more telomeres per unit of
460 time than slow-living species) in 14 species of birds (Dantzer & Fletcher, 2015). One potential
461 explanation for this discrepancy with past studies of birds is that our analysis was performed in
462 four different classes of vertebrates, encompassing 98 different species, with four different
463 methods of TL measurement, while the two previous findings were made on birds only, whose

464 telomeres were measured using TRF only. Thus, the heterogeneity due to the high number of
465 species and the various methodologies in our dataset could prevent us from finding a detectable
466 effect. We also did not find any effect of the type of study on the association between TL and
467 age. A possible source of heterogeneity that could potentially explain the weak relationship we
468 observed in adults is the tissue sampled. While some studies did not find any effect of the
469 interaction between tissue and age on TL, a recent study made on humans found different
470 telomere attrition rates depending on the tissue sampled (Demanelis et al., 2020). At the within-
471 tissue level, tissues are composed of various cell types that can have their own telomere
472 dynamics. In the Australian Painted Dragon (*Ctenophorus pictus*), white blood cell (WBC)
473 populations (lymphocytes and azurophils) have different TL, and TL is also much longer in
474 WBC than in red blood cells (RBC) (Olsson et al., 2020). Given the lack of a nucleus in their
475 erythrocytes, telomeres in mammals are mostly measured in WBC, which equates to measuring
476 the average TL in a heterogeneous population of cells, each with potentially different sized
477 telomeres. More problematically, it is known that the composition of WBC varies considerably
478 with the age of individuals (Cheynel et al., 2017; Watson et al., 2017), which might cloud the
479 pattern of telomere dynamics with age. From the few studies that measured cell-specific
480 telomere dynamics, contrasting results occur. In the Soay sheep, while the composition of WBC
481 varies with the age of individuals, it seems that those changes do not impact age-specific
482 telomere dynamics (Watson et al., 2017). However, telomere attrition rates vary between
483 subpopulations of leukocytes in humans (Lin et al, 2016), suggesting that average leukocytes
484 TL might also vary following the composition of the cell population being measured. In our
485 meta-analysis it was not possible to take into account the tissue sampled nor the cell type within
486 tissue since most of the studies included (76%) measured TL in blood (whether RBC in birds,
487 fish and reptiles or WBC in mammals) and because WBC are only measured in mammals, the
488 tissue is confounded with the taxa. In addition, most of the other tissues present in our dataset
489 were sampled once or twice (15 out of 21 tissues) meaning that we would not have enough
490 repeated measures per tissue to detect tissue-specific telomere dynamics with age. We then need
491 more studies that compare TL change with age over different tissues.

492 We also found evidence for asymmetry in the funnel plot of the adult dataset. The trim
493 and fill method estimated 51 missing effect sizes on the right-hand side of the funnel plot. Once
494 these studies were accounted for, there was no evidence for a relationship between TL and age.
495 However, the trim and fill method has shortcomings (especially when between-study
496 heterogeneity exists (Peters et al., 2007)) and should be interpreted cautiously. Two hypotheses

497 could explain the funnel plot asymmetry. First, positive associations between TL and age might
498 be less likely to be published without strong statistical support (i.e. high precision) since TL is
499 commonly expected to decline with increasing age. Alternatively, such positive relationships
500 could be truly rarely observed. Indeed, due to the ‘end-replication problem’ and oxidative
501 damages, it is biologically less likely that TL declines than increases with age, meaning that, in
502 this case, funnel plot asymmetry might be due to biological constraint rather than publication
503 bias. Either way, we highly recommend that researchers measuring TL in known age
504 individuals publish their data, no matter the effect found nor the statistical significance because
505 only a higher number of studies will allow us to clarify whether this asymmetry is due to
506 publication bias or biological constraint.

507 Our heterogeneity analysis reveals that the part of the total variance explained by the
508 between-study variance in the meta-analysis performed on adults was mostly due to the
509 heterogeneity among species (independently of the phylogeny) and populations (for species that
510 were sampled in different populations), highlighting the role that environmental conditions can
511 have on telomere dynamics. For example, in great tits (*Parus major*), individuals living in urban
512 environments have shorter telomeres than individuals living in forest regardless of nestling
513 origin (Salmón et al., 2016). In roe deer (*Capreolus capreolus*), shorter telomeres were
514 observed in old individuals from a population facing strong resource limitation compared to
515 those from a population experiencing better environmental conditions (Wilbourn et al., 2017).
516 However, due to the lack of multiple sampling of the same species in contrasting environments,
517 it was not possible to thoroughly examine the role played by environmental conditions on the
518 relationship between telomere length and age.

519 Available data indicate that telomere dynamics are complex both within and among
520 species. While we found an overall decline of TL with increasing age among adult vertebrates,
521 the publication bias we found might weaken the strength of the association. In addition, our
522 results mainly point out the variability of the relationship between TL and age and, because
523 none of the biological moderators we tested explained this variability, suggesting that there is
524 much we still do not know about telomere dynamics. In addition, as highlighted in previous
525 meta-analyses (Chatelain et al., 2020; Wilbourn et al., 2018), the methodology used to measure
526 telomeres remains an important source of heterogeneity, which is worrying since at least four
527 different methods are currently used, potentially giving different results. It is important that
528 future research aims to better understand how methodologies and phylogeny influence patterns
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530

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551

552 **References:**

553 **References marked with an asterisk have been included in the meta-analyses*

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1021

1022 **Data accessibility:** Data are available via the Dryad Digital Repository
1023 <https://doi.org/10.5061/dryad.000000048>

1024

1025 **Author Contributions:** F.R., D.H.N. and J.F.L. conceived the study with inputs from H.F.,
1026 B.R. and J.M.G. F.R. compiled the dataset. F.R. and V.R. analysed the data with inputs from
1027 J.F.L. and J.M.G. F.R. wrote the first draft of the paper and then received input from all authors.

1028

1029 **Tables and Figures legends:**

1030

1031 **Table 1:** Number of species, studies and effect sizes for the two meta-analyses performed on
1032 juveniles and adults.

1033

1034 **Table 2:** Effect size of the relationship between TL and age estimated from the meta-analyses
1035 we performed and I^2 associated with each random factor.

1036

1037 **Table 3:** Estimate and 95% confidence interval for the effect of the method used to measure
1038 TL in adults on the effect size of the relationship between TL and age.

1039

1040 **Figure 1:** PRISMA statement (adapted from Liberati et al., 2009).

1041

1042 **Figure 2:** The relationship between telomere length and age across adult non-human
1043 vertebrates. Species-specific estimates were calculated using the factor 'Species' as a moderator
1044 in the meta-regression model to calculate a mean relationship for each species.

1045

1046 **Figure 3:** Orchard plots for juveniles (A, in blue) and adults (B, in yellow). The point on the x-
1047 axis represents the estimate of the model, the black line in bold the confidence interval, the grey
1048 line in bold the prediction interval and coloured points represent the effect size of each study
1049 (the size of the points is proportional to the precision, calculated as the inverse of the standard
1050 error, of the study). Individual effect sizes are distributed on the y-axis to make them all visible.
1051 For the ease of interpretation, all effect sizes were back-transformed into correlation
1052 coefficients ($r = \tanh Zr$). The I^2 total is also reported.

1053

1054 **Figure 4:** Orchard plot for juveniles (A) and adults (B) split among taxonomic groups. The
1055 point on the x-axis represents the estimate of the model (back-transformed into correlation
1056 coefficients), the black line in bold the confidence interval, the grey line in bold the prediction

1057 interval and coloured points represent the effect size of each study (the size of the points is
1058 proportional to the precision, calculated as the inverse of the standard error, of the study). k is
1059 the number of effect sizes for each level.

1060

1061 **Figure 5:** Orchard plot displaying the effect of the method of TL measurement in adults. The
1062 point on the x-axis represents the estimate of the model (back-transformed into correlation
1063 coefficients), the black line in bold the confidence interval, the grey line in bold the prediction
1064 interval and coloured points represent the effect size of each study (the size of the points is
1065 proportional to the precision, calculated as the inverse of the standard error, of the study). k is
1066 the number of effect sizes for each level.

1067

1068 **Figure 6:** Contour-enhanced funnel plot for the meta-analyses on juveniles (A) and adults (B).
1069 The precision (inverse of the standard error) is plotted against meta-analytic residuals. Areas of
1070 statistical significance are displayed in grey. While there was no detectable publication bias in
1071 juveniles, we found an important publication bias in adults with 56 missing studies on the right
1072 side of the funnel plot (white dots), estimated by the trim and fill method.