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REVIEW AND SYNTHESIS

The association between stressors and telomeres in non-human vertebrates: a meta-analysis

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Abstract

Animal response to stressors such as harsh environmental conditions and demanding biological processes requires energy generated through increased mitochondrial activity. This results in the production of reactive oxygen species (ROS). *In vitro* and some *in vivo* studies suggest that oxidative damage of DNA caused by ROS is responsible for telomere shortening. Since telomere length is correlated with survival in many vertebrates, telomere loss is hypothesised to trigger cellular ageing and/ or to reflect the harshness of the environment an individual has experienced. To improve our understanding of stress-induced telomere dynamics in non-human vertebrates, we analysed 109 relevant studies in a meta-analytical framework. Overall, the exposure to possible stressors was associated with shorter telomeres or higher telomere shortening rate (average effect size = -0.16 ± 0.03). This relationship was consistent for all phylogenetic classes and for all *a* priori-selected stressor categories. It was stronger in the case of pathogen infection, competition, reproductive effort and high activity level, which emphasises their importance in explaining intraspecific telomere length variability and, potentially, lifespan variability. Interestingly, the association between stressor exposure and telomeres in one hand, and oxidative stress in the other hand, covaried, suggesting the implication of oxidative stress in telomere dynamics.

Keywords

Ageing, competition, habitat quality, oxidative stress, reproduction, senescence, stressor, telomere.

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INTRODUCTION

Telomeres are repetitive nucleotide sequences located at the end of each eukaryotic chromosome that ensure chromosomal stability and cell viability (Blackburn 1991). Yet, progressive telomere shortening occurs in all dividing normal cells due to incomplete end-replication problems, oxidative damage and other end processing events (Shay & Wright 2019). The recent meta-analysis from Wilbourn *et al*. (2018) demonstrated a moderate but significant negative correlation between telomere length and mortality risk in non-model vertebrates. Therefore, telomere length, by predicting lifespan, has broad implications in life history and fitness variation in natural populations. However, our understanding of intraspecific variation in telomere length and shortening remains to date elusive.

Starting from the early 1990s, telomere attrition (also defined as telomere erosion or shortening) or elongation raised enthusiasm in the medical research community (reviewed in Greider 1998), and later – in the early 2000s, in ecology (reviewed in Horn *et al*. 2010): indeed, telomere length was hypothesised to be the underlying mechanisms of cell replicative senescence – the cessation of mitosis after a number of cell divisions. This would contribute to ageing – the progressive accumulation of defects, increased fraction of inactive proteins and of damaged mitochondria (Ju & Rudolph 2008). Specifically, DNA polymerase is unable to convert the most distal RNA primer during lagging-strand synthesis; eventually, the RNA primer is degraded, which leads to telomere shortening with each round of DNA replication (Blackburn 1991). Ultimately the accumulation of critically short telomeres leads the cell to exit the cell cycle, meaning to stop its replication (Hemann *et al*. 2001; Zou *et al*. 2004). However, such a fix mitotic clock does not explain the high variability in telomere length observed among individuals of the same age (e.g. Hall *et al*. 2004; Pauliny *et al*. 2006).

In addition to replicative history, telomere length would also depend on stress experienced by the individual (also called allostatic load; McEwen & Wingfield 2003). Individuals have different life histories and experience different environmental biotic (e.g. parental phenotype, intra and interspecies competition) and abiotic (e.g. pollutant exposure, weather harshness) conditions. Several of these environmental factors may be seen as stressors in the sense that they trigger an integrated stress response, that is a physiological and behavioural change that ensure survival in return for a physiological cost (Romero 2004). Although the stress response was not always explicitly measured, stress-induced telomere attrition was

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suggested by numerous recent reviews of epidemiological studies in humans; these studies highlighted negative correlations between telomere length and psychological stress (Epel *et al*. 2004; Kiecolt-Glaser & Glaser 2010; Lin *et al*. 2012; Price *et al*. 2013; Law *et al*. 2016) but also dietary patterns (Freitas-Simoes *et al*. 2016; Rafie *et al*. 2017), pre-natal exposure to stressors, health-risk behaviours (Shalev *et al*. 2013; Astuti *et al*. 2017) and exposure to chemicals (Zhang *et al*. 2013). Five recent meta-analyses confirmed the negative effect of different kinds of stressors on telomere length and shortening in humans (effect sizes from − 0.06 to − 0.25; Schutte & Malouff 2014, 2016; Mathur *et al*. 2016; Oliveira *et al*. 2016; Pepper *et al*. 2018). In contrast, while the number of studies investigating telomeres (i.e. telomere length and dynamics) in non-human animals have substantially increased in the last decade (reviewed in Haussmann & Marchetto 2010; Monaghan 2014; Bateson 2016; Reichert & Stier 2017; Angelier *et al*. 2018; Monaghan *et al*. 2018), general conclusions about stress-induced telomere dynamics are lacking due to the paucity of comparative studies that would quantify the effect size of the association between the exposure to potential stressors and telomere length and dynamics.

Another main gap in our knowledge of telomeres is about the physiological mechanisms that would underlie stress-induced telomere erosion. In animals, the stress response is complex and involves several pathways. Acute and chronic stress trigger the activation of the hypothalamic–pituitary–adrenal axis, which leads to the secretion of glucocorticoids. Such endocrine response, aiming at coping with a higher energy requirement, is typically associated with increased metabolic rate, resulting in increased rate of DNA synthesis (i.e. mitotic activity), and mitochondria activity (Silverin 1986; McEwen & Wingfield 2003; Boonstra 2004; Haase *et al*. 2016). Interactions between electrons transiting through the mitochondrial electron transport chain and molecular oxygen generate reactive oxygen species (ROS; e.g. superoxide anion radical and hydroxyl ion radicals). Consequently, mitochondrial activity increased by stress stimuli is responsible for increased oxidative stress (Cadenas & Davies 2000). Oxidative stress may also occur independently of mitochondria activity; for example the exposure to some pollutants may also induce oxidative damages (Isaksson 2010); For instance metallic trace elements such as lead or copper can catalyse oxidation reactions (e.g. Fenton reaction), leading to ROS production; metal ion binding to antioxidant thiol groups can also lead to antioxidant depletion, as in the case of glutathione (Koivula & Eeva 2010).

In vitro studies suggest that oxidative stress level experienced by the individual would be one of the main drivers of telomere shortening and would therefore explain telomere attrition rate variability that could not be accounted for by the replicative history of cells (von Zglinicki 2000, 2002; Sozou & Kirkwood 2001; Houben *et al*. 2008). Cell cultures exposed to mild stressors such as chronic hypoxia and low doses of hydrogen peroxide showed accelerated telomere attrition (von Zglinicki *et al*. 1995; Liu *et al*. 2003; Tchirkov 2003; Kurz 2004; Richter & Zglinicki 2007); in contrast, antioxidant exposure reversed the negative effect of such stressors on telomere dynamic, prolonged the replicative lifespan of cells, and slowed down telomere attrition rate compared with cell cultures not exposed to the stressor (Furumoto *et al*. 1998; Liu *et al*. 2003; Saretzki *et al*. 2003; Serra 2003; Tchirkov 2003). All in all, these studies suggest that telomere attrition in cell cultures can be triggered by a wide range of stressors and can be mediated by oxidative stress. The possible underlying mechanisms of telomere sensitivity to oxidative stress are threefold: (1) the proportion of guanine nucleotides is particularly high in telomeric regions, which make the DNA sequence highly sensitive to damage by oxidative stress (Henle *et al*. 1999; Oikawa & Kawanishi 1999; Kawanishi *et al*. 2001; Kawanishi & Oikawa 2004), (2) DNA repair machinery is less efficient in the telomeric regions compared with the rest of the genome (Petersen *et al*. 1998); both mechanisms lead to the presence of unrepaired nucleotides, which consequently affects the processivity of the replication fork in the telomeric region and increases the proportion of unreplicated ends; finally, (3) oxidative damage to DNA has inhibitory effects on the activity of telomerase, a ribonucleoprotein adding new nucleotides to the telomere sequence (Ahmed & Lingner 2018). However, empirical evidence supporting the role of oxidative stress in telomere attrition *in vivo* is limited (Boonekamp *et al*. 2017; Reichert & Stier 2017). A recent review discussed the correlative and experimental studies testing the link between oxidative stress and telomeres in vertebrates (including humans): only 4 correlative studies out of 10, and 7 experimental studies out of 8 carried out on non-human vertebrates measured significant and mainly negative correlations between some markers of oxidative stress and telomeres, although these correlations were sometimes only significant for one group of animals (e.g. different effects in males and in females; Reichert & Stier 2017). In other words, 40% of the studies failed to measure any significant link between oxidative stress and telomeres. Amongst them, Boonekamp *et al*. (2017) found that telomere attrition was correlated with none of the six markers of oxidative damage and antioxidant protection in nestlings of wild jackdaws (*Corvus monedula*). Statistical approaches quantifying the link between oxidative stress and telomere length and/or dynamics are thus needed to conclude on whether oxidative stress is the unifying physiological mechanism driving telomere shortening.

In order to quantify the effect size of the association between the exposure to potential stressors and telomeres (i.e. both telomere length and dynamics) in non-human vertebrates and to test whether it is mediated by oxidative stress, we conducted a meta-analysis using both experimental and correlative studies. The aim of our study was fourfold: to (1) test for a systematic trend in stressor exposure–telomeres relationships, (2) compare the magnitude of the effect sizes of various categories of stressors, (3) understand the differences between studies due to animal intrinsic characteristics (i.e. age, sex, species), telomere measurement (measure of telomere length vs. telomere dynamics), or methodological aspects (i.e. measure of telomeres with quantitative PCR vs. terminal restriction fragment analysis, experimental vs. correlative approach, type of tissue sampled, laboratory vs. captive vs. wild populations) and (4) estimate whether oxidative stress mediates the association between the exposure to a stressor and telomeres.

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MATERIAL AND METHODS

Search strategy and inclusion criteria

Papers were located by key word searches in *Web of Science*. The key words used were 'telomere' and 'stress'. Because our study focused on the link between potential stressors and non-human vertebrate telomeres, the search was refined by specifying the taxa (i.e. 'bird', 'mammal', 'amphibian', 'reptile' or 'fish'; for example 'telomere' + 'stress' + 'bird'). In an attempt to be exhaustive and to increase the data set, we rerun the search associating 'telomere' with one of the key identified stressors (i.e. 'reproduction', 'disturbance', 'competition', 'parasite', 'immunity', 'pollutant', 'nutrition', 'diet', 'temperature', 'noise', 'parental effect', 'growth' or 'development'). The search was stopped on the 22nd of July 2019. We retained all studies on non-human vertebrates (wild, captive and laboratory vertebrates) from which it was possible to identify a unique stressor involved in telomere dynamics. It resulted in the selection of 98 papers from which 2 were removed because of lack of informative statistical values about the association between the stressor and telomeres. Finally, 13 additional papers were found by screening the reference list of the papers selected in the previous step. In total, 109 papers were included in the analysis. This resulted in 393 effect sizes, from which 46 were removed either because the measure of telomere length occurred less than 24 h after the onset of the experiment, because informative statistical values were missing or because it was impossible to extract the effect of the stressor independently of the other variables included in the statistical model. In total, 347 individual effect sizes were used to test the link between stressor exposure and telomeres (Fig. 1).

From those 109 papers, 28 also contained data on the link between stressor exposure and oxidative stress – either the level of antioxidant or the extent of oxidative damage, which became a subset unit of analysis explicitly focused on the link between stressor exposure, telomeres and oxidative stress. Two papers were excluded because oxidative stress was assessed either by pooling different biomarkers into PCA components or by calculating the ratio between an oxidative damage and an antioxidant defence; both ways prevented to disentangle the relationship between telomeres and oxidative damage and between telomeres and oxidative defences. A third study was removed because informative statistical values were missing. In total, this data set included 25 papers and 156 effect sizes (Fig. 1). In 4 papers, only one oxidative stress biomarker has been measured, whereas the other studies measured between 2 and 5 biomarkers. In 22 papers, oxidative stress biomarkers and telomere length have been measured in the same time. In three papers, oxidative stress biomarkers have been measured at the start or within the course of the experiment, whereas telomere length variation has been calculated between the start and the end of the study.

Moderators included and categorisation

Our analysis on the link between stressor exposure and telomeres included 12 moderators: taxonomic class, stressor category, age, whether a study accounted for age or not, sex, cell turnover (linked directly to the type of sampled tissues), telomere measure, method for telomere measurement, study type, population, whether the effect size has been corrected or not for other factors (e.g. through a multivariate linear model) and publication year (Table 1). Stressors were extracted as described in the papers and then sorted within 10 stressor categories: these corresponded to either harsh environmental conditions (categorised as competition, human disturbance, pathogen infection, poor diet, harsh abiotic conditions, low parental quality), demanding biological processes (i.e. reproductive effort, development, high activity level) or a consequence of unspecified stressors (i.e. low body condition). The decision on whether an environmental variable or a biological process should be considered as a potential stressor followed the assumptions of the authors of the original papers. For instance in the case of juveniles, the exposure to noise pollution, a late laying date and a high hatching order were all considered as potential stressors and were categorised as human disturbance, low parental quality and competition respectively (Foote *et al*. 2011; Meillère *et al*. 2015; Soler *et al*. 2015; Stier *et al*. 2015; Mizutani *et al*. 2016; Young *et al*. 2017).

Cell turnover was classified into short or long depending on whether the cell turnover time range involved a timespan of a few days (e.g. white blood cells, mucosa, skin epidermis cells, lungs) to a few months (i.e. red blood cells) or at least a year (e.g. liver, muscles, brain, fat, kidney); 83 studies measured telomeres in the blood.

Our analysis of the link between stressor exposure, telomeres and oxidative stress took into account the oxidative stress biomarker; either the level of antioxidant levels or the level of oxidative damage. For each moderator, its modalities, the number of data point per modality and the justification for including it in the analysis (i.e. – the expected influence on stressor exposure–telomeres association) are described in Table 1.

Effect size calculation

For all the relationships between stressor exposure and telomeres, and stressor exposure and oxidative stress extracted from the papers, Z-scores were calculated using the means and standard deviations, *t*-values, *F*-values, correlation coefficients r or *P*-values (Koricheva *et al*. 2013). Results involving comparisons of experimental groups were first transformed to standardised mean differences (Cohen's *d*), whereas results describing relationships between continuous variables were transformed into correlations. In the second step, resulting intermediate effect sizes were recalculated to yield Fisher's Z estimates (the advantage of using Fisher's Z is (1) ease of calculating its associated sampling variance which is $(n - 3)^{-1}$, where n equals study sample size and (2) its distributional properties, more statistically tractable than in the case of pure correlations). The sample size and the direction of the relationship between the stressor and telomere length or dynamic (either positive or negative) were also extracted. Regarding the link between a stressor and telomeres, a positive effect means a positive correlation between the stressor and telomere length but a negative correlation between the stressor and telomere shortening rate. Regarding the link between a stressor and oxidative stress, a positive effect means a positive

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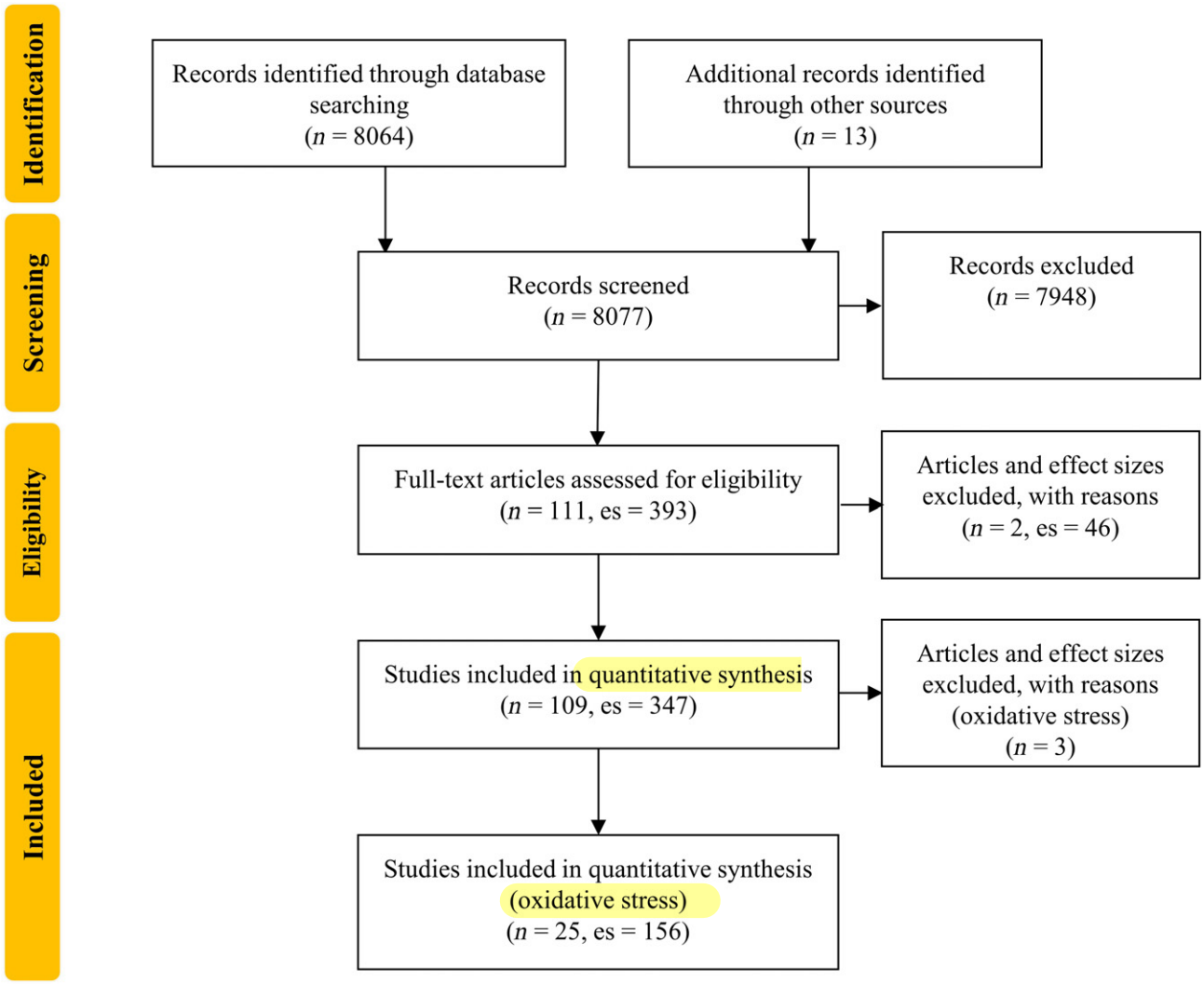

Figure 1 PRISMA diagram describing the flow of information through the different phases of the systematic review on the association between stressor exposure and telomeres in non-human vertebrates where n = number of studies and es = number of effect sizes. A subset database was selected to analyse the association between stressor exposure, telomeres and oxidative stress.

correlation between the stressor and the level of oxidative defences but a negative correlation between the stressor and the level of oxidative damages.

Meta-analytic technique

We used a series of general linear mixed models to analyse the variation and overall magnitude of published effect sizes relating stressors and telomeres metrics in vertebrates. All models were analysed using the *metafor* package (Viechtbauer 2010). More specifically, we used a number of phylogenetically corrected linear mixed models of general form:

$$Y_j \sim \mu + a_j + s_j + t_j + m_j + e_j, \quad (1)$$

where $a \sim \mathbf{N}(0, \sigma_A^2\mathbf{A})$; $s \sim \mathbf{N}(0, \sigma_S^2\mathbf{I})$; $t \sim \mathbf{N}(0, \sigma_T^2\mathbf{I})$; $m \sim \mathbf{N}(0, \sigma_M^2\mathbf{M})$ and $e \sim \mathbf{N}(0, \sigma_E^2\mathbf{I})$. Such model fits a form of a random-effects meta-analysis. In the type of model employed (hierarchical random effects meta-analysis) σ_M^2 was fixed at unity, an **M** (a diagonal matrix of sampling variances) captured the realised sampling error of each study. Observed outcome Y_j is then modelled as a function of the main effect μ (i.e. the intercept of the model), which can be combined with a number of fixed predictors to form βXi – in which case one gets a meta-regression model. First, the overall association between stressor exposure and telomeres was quantified using the intercept model. Second, we tried to explain the variability of this association by adding fixed effects. Fixed effects reflected moderators described in Table 1(a). We have also considered biologically meaningful interactions between telomere measure and age, telomere measure and stressor category, cell turnover and stressor category, and age and stressor category. The best set of models was selected based on AICc (corrected Akaike Information Criterion) using the *MuMIn* package (Bartoń 2019). Following model selection, the best set of models (within the range of ΔAICc ≤ 2) was used in the model-averaging procedure. To average models, we have computed mean values of estimates (using the principle of so called 'full-averages'; that is assuming zero values

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Table 1 List of moderators taken into account in the analyses

	Moderator	Modalities (number of data points)	Expected influence on stressor–telomeres association
a	Stressor category	Reproductive effort (38), Competition (52), Human disturbance (55), Pathogen infection (32), Development (31), Low body condition (14), Poor diet (61), High activity level (6), Harsh abiotic conditions (33), Low parental quality (25)	Stressor-linked energy expenditure.
	Age	Juvenile (177), Adult (156), Both (14)	Higher cellular divisions and energy expenditure during growth (i.e. early-life stages). Difference of energy allocation along the life cycle.
	Accounted for age	Yes (279), No (68)	Age-dependant telomere length and attrition rate.
	Sex	Female (40), Male (76), Both (231)	Different allocation of resources between males and females (e.g. growth and sexual ornaments in dimorphic species, reproductive strategy and investment).
	Cell turnover	Short (261) e.g. blood, mucosa, Long (86) e.g. brain, muscle	Various cell turnover time, division properties and telomerase activity (e.g. somatic vs. differentiated cells).
	Telomere measure	Length (259), Shortening (88)	Telomere shortening reduces differences of telomere length due to the initial telomere length, age and previous history; it depends on the time between the two measures.
	Method for telomere measurement	qPCR (258), TRF (89)	Telomere size-specific attrition rate (TRF but not q-PCR splits telomeres into size classes).
	Type of study	Correlative (214), Experimental (133)	Different statistical power to identify the cause of telomere dynamics.
	Population	Wild (222), Captivity* (59), Laboratory† (66)	Different response to stress in response to various evolutionary histories and previous experiences. Different statistical power to identify the cause of telomere dynamics.
	Effect size correction	Yes (119), No (228)	Partial correlation between stress and telomeres that takes into account potential confounding variables.
	Taxonomic class	72 species: Bird (218), Mammal (78), Fish (34), Reptile (10), Amphibian (7)	Taxa-specific telomere initial length and telomere dynamics as a response to variations in lifespan, life history including growth pattern, metabolic rate and telomerase activity.
	Publication year	From 1999 to 2019	Bias linked to technical advancements, study system and question diversity.
	Oxidative stress biomarker	Antioxidants (111), Oxidative damage (45)	Different physiological pathways.

For each moderator, its modalities, the number of data point per modality and the justification for including it in the analysis (that is – the expected influence on stressor exposure–telomeres association) is detailed.
*Wild population transferred in captivity.
†Bred in captivity during several generations.

for predictors in models where they did not occur). The link between either the taxonomic class or the publication year and telomeres were also tested in separate models to provide additional insights into the diversity of effect sizes with respect to the phylogenetic classification, and the progression of this field of study captured by the publication year.

Each model included a number of random terms: the phylogenetic effect a (see below for details), which accounted for phylogenetic dependency of meta-analytic residuals; the effect of a specific study s, which accounted for the non-independence of effect sizes within studies; the effect of a species independent of its phylogenetic position t and the random residual e (unexplained variance on top of the sampling variance); a diagonal matrix **M** with its diagonal terms containing sampling variances (var_d) of effect sizes, linked to the random term m of meta-analytic sampling variance.

Since there is no single pan-vertebrate phylogeny that can be used in such studies, we have combined several published phylogenies by merging them root-to-branch and resetting all branch lengths, which was followed by their recalculation using the Grafen's method (Grafen 1989). We used the most recent phylogenies for birds (Jetz *et al*. 2012), mammals (Bininda-Emonds *et al*. 2007), reptiles (Pyron *et al*. 2013), amphibians (Pyron & Wiens 2011) and teleost fish (Betancur-R. *et al*. 2013). In our initial analysis the phylogenetic and study random effects appeared non-significant (likelihood ratio test: LRT = 0, $P = 1$ and LRT = 0.01, $P = 0.87$ respectively); they were removed from subsequent analyses. As the species random effect was marginally supported (LRT = 1.3, $P = 0.10$), it was included in the analyses to account for pseudo-replication resulting from having multiple effect-sizes for a given species.

Residual heterogeneity I^2 of effect sizes (i.e. at the level of individual effect sizes) in respective models was estimated following Nakagawa & Santos 2012 (Nakagawa & Santos 2012) as:

$$I^2 = \frac{\sigma_E^2}{\sigma_A^2 + \sigma_S^2 + \sigma_T^2 + \sigma_m^2 + \sigma_e^2}, \quad (2)$$

where ${\sigma_m}^2$ is calculated using individual effect size sampling variances ${\sigma_j}^2$ as (N = number of effect sizes):

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$$\sigma_m^2 = \frac{\sum_{j=1}^{N} \frac{1}{\sigma_j^2}(N-1)}{\left(\sum_{j=1}^{N} \frac{1}{\sigma_j^2}\right)^2 - \sum_{j=1}^{N}\left(\frac{1}{\sigma_j^2}\right)^2}. \quad (3)$$

Methods used to estimate publication bias are presented in Supplementary material (Appendix S1).

In order to analyse the link between stressor exposure, telomeres and oxidative stress response, we used a subsample of studies providing effect sizes of stressor exposure dependencies for both telomeres and oxidative stress metrics. As they are both associated with their respective sampling variances, we have employed a simplified method to test for a significant relationship between them. First, we generated 5000 simulated draws by sampling each observation from its associated bivariate normal distribution (defined by each observation's original effect sizes, and its two sampling variances). Resulting simulated realisations of the analysed relationship were used to construct confidence intervals around the estimate generated from original data. Three models were run: the first one included all the effect sizes (i.e. whatever the oxidative stress biomarkers), whereas the two others included either the effect sizes for oxidative defences or for oxidative damage. Additionally, we have used the marginal method of moments proposed by Chen *et al*. (2016) to verify this result.

RESULTS

Stressor exposure and telomeres

The overall link between the exposure to potentially stressful conditions and telomeres was unequivocally negative (estimate ± SE = −0.16 ± 0.03; CI = [−0.22, −0.10]); its heterogeneity – $I^2 = 0.91$ (Cochran's Q test: $Q = 1815.22$, d.f. = 346, $P < 0.001$) and $I^2 = 0.87$ ($Q = 1456.86$, d.f. = 297, $P < 0.001$) in the intercept and full models, respectively – was considerable (defined as $I^2 > 0.75$; Higgins *et al*. 2003).

When comparing the association between taxonomic classes, independently of the other moderators, the association was negative in birds (estimate ± SE = −0.17 ± 0.04; CI = [−0.25, −0.10]) and mammals (estimate ± SE = −0.14 ± 0.17; CI = [−0.28, 0.00]), whereas it was negative but with confidence intervals including positive values in reptiles (estimate ± SE = −0.22 ± 0.13; CI = [−0.49, 0,04]), fish (estimate ± SE = −0.11 ± 0.09; CI = [−0.29, 0,07]) and amphibians (estimate ± SE = −0.02 ± 0.16; CI = [−0.33, 0.29]). Importantly, effect sizes were not significantly different between the taxonomic classes (i.e. their respective confidence intervals included each other mean effect size).

The outputs of the full model are presented in the Supplementary material (Appendix S2). Effect size correction, stressor category, population, whether the study accounted for age, method for telomere measurement, cell turnover, age, type of study and telomere measure were retained in the best subset models ($\Delta AIC \leq 2$; Table 2). Effect size correction and stressor category in one hand, and population in the other hand, were retained in 100 and 90% of the best models respectively (Table 3). The association between stressor exposure and telomeres was strongly negative for all stressor categories except for development and low body condition, for which the association was only marginally negative (Fig. 2). Importantly, the association was stronger (i.e. more negative) in the case of pathogen infection than for several other stressor categories: harsh abiotic conditions, development, human disturbance, low body condition and low parental quality. It was also stronger in the case of

Table 2 List of the best models predicting the association between stressor exposure and telomeres in non-human vertebrates. Models were ranked using AICc. Only models with a maximum of 2 AIC units above the best model are presented

Models	AICc	ΔAICc	Weight
Intercept + Effect size correction + Stressor category + Population	395.40	0.00	0.03
Intercept + Effect size correction + Stressor category + Population + Accounted for age	395.80	0.39	0.02
Intercept + Effect size correction + Stressor category + Population + Method for telomere measurement	396.00	0.61	0.02
Intercept + Effect size correction + Stressor category + Population + Method for telomere measurement + Accounted for age	396.20	0.78	0.02
Intercept + Effect size correction + Stressor category + Population + Accounted for age + Cell turnover	396.60	1.17	0.01
Intercept + Effect size correction + Stressor category + Population + Cell turnover	396.70	1.29	0.01
Intercept + Effect size correction + Stressor category + Population + Accounted for age + Age	396.80	1.36	0.01
Intercept + Effect size correction + Stressor category + Population + Accounted for age + Cell turnover + Method for telomere measurement	396.90	1.45	0.01
Intercept + Effect size correction + Population	396.90	1.49	0.01
Intercept + Effect size correction + Stressor category + Population + Type of study	397.10	1.65	0.01
Intercept + Effect size correction + Population + Type of study	397.10	1.70	0.01
Intercept + Effect size correction + Stressor category + Population + Telomere measure	397.20	1.79	0.01
Intercept + Effect size correction + Stressor category + Population + Age	397.20	1.81	0.01
Intercept + Effect size correction + Stressor category + Population + Cell turnover + Method for telomere measurement	397.30	1.86	0.01
Intercept + Effect size correction + Stressor category + Population + Accounted for age + Type of study	397.30	1.86	0.01
Intercept + Effect size correction + Stressor category + Population + Accounted for age + Type of study + Cell turnover	397.40	1.95	0.01

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Table 3 Results of the final averaged model testing whether the variation in the association between stressor exposure and telomeres in non-human vertebrates is explained by the type of stressor, individual intrinsic variables, telomere measurement and/or methodological aspects

	Estimate ± SE	CI	RI
Intercept	−0.23 ± 0.10	−0.42, −0.04	
Effect size correction	−1.34 ± 0.44	−2.21, −0.48	1
Stressor category (high activity level)	−0.41 ± 0.18	−0.76, −0.06	1
Stressor category (competition)	−0.15 ± 0.08	−0.31, 0.00	
Stressor category (development)	0.07 ± 0.09	−0.10, 0.25	
Stressor category (human disturbance)	−0.05 ± 0.08	−0.22, 0.11	
Stressor category (low body condition)	0.08 ± 0.11	−0.14, 0.30	
Stressor category (pathogen infection)	−0.26 ± 0.09	−0.43, −0.08	
Stressor category (low parental quality)	−0.05 ± 0.10	−0.24, 0.13	
Stressor category (poor diet)	−0.09 ± 0.10	−0.29, 0.10	
Stressor category (reproductive effort)	−0.09 ± 0.09	−0.25, 0.08	
Population (laboratory)	0.22 ± 0.09	0.04, 0.40	0.9
Population (wild)	0.17 ± 0.07	0.03, 0.31	
Accounted for age (yes)	0.10 ± 0.06	−0.03, 0.22	0.44
Method for telomere measurement (qPCR)	−0.08 ± 0.06	−0.19, 0.04	0.27
Cell turnover (short)	−0.07 ± 0.07	−0.20, 0.06	0.27
Age (juvenile)	−0.05 ± 0.05	−0.15, 0.05	0.15
Type of study (experimental)	−0.06 ± 0.06	−0.18, 0.06	0.15
Telomere measure (shortening)	−0.03 ± 0.05	−0.12, 0.06	0.05

For each moderator, the reference group were as follows: Age (adult), Population (captivity), Cell turnover (long), Stressor category (harsh abiotic conditions), Type of study (correlative), Telomere measure (length), Method for telomere measurement (TRF), Effect size correction (no), Accounting for age (no).

high activity level than for harsh abiotic conditions, development and low body condition, and in the cases of competition and reproduction than for development and low body condition (Fig. 2). The association between stressor exposure and telomeres was strongly negative in captive populations (estimate ± SE = −0.23 ± 0.08; CI = [−0.38, −0.09]), whereas it was negative but with confidence intervals including positive values in wild (estimate ± SE = −0.06 ± 0.07; CI = [−0.19, 0.07]) and laboratory populations (estimate ± SE = −0.00 ± 0.10; CI = [−0.20, 0.20]). In accordance, the association was stronger in captive than in wild and laboratory populations. The association between stressor exposure and telomeres was stronger when accounting for the other factors included in the models by the authors of the original studies (estimate ± SE = −1.57 ± 0.45; CI = [−2.45, −0.68]), although it was also negative when the effect sizes were not corrected (estimate ± SE = −0.23 ± 0.08; CI = [−0.38, −0.09]).

The other moderators were retained in less than 50% of the best models (Table 3). The association between stressor exposure and telomeres was on average (1) 42% weaker when studies accounted for age than when they did not. On the contrary, it was 34% and 33% stronger when telomeres were measured (2) through qPCR than TRF and (3) in cells with short than long turnover respectively. Finally, the association was 25, 22 and 13% stronger in the case of (4) experimental than correlative studies, (5) juveniles than adults and (6) telomere shortening than telomere length respectively.

Stressor exposure, oxidative stress and telomeres

Out of 25 studies, two consistently measured that stressor exposure was negatively associated with telomeres (i.e. negatively associated with telomere length or positively associated with telomere shortening) and positively associated with oxidative stress; one measured the reverse pattern. Three studies measured a consistent negative effect of stressor exposure on both telomeres and oxidative stress. Finally, 19 studies measured mixed effects.

Overall, the correlation between the effect size of the association between stressor exposure and telomeres, and the effect size of the association between stressor exposure and oxidative stress (in other words: the relationship between telomeres and oxidative stress response) was significantly negative (r = −0.11; CI = [−0.21, −0.001]; Fig. 3a). When considering data on oxidative damage and antioxidant level separately, the correlation was non-significantly positive (r = 0.16; CI = [−0.02, 0.35]) and significantly negative (r = −0.16, CI = [−0.27, −0.03]) respectively (Fig. 3b and c). However, the telomeres vs. oxidative stress response covariance matrices for oxidative damage and antioxidant levels were not significantly different (λ = −0.02, d.f. = 3, P = 1).

DISCUSSION

Stressor exposure unequivocally influences telomeres

Recent meta-analyses measured a consistent negative association between the exposure to different kinds of stressors and telomeres (i.e. the greater the adversity, the shorter the telomeres or the higher the telomere attrition rate) in humans (Schutte & Malouff 2014, 2016; Mathur *et al.* 2016; Oliveira *et al.* 2016; Pepper *et al.* 2018). For the first time, this meta-analysis quantified the strength and direction of the association between the exposure to potentially stressful conditions and telomere dynamics in non-human (and mostly non-model) vertebrates. Similar to previous meta-analyses on humans, we highlighted an overall moderate but significantly negative correlation between stressor exposure and telomeres across all taxa (i.e. a negative and positive correlation between stressor exposure and telomere length and telomere shortening

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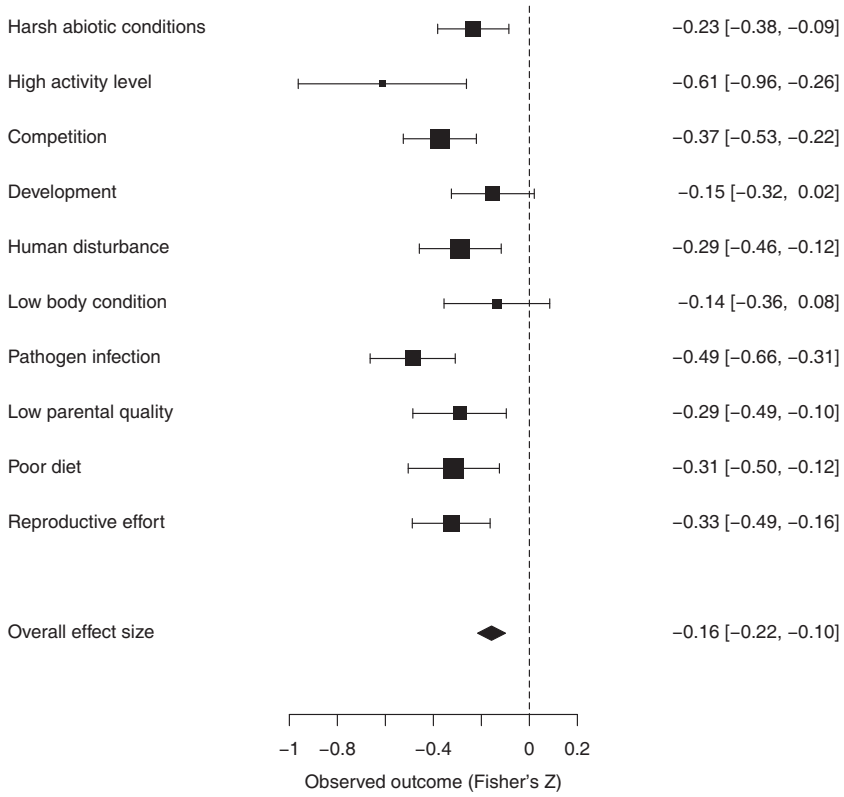

Figure 2 Forest plot of the effect size for observed relationships between stressor exposure and telomeres in non-human vertebrates depending on the stressor category (Fisher's Z [± 95% confidence interval]). The dashed line represents a null effect size (Fisher's Z = 0). Negative effect sizes indicate decreased telomere length or increased telomere erosion with stressor exposure. The size of the square for the mean effect size is proportional to the number of data points.

respectively). Notably, the negative association between stressor exposure and telomeres was consistent for all phylogenetic classes, for all *a priori*-selected stressor categories, and throughout life (although the stressor-telomeres association tended to be stronger in juveniles than in adults). Importantly, our study measured a rather minor publication bias (see Supplementary material; Appendix S1), suggesting that the consistent negative association between stressor exposure and telomeres measured in this meta-analysis is not an artefact of an unbalance in the current literature. In the same way, the strength of this association did not depend of the publication year, suggesting that the probability to publish highly significant and negative associations between stressor exposure and telomeres did not increase with increasing interest in this field.

The interaction between stressor category and telomere measure poorly explained variability in the association between stressor and telomeres. In other words, the exposure to stressor had similar impact on telomere length and the rate of telomere shortening. Amongst other things, current telomere length depends on initial telomere length and cell replicative history. Therefore, we expect more interindividual variability in telomere length than in telomere shortening rate as a result of different initial telomere length, age and previous history (Dugdale & Richardson 2018); such variation could thus mask the association between stressor exposure and telomere length. Yet, our study highlights that telomere length also strongly varies as a consequence of stress-induced telomere attrition (suggested by the significant association between the exposure to harsh environmental conditions and/or the experience of demanding biological processes and telomere dynamics). Concordantly, several studies measured a positive association between telomere loss and telomere length after the exposure to a stressor (i.e. the higher the telomere attrition, the shorter the telomeres after the treatment; e.g. Asghar *et al*. 2015; Bauch et al. 2013; Herborn *et al*. 2014; Mizutani *et al*. 2016; Watson *et al*. 2015). Therefore, post-natal exposure to harsh environmental conditions or demanding biological processes is likely to explain part of the variability in telomere attrition rate, and, consequently, in telomere length between individuals of the same age in non-human vertebrates (Fig. 4).

The recent meta-analysis from Wilbourn *et al*. (2018) demonstrated a moderate but significant negative correlation between telomere length and mortality risk in non-model vertebrates. Our study suggests that telomere-linked lifespan variability within species likely results, at least in part, from an individual post-natal experience: individuals exhibiting shorter telomeres may have been exposed to harsh environmental conditions (e.g. low food availability) or may have gone through demanding biological processes (e.g. reproduction; Reichert *et al*. 2014; Sudyka *et al*. 2019) (Fig. 4). Consequently, this could have led to the exhaustion of the cell

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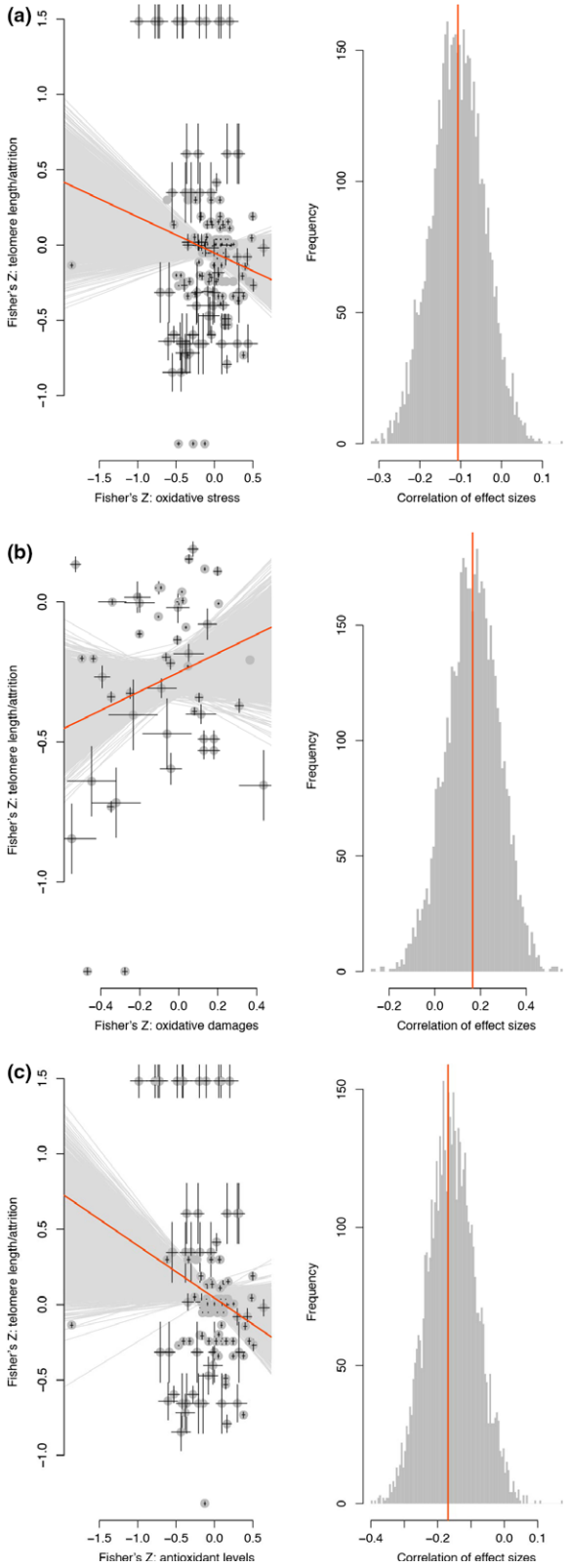

Figure 3 Analysis of the relationship between telomeres and (a) oxidative stress, (b) oxidative damage and (c) antioxidant levels in response to stressor exposure. Left panel: recorded effect sizes with their sampling variances. The red line and the grey interval represent the overall regression line and its meta-analytic confidence band (calculated as 5000 independent replicates) respectively. Right panel: frequency of each correlation coefficient between the effect size of the association between stressor exposure and telomeres, and the effect size of the association between stressor exposure and oxidative stress (based on the simulation of 5000 independent replicates). The red line represents the correlation coefficient observed in the original sample ($r = -0.016$).

replicative capacity early in life compared to the species' mean lifespan (Liu *et al.* 2019) as the length of the shortest telomere triggers cell senescence (Hemann *et al.* 2001; Zou *et al.* 2004). However, there is still no clear evidence from *in vivo* studies that telomere shortening is a causal factor in ageing and mortality risk (de Magalhães & Passos 2018). Alternatively, stressful life history may have resulted in stress-induced mortality independent of cell senescence. For instance the exposure to metallic trace elements has been found to covary with shorter telomeres in great tit nestlings and decreased immunity in feral pigeons (Stauffer *et al.* 2016; Chatelain *et al.* 2016b, a). The fact that qPCR, a method providing information on average telomere length rather than on the length and quantity of the shortest telomeres, allows to detect the strongest correlation between telomere length and mortality risk supports this hypothesis (Wilbourn *et al.* 2018). A third hypothesis, proposing that telomere length shapes an individual's behaviour or that telomere length and behaviours vary as a response to a third variable – the 'selective adoption' hypothesis – recently emerged (reviewed in Bateson & Nettle 2018). For instance we could imagine that telomere length, by influencing an individual's foraging behaviour, habitat choice or social interactions, would affect an individual probability to be infected by pathogens, and, consequently, its mortality risk. However, such a mechanism cannot account for the association between telomere length and stressors that are extrinsic to individuals such as low parental quality, competition with siblings or any other early-life adversity. Also, in the case of our analysis, this mechanism cannot explain the fact that telomeres were correlated with the exposure to stressors rather similarly in experimental and correlative studies. Most likely, the causation and the selective adoption hypotheses are not mutually exclusive. Given current evidence however, teasing apart the extent to which telomere length determines cell senescence or is a marker of an individual life history remains unclear (Bateson & Nettle 2018; Monaghan & Ozanne 2018).

Heterogeneous association between stressor exposure and telomeres

Despite the overall negative association between stressor exposure and telomeres, our meta-analysis also highlighted a rather high heterogeneity among the extracted effect sizes. Indeed, while the average direction of this association was consistently negative for all kinds of stressors, the strength of the association varied between stressor categories: it was the strongest in the case of pathogen infection (i.e. infection by bacteria, viruses or protozoa), high activity level, competition and reproductive effort. For the first time, this comprehensive study identifies key environmental conditions and life-history traits correlated with telomere length and dynamics. These correlations might highlight a causal link between those specific kinds of stressors

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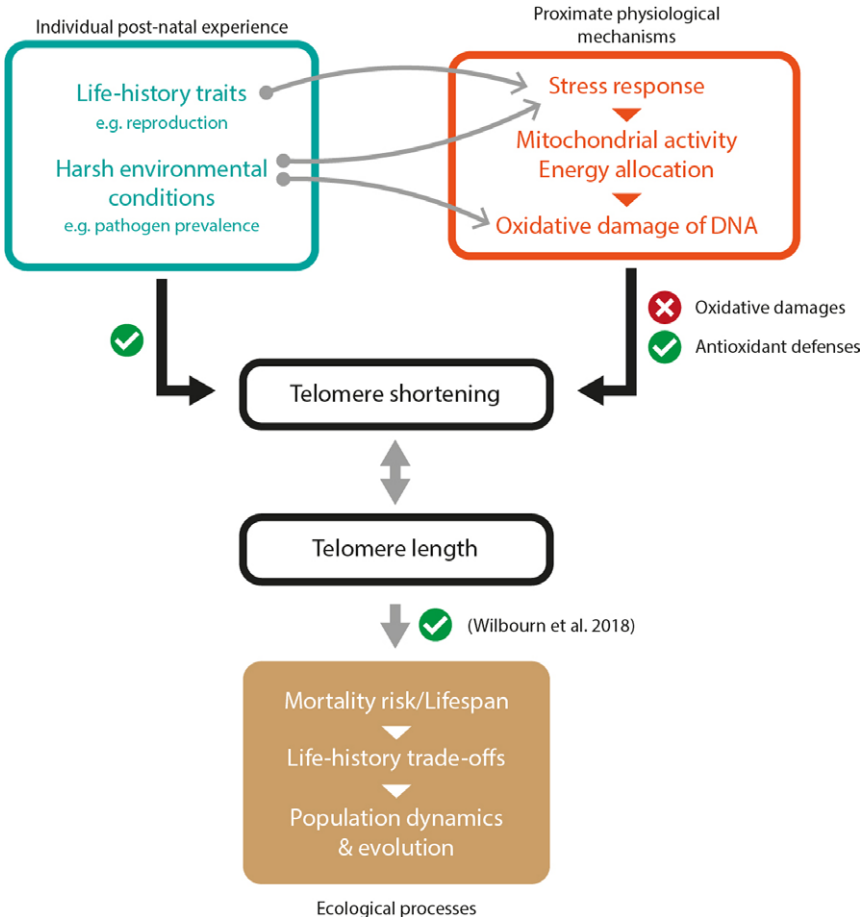

Figure 4 Diagram summing-up the expected cascade effects triggered by individual post-natal experience on ecological processes through telomere dynamics. Those potential pathways are based on the literature. Black arrows highlight the pathways tested in this study. Green ticks and red crosses highlight pathways tested within our meta-analytical framework that have been confirmed and that remain elusive respectively.

and telomere dynamics resulting from physiological costs; these are discussed in further detail below.

Pathogen infection

The effect of pathogen infection on telomeres may be fourfold: first, pathogens are responsible for damage to cells, including breaks in the DNA sequence that result in interferences with the host's metabolism. Second, such damage can lead to cell apoptosis, which triggers the compensatory proliferation of cells and, therefore, accelerates stem cell turnover (Bergmann & Steller 2010). Third, some pathogens also induce the development of cancers leading to the production of high amounts of ROS susceptible to damage the DNA sequence (Sosa *et al.* 2013). Fourth, pathogens activate an immune response; part of this response relies on phagocytes and some lymphocytes synthesising an enzyme (NADPH) also responsible for the production of ROS (Costantini & Møller 2009). While pathogen sensitivity partially depends on an individual investment in other biological function (e.g. reproduction; Sheldon & Verhulst 1996; Norris 2000), both correlative and experimental studies measured a negative effect of pathogen infection on telomeres, excluding, therefore, a potential confounding effect with reproduction costs (Ilmonen *et al.* 2008; Olsson *et al.* 2010; Asghar *et al.* 2015, 2016; Badás *et al.* 2015).

Competition

Competition-induced telomere attrition (mainly brood size and hatching order) could, by decreasing food intake, intensify energy allocation trade-offs between growth and other biological functions (Monaghan & Ozanne 2018). It could also result from an integrated stress response involving the synthesis of cortisol – in mammals and fish, or corticosterone – in birds (i.e. the stress hormone). Indeed, a recent review emphasised that several stress-induced telomere shortening could result from a prolonged exposure to high levels of glucocorticoids increasing oxidative stress, reducing antioxidant defences and modulating telomerase activity (Angelier *et al.* 2018). In birds, several experimental studies measured higher corticosterone levels in enlarged broods, in subordinate and in food deprived chicks (Saino 2003; Mora *et al.* 2010 but see Gil *et al.* 2008).

Reproductive effort

Numerous studies tried to understand the costs of reproduction. Those costs would be both direct – as a result to changes in the levels of hormones (e.g. insulin and glucocorticoids) regulating many aspects of the metabolism, and indirect – as a result to resource allocation. Indeed, the investment in

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reproduction decreases the investment in somatic maintenance. As described above, it reduces immunocompetence, consequently increasing pathogen sensitivity, but also the investment in costly detoxification systems; both mechanisms result in the accumulation of cell damage and, likely, in telomere attrition (Harshman & Zera 2007).

High activity level

A higher activity translates into increased metabolic rate, resulting in an increased rate of DNA synthesis (i.e. mitotic activity) and mitochondria activity (Silverin 1986; McEwen & Wingfield 2003; Boonstra 2004; Haase *et al*. 2016); both mechanisms resulting in telomere attrition. However, our analysis included only four studies investigating the association between activity level and telomeres. Three of them referred to hibernation in rodents and one to migration in a bird species. Therefore, additional studies are needed to draw general conclusions about the association between activity level and telomeres.

Interestingly, our analysis highlighted a weak association between development and telomeres, which contradicts previous ideas (Monaghan & Ozanne 2018). Several studies measured a higher rate of telomere loss early in life and/or a significant negative association between growth speed and telomere length (reviewed in Monaghan & Ozanne 2018). In their review, Monaghan & Ozanne highlight the variation in development metrics between studies (i.e. growth rate and final size) and the difficulty to disentangle the effects of development from other environmental factors such as competition with siblings during growth (Monaghan & Ozanne 2018). In our meta-analysis, development and competition were considered as two separate stressor categories, which might explain that the negative association between development and telomeres was only marginal. Further studies are needed to assess the causal link of development on telomere dynamics (see detailed recommendations in Monaghan & Ozanne 2018). In the same way, low body condition was not consistently associated with shorter telomeres or higher telomere shortening. This stressor category included size-adjusted body mass, body mass, and skin and feather colouration. Body condition is expected to decrease in response to intrinsic and extrinsic stressors (e.g. low nutritional status, migration or high reproductive investment). However, some body condition proxies might not consistently reflect individual overall health status. Especially, size-adjusted body mass and body mass are often prone to short-term variations (Brown 1996). In addition, body condition may covary with individual quality in a non-linear way (Moreno 1989; Blums *et al*. 2005).

Methodological considerations for stress-induced telomeres assessment

The correlation between stressor exposure and telomeres was the weakest when measured in population bred in captivity during several generations (laboratory populations), whereas it was the strongest in wild populations transferred in captivity (captive populations). While both laboratory and captive populations are exposed to control conditions, the response of laboratory breeds may be biased by the fact that the individuals might be exposed to novel environments they have never experienced in their recent evolutionary history; this could lead to idiosyncratic responses or to an absence of a response in the case the stimuli are not detected (Saltz *et al*. 2018). Interestingly, several established inbred stains of rodents exhibit longer telomeres than outbred populations, although the underlying mechanism of inbreeding-linked telomere elongation remains unknown (Hemann 2000; Manning *et al*. 2002). Whatever the mechanism, our study suggests that some laboratory stains might not be relevant models to understand telomere dynamics. The correlation between stressor exposure and telomeres was also weaker in wild than in captive populations. In the wild, individuals are exposed to multiple environmental factors that are difficult to control. Therefore, studies on wild populations might lack statistical power to identify the cause of telomere length and/or dynamic variation, compared to captive populations – exposed to relatively standardised environmental conditions. In a similar way, experimental studies, in which the potential stressor was clearly identified and controlled, tended to detect a stronger stressor–telomeres association, although both experimental and correlative studies measured an overall negative link between stressor exposure and telomeres.

While the link between stressor exposure and telomeres did not vary according to the telomere metric, the overall association (i.e. whatever the stressor category) tended to be slightly stronger in studies that measured telomere shortening compared to studies that measured telomere length. In wild populations, it is easier to measure telomere length rather than telomere shortening because it requires to capture each individual only once; our results suggest that measuring telomere length (involving a one-off sampling in the wild) thus appears to be an appropriate measure to test the link between stressor exposure and telomeres, minimising at the same time disturbance related to repeated animal capture. In the same way, measuring telomeres in blood (i.e. cells with a rather short turnover time) – a usually non-invasive method – generates slightly stronger results than when measuring telomeres in other cells (the latter may also involve sacrificing the life of sampled individuals). Consequently, cells with short turnover time should be preferred to cells with long turnover time (e.g. brain, muscles) whenever the purpose of the study is to assess the overall effect of a potential stressor on telomeres. All the more so because telomere length strongly correlates between red blood cells and other tissues, suggesting that telomere length in red blood cells is a good proxy for telomere length in the whole organism (Reichert *et al*. 2013).

Interestingly, the variation in the strength and direction of the association between stressor exposure and telomeres was poorly explained by methodological differences between studies. Those studies included in this meta-analysis invariably applied one of two methodologies to measure telomeres: quantitative PCR (qPCR) or terminal restriction fragment analysis (TRF). The qPCR method provides information on average and relative telomere length; it indistinctly measures telomeric repeats located at the extremity and within chromosomes. On the contrary, the TRF method measures the heterogeneous range of telomere lengths in a cell population using the length distribution of the terminal restriction

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fragments**.** A recent study comparing the accuracy and relevance of all the different methods used to measure telomeres stressed that, because only the shortest telomeres leads to cell dysfunction, methods measuring an average telomere length (as assessed by qPCR) is likely to have limited applications (Lai *et al*. 2018). However, the meta-analyses from Wilbourn *et al*. (2018) demonstrated that the negative association between telomere length and mortality risk was stronger in studies using qPCR relative to TRF methods. The authors suggest that such a difference might result from differential publication bias: non-significant results obtained using the qPCR method, a both cheaper and faster method, would have a lower probability to be published than similar results obtained using the TRF method. However, the authors also point out that such differences may be driven by the fact that mean telomere length may be more accurately estimated when using the qPCR than the TRF method; indeed, mean telomere length reported by the TRF method may be misleading as telomere length distributions can be highly skewed and thus poorly be reflected in average values. Thus, mean telomere length estimated through qPCR may better estimate the overall physiological costs experienced by an individual (Wilbourn *et al*. 2018). Our meta-analysis measured a negative association between stressor exposure and telomeres independently of the type of method that has been used to measure telomere length, although the association tended to be slightly stronger (i.e. more negative) in the case of qPCR compared to TRF. This suggests that both methods allow the detection of stress-induced telomere attrition; specifically, it appears that the noise in telomere length resulting from interstitial repeats does not mask the differences in the length of end-cap telomeres between individuals. Nonetheless, a shorter average telomere length may not be associated with a higher cell senescence rate (as mortality risk might not directly result from telomere length; see above). In order to test for the association between stressor exposure, telomere dynamics and ageing, future studies are encouraged to adopt advanced methods to measure telomeres such as the single telomere length analysis (STELA) or the telomere shortest length assay (TeSLA) that measure chromosome-specific abundance of the shortest telomeres (Lai *et al*. 2018).

Support for oxidative stress-mediated effects on telomeres

Harsh environmental conditions (e.g. low food availability) or demanding biological processes (e.g. reproduction) are expected to trigger an integrated stress response that translates into an increased metabolic rate resulting in the production of reactive oxygen species (ROS), and may also raise cell division rate. Stress-induced ROS production would accelerate telomere attrition rate by increasing damage to the telomeric sequence, decreasing its ability to replicate, which would ultimately translate into a faster mitotic clock and a shorter cell lifespan (Petersen *et al*. 1998; Henle *et al*. 1999; Oikawa & Kawanishi 1999; Kawanishi *et al*. 2001; Kawanishi & Oikawa 2004; Ahmed & Lingner 2018). Accordingly, the review by Reichert & Stier (2017) concluded that there is strong evidence from both experimental and correlative *in vivo* studies in vertebrates for oxidative-stress-induced effects in telomere dynamics. Our meta-analysis, targeting all non-human vertebrates, measured an overall significant negative correlation between stressors-telomeres and stressors-oxidative stress associations (Fig. 3a). In other words, when the effect of the stressor on telomeres was more negative, its effect on oxidative stress was more positive. However, it is important to highlight that we did not observe large positive effect sizes (i.e. higher than 0.5) of the association between stressor exposure and oxidative stress in our data set; the effect sizes ranged from -1.86 to 0.64. When separately investigating oxidative damage and antioxidant levels, the link between telomeres and oxidative stress was non-significantly positive in the case of oxidative damage (Fig. 3b) and significantly negative in the case of antioxidant levels (Fig. 3c). We might expect variable strengths of association between different oxidative stress biomarkers and telomeres. Indeed, the sensitivity of different oxidative stress markers to environmental conditions can vary. A recent study showed that markers of oxidative defences are more canalised compared to markers of oxidative damage; the constraint strength would vary according to the association of the marker with fitness (Boonekamp *et al*. 2018). In addition, different oxidative stress markers are likely to provide different information about physiological state (Monaghan *et al*. 2009). Similar to recent studies on oxidative stress, we expected stressor exposure to decrease antioxidant defences (Reichert & Stier 2017; Boonekamp *et al*. 2018). However, it is noteworthy that the reverse relationship could also be predicted. For instance a higher level of ROS may lead to the overexpression of the antioxidant response (i.e. of the level of enzymatic antioxidants). Therefore, antioxidant capacity is not sufficient to make inferences about oxidative stress (Costantini & Verhulst 2009).

Our meta-analysis on the association between stressor exposure, oxidative stress and telomeres included only 25 studies; this sample size might result in a relatively low statistical power. Particularly, the covariation of telomeres and oxidative stress with stressor exposure was highly variable. Moreover, only two studies measured biomarkers of oxidative damage of DNA. While only oxidative damage of DNA could directly explain oxidative stress-induced telomere shortening, this association remains unclear. Our meta-analysis stresses the need for additional studies that would improve our understanding of the physiological mechanisms underlying the link between stressor exposure and telomere dynamics. Studies that measure several biomarkers of oxidative stress (including DNA damage) and/or levels of glucocorticoids, in addition to telomere length or shortening, would be helpful in identifying the physiological mechanisms that have a causal effect on telomere dynamics (Boonekamp *et al*. 2017). Importantly, it appears essential to agree on guidelines formulating the most appropriate methodological approach to test for the causal relationship between the exposure to stressful conditions, oxidative stress and telomere dynamics. We suggest that a relevant approach would involve (1) experimentally manipulating the stressor within the range of the natural variation and (2) on a wild population of known age class, (3) measuring a panel of oxidative damage and oxidative defence biomarkers. If repeated measurements are taken, we recommend (3) assessing oxidative stress biomarkers and telomere length simultaneously both before and after the individuals are exposed to the

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stressor and with a minimum interval that should account for the turnover time of the tissue used to measure telomeres. The study of Boonekamp *et al*. (2017) probably illustrates the most relevant methodology to date and constitutes a valuable starting point to lay the foundation of such methodological guidelines. Undoubtedly, increasing the number of studies would allow to identify novel moderators underlying the heterogeneity in the association between oxidative stress and telomeres, and to increase the statistical power of future meta-analyses in the field. Finally, the combination of those physiological measurements with survival estimation (e.g. offspring survival or recruitment) would be of great value to draw a bigger picture of the cascade effects triggered by the exposure to challenging environmental conditions, their effects on telomeres and on possible resulting fitness impairments (Fig. 4).

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AUTHORSHIP

MC and MS designed the study. MC and SMD collected the data. SMD performed the statistical analyses. MC wrote the first draft of the manuscript and all the authors contributed substantially to revisions.

DATA AVAILABILITY STATEMENT

The list of papers used in the meta-analysis is listed within the reference list. The database supporting the results and the R scripts used for analysis are available from the Figshare Repository: https://doi.org/ 10.6084/m9.figshare.10003334.

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