



Inbreeding is associated with shorter early-life telomere length in a wild passerine

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Abstract

Inbreeding can have negative effects on survival and reproduction, which may be of conservation concern in small and isolated populations. However, the physiological mechanisms underlying inbreeding depression are not well-known. The length of telomeres, the DNA sequences protecting chromosome ends, has been associated with health or fitness in several species. We investigated effects of inbreeding on early-life telomere length in two small island populations of wild house sparrows (*Passer domesticus*) known to be affected by inbreeding depression. Using genomic measures of inbreeding we found that inbred nestling house sparrows ($n=371$) have significantly shorter telomeres. Using pedigree-based estimates of inbreeding we found a tendency for inbred nestling house sparrows to have shorter telomeres ($n=1195$). This negative effect of inbreeding on telomere length may have been complemented by a heterosis effect resulting in longer telomeres in individuals that were less inbred than the population average. Furthermore, we found some evidence of stronger effects of inbreeding on telomere length in males than females. Thus, telomere length may reveal subtle costs of inbreeding in the wild and demonstrate a route by which inbreeding negatively impacts the physiological state of an organism already at early life-history stages.

Keywords Biomarker · Conservation physiology · Heterosis · Inbreeding depression · SNP · Telomere dynamics

Introduction

Inbreeding has significant detrimental effects on survival, reproduction, and resistance to disease and other stressors in wild populations (Keller and Waller 2002). Such decline in fitness resulting from an increase in genome-wide homozygosity is known as inbreeding depression (Charlesworth and Willis 2009) and is of major concern in small and isolated populations, in particular of endangered species (Bozzuto

et al. 2019; Harrison et al. 2019; Hedrick and Kalinowski 2000). Increased homozygosity can lead to reduced fitness due to expression of deleterious recessive alleles (“dominance hypothesis”) or increased homozygosity at loci with heterozygote advantage (“overdominance hypothesis”, Charlesworth and Willis 2009). Regardless of the genetic basis for inbreeding depression, it is difficult to identify and quantify the physiological mechanisms underlying the fitness costs of inbreeding (Fox and Reed 2011; Kristensen et al. 2010; Losdat et al. 2016).

Telomeres are short DNA tandem repeats that are found at the tips of most eukaryotic chromosomes (Blackburn and Gall 1978; Červenák et al. 2021). Telomeres shorten during cell division (Harley et al. 1990), but may also shorten due to several other reasons including physiological processes generating oxidative stress (Barnes et al. 2019; Monaghan and Ozanne 2018; Reichert and Stier 2017; von Zglinicki 2002). The high guanine content of telomeres (50%) makes them particularly vulnerable to oxidative stress (Kawanishi and Oikawa 2004). Short telomeres can trigger apoptosis and telomere attrition is considered a hallmark of aging

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(López-Otín et al. 2013), although the causal involvement of telomere shortening in organismal senescence is not well understood (Simons 2015). However, telomere length (TL) may reflect the cumulative stress experienced by an individual (Bateson 2016; Monaghan 2014), and TL or TL shortening are associated with health or fitness in several species (Barrett et al. 2013; Chatelain et al. 2020; Froy et al. 2021; Heidinger et al. 2021; Wilbourn et al. 2018). Thus, TL is increasingly used as a biomarker of somatic integrity in studies of physiological or evolutionary ecology (Bateson and Poirier 2019; Haussmann and Marchetto 2010; Pepper et al. 2018; Young 2018).

Inbreeding depression can be caused by reduced immune response (Charpentier et al. 2008; Reid et al. 2003) and higher maintenance metabolism (Ketola and Kotiaho 2009), which increases oxidative stress de Boer et al. 2018a; Okada et al. 2011). Thus, inbred individuals may experience higher levels of oxidative stress (Kristensen et al. 2005; Pedersen et al. 2008) and thus have shorter telomeres (von Zglinicki 2002). We therefore hypothesize that TL could provide an integrative measure of the somatic costs associated with inbreeding depression in wild populations, with inbred individuals having shorter telomeres than outbred individuals. However, the few studies investigating associations between inbreeding and TL have found equivocal results. In line with our expectations, Bebbington et al. (2016) found that homozygosity was negatively associated with TL in wild Seychelles warblers (*Acrocephalus sechellensis*) and Seluanov et al. (2008) reported that telomeres were shorter in inbred laboratory strains of Norway rats (*Rattus norvegicus*) in captivity compared to a single wild-caught rat. Many domesticated species are generally assumed to be more inbred than their wild counterparts (Bosse et al. 2018; Moyers et al. 2018; Wiener and Wilkinson 2011). However, several studies have found that telomeres were longer in inbred domesticated strains of laboratory mice (*Mus* spp. and *Peromyscus* spp., Hemann and Greider 2000; Manning et al. 2002; Seluanov et al. 2008), in domesticated strains of pearl millet (*Pennisetum glaucum*, Sridevi et al. 2002), in domesticated inbred chicken (*Gallus gallus*, O'Hare and Delany 2009), and across several species of domesticated mammals (Pepke and Eisenberg 2021) compared to non-domesticated species. However, there were no clear differences in TL between inbred and wild leporid strains (Forsyth et al. 2005). Other studies found no association between pedigree-based inbreeding coefficients and TL or telomere attrition in humans (*Homo sapiens*, Mansour et al. 2011), wild sand lizards (*Lacerta agilis*, Olsson et al. 2018), or wild natterjack toads (*Epidalea calamita*, Sánchez-Montes et al. 2020). Becker et al. (2015) reported a weak non-significant but positive association between inbreeding and TL in wild white-throated dippers (*Cinclus cinclus*).

These contrasting results suggest that the telomere dynamics of captive, domesticated species living in a controlled environment may not be representative of wild, free-living populations (Chatelain et al. 2020; Pepke and Eisenberg 2021; Weinstein and Ciszek 2002). For instance, captive populations may be less vulnerable to inbreeding because inbreeding depression is greater under stressful environmental conditions (Fox and Reed 2011; Reed et al. 2002). Furthermore, captivity may in itself provide conditions that change the telomere dynamics of the populations (Eisenberg 2011), e.g. Hemann and Greider (2000) attributed the longer telomeres of inbred mice to effects of captive breeding and not inbreeding *per se*. For instance, TL shortening rates may increase during metabolically costly processes such as reproduction (Sudyka et al. 2019; Wood et al. 2021) and inbreeding may reduce fecundity (Keller and Waller 2002). Such effects have been suggested to explain the observation of longer adult TL in some inbred domesticated species (Eisenberg 2011), which could be resolved by measuring TL in early-life. Furthermore, most of the studies of domesticated animals compared TLs of different populations or species and their results may not be extrapolated to natural variation in TL and inbreeding levels within wild populations. Indeed, TL can vary considerably within species (Tricola et al. 2018) and across closely related species (Pepke et al. 2021c) in the wild. Finally, it is not known if outbreeding could be accompanied by a heterosis effect (hybrid vigor, e.g. Charlesworth and Willis 2009) acting on TL. Physiological mechanisms underlying heterosis are not well-known (Wu et al. 2021), but we hypothesize that the observed fitness benefits of outcrossing inbred populations (Frankham 2015) could be reflected in TL restoration (Nuzhdin and Reiwitch 2002; Ozawa et al. 2019).

In this study, we utilized a long-term metapopulation study to examine how inbreeding affects early-life TL in wild house sparrows (*Passer domesticus*). Inbreeding has been shown to reduce fitness components such as recruitment probability, adult lifespan, and both annual and lifetime reproductive success in this metapopulation (Billing et al. 2012; Jensen et al. 2007; Niskanen et al. 2020), but the physiological effects underlying these phenomena remain unknown. We expect that inbred individuals will have shorter telomeres if TL is a general biomarker of somatic integrity and health (e.g. Bebbington et al. 2016; Boonekamp et al. 2013; Wilbourn et al. 2018). The effects of inbreeding on TL might be sex-specific Benton et al. 2018; Billing et al. 2012; de Boer et al. 2018a; de Boer, Eens, & MülleBoer et al. 2018b) or depend on environmental conditions (Armbruster and Reed 2005; Szulkin and Sheldon 2007). However, TL is negatively associated with body size or growth rate within many species (Monaghan and Ozanne 2018; Ringsby et al. 2015) and may change with age (Hall et al. 2004; Remot

et al. 2021) or vary between sexes (Barrett and Richardson 2011; Remot et al. 2020) and habitat quality (Angelier et al. 2013; McLennan et al. 2021; Wilbourn et al. 2017). We therefore account for body size (measured as tarsus length), age, sex, and habitat type, and test for an interaction between inbreeding levels and sex or habitat type, when investigating the association between TL and inbreeding. We use three different measures of inbreeding; marker-based estimates ($n=371$) which are better at capturing homozygosity and inbreeding caused by distant ancestors not included in a pedigree, and pedigree-based estimates (Kardos et al. 2016) for which larger samples size may be obtained from long-term field studies ($n=1195$). Finally, to investigate a potential heterosis effect on TL, we test if the association between TL and inbreeding is different among outbred and inbred individuals.

Materials and methods

Study system

This study was conducted in two natural populations of house sparrows in northern Norway. On the island of Hestmannøy (66°33'N, 12°50'E), the sparrows live around dairy farms, where they nest inside barns in cavities or nest boxes. The island is characterized by cultivated grassland, mountains, forest, and heathland. On the island of Træna (66°30'N, 12°05'E), 34 km further from the mainland, the sparrows live in gardens of a small human settlement and nest in nest boxes. This island is dominated by heathland, sparse forest, and gardens. The natural breeding environment for house sparrows is human habitation (Hanson et al. 2020) and they have evolved their commensal relationship with humans for millennia (Ravinet et al. 2018). While human presence or farming provide the natural basis of existence for house sparrows (Ringsby et al. 2006), demographic characteristics, breeding densities, and inbreeding rates are comparable to other small isolated wild animal populations (Araya-Ajoy et al. 2021; Jensen et al. 2007; Niskanen et al. 2020). In the years 1994–2013 (on Hestmannøy) and 2004–2013 (on Træna), nestlings at the age of 5–14 days were ringed with a unique combination of color rings for identification. Nestlings were also blood sampled by brachial venipuncture, and tarsometatarsus (tarsus) was measured with slide calipers to the nearest 0.01 mm. Tarsus length is here used as an index of body size (Rising and Somers 1989; Senar and Pascual 1997). Blood samples (25 μ L) were stored in 96% ethanol at room temperature in the field and at -20 °C in the laboratory until DNA extraction (described in Pepke et al. 2021b). Birds that were resighted or recaptured in the year following hatching (i.e. from 1995

to 2014 on Hestmannøy and from 2005 to 2014 on Træna) were categorized as first-year survivors (i.e. recruits).

Telomere length measurements

Relative erythrocyte telomere length (TL) was successfully measured in DNA derived from 2746 whole blood samples from house sparrow nestlings using the qPCR method (Cawthon 2002) as described in Pepke et al. (2021a). For this study, we included only individuals with two known parents and at least two known grandparents, or for which genomic inbreeding coefficients could be estimated (described below), resulting in a sample size of $n=1370$ individuals ($n=679$ males and $n=691$ females of which $n=1161$ were from Hestmannøy and $n=209$ from Træna, see sample size details in Table 1). TL was determined relative to the amount of a non-variable gene (*GAPDH*, Criscuolo et al. 2009) and a reference sample, which was included as a two-fold serial dilution (40–2.5 ng/well) on all plates to produce a standard curve. All samples were randomized and run in triplicates on 2 × 125 96-well plates, which all included a nontarget control sample. All samples were processed within a few months by the same researcher (MLP) to reduce technical effects. Relative TL was computed using qBASE (Hellemans et al. 2007) while controlling for inter-run variation. All individual plate efficiencies were within $100 \pm 10\%$ (see Pepke et al. 2021a).

Sex was successfully determined for $n=1360$ individuals by amplification of the *CHD* gene on the avian sex chromosomes as described in Jensen et al. (2007). For $n=10$ individuals, sex was determined based on their adult plumage.

Microsatellite pedigree construction

Microsatellite (MS) pedigrees were constructed based on 13 polymorphic microsatellite markers using CERVUS 3.0 (Kalinowski et al. 2007) as described in previous studies (Billing et al. 2012; Jensen et al. 2003, 2008). The assignment of parentage was correct in at least 90% of cases (see Jensen et al. 2008). Nestlings within the same clutch were assumed to have the same mother. This metapopulation pedigree (Jensen et al. 2008) was pruned to contain $n=2184$ informative ancestors ($n=1710$ maternities and $n=1734$ paternities), including non-phenotyped ancestors, using the R package *MCMCglmm* (Hadfield 2010). Maximum pedigree depth was 13 generations, the number of equivalent complete generations (i.e. the sum of the proportion of known ancestors across all generations, Wellmann 2021) was 1.834, and the mean pairwise relatedness was 0.006. We calculated inbreeding coefficients (F_{PED}), which estimate the expected proportion of an individual's genome that is identical by descent (IBD), based on the MS pedigree for

Table 1 Number of nestling house sparrows of each sex and in total with early-life telomere length and inbreeding coefficient measurements within each population (Hestmannøy and Træna) for each measure of inbreeding (microsatellite pedigree-based inbreeding coefficient [F_{PED}], genomic inbreeding coefficient [F_{GRM}], and runs-of-homozygosity [F_{ROH}]). Number of individuals with at least two known full ancestral generations (gen.) are shown. Number of individuals with F_{GRM} values above and below the mean F_{GRM} , which is used as a break point to differentiate individuals that were more and less inbred than average, respectively, are also shown

Island population:	Hestmannøy			Træna			Total:
	Males	Females	Sum:	Males	Females	Sum:	
F_{PED} (≥ 1.5 gen.)	511	546	1057	78	60	138	1195
F_{PED} (≥ 2 full gen.)	148	165	313	4	3	7	320
F_{GRM}	140	135	275	49	47	96	371
$F_{GRM} > 0.016$	43	63	106	26	32	58	164
$F_{GRM} < 0.016$	97	72	169	23	15	38	207
F_{ROH}	140	135	275	49	47	96	371

individuals with two known parents and at least two known grandparents ($n = 1057$ from Hestmannøy and $n = 138$ from Træna, Table 1) using the R package *pedigree* (Coster 2012). We also selected a subset of individuals with at least two full ancestral generations (i.e. four known grandparents) to only include the most robust estimates of F_{PED} ($n = 313$ from Hestmannøy and $n = 7$ from Træna).

Genomic inbreeding estimation

Starting from year 1997 (Hestmannøy) or 2004 (Træna), birds that survived until recruitment ($n = 275$ from Hestmannøy and $n = 96$ from Træna) were genotyped for 200,000 Single Nucleotide Polymorphisms (SNPs) as described in Lundregan et al. (2018). Two genomic inbreeding coefficients were then estimated using 118,810 autosomal SNPs not in strong linkage disequilibrium, as described in Niskanen et al. (2020).

The weighted average homozygosity over all loci from the genomic relationship matrix (F_{GRM}) was estimated for the whole metapopulation (consisting of eight island populations) simultaneously using the GCTA software (\hat{F}^{III} in Yang et al. 2011). F_{GRM} gives more weight to homozygotes of the minor allele than of the major allele, and it is an estimate of the correlation between homologous genes of the two gametes of an individual relative to the current population (Yang et al. 2011). F_{GRM} can be negative if the probability that the two homologous genes of an individual are IBD is smaller than that of two homologous genes being drawn at random from the reference population (Wang 2014; Yang et al. 2011). Thus, the individuals with the smallest estimates of F_{GRM} are expected to be outbred (hybrids) because of e.g. mating involving immigrants (Wang 2014). Thus, we suggest that if an association between F_{GRM} and TL is stronger among outbred individuals (with F_{GRM} values smaller than average) than among inbred individuals (with F_{GRM} values larger than average), it may be partly attributed to a heterosis effect acting on TL. Alternatively, an association between F_{GRM} and TL may be mainly driven by highly inbred individuals, or the effect of inbreeding on TL may be linear across different levels of homozygosity.

The proportion of the genome within runs-of-homozygosity (F_{ROH} ranging from 0 to 1, McQuillan et al. 2008) was estimated using the PLINK software (Purcell et al. 2007). Homozygous sequences of minimum length of 2 Mbp were extracted using the PLINK settings: --homozyg-group --homozyg-density 10 --homozyg-gap 1000 --homozyg-kb 2000 --homozyg-snp 50 --homozyg-window-het 0 --homozyg-window-missing 5 --homozyg-window-snp 50 (see Niskanen et al. 2020). ROH arise through mating of individuals that are IBD, and may therefore be used to estimate inbreeding (Curik et al. 2014). Based on the house

sparrow reference genome (Elgvin et al. 2017) and linkage map (Hagen et al. 2020), homozygous sequences of 2 Mbp would be caused by inbreeding that occurred up to 12 generations ago (Niskanen et al. 2020).

Statistical analyses

To test whether TL was affected by inbreeding, we fitted linear mixed models (LMMs) using the package *lme4* (Bates et al. 2015) in R v. 3.6.3 (R Core Team 2020). TL (response variable) was \log_{10} -transformed to conform to the assumption of normally distributed residuals and the models were fitted with a (continuous) fixed effect of one of the inbreeding coefficients (F_{PED} [$n=1195$], F_{PED} with at least two full generations known [$n=320$], F_{GRM} [$n=371$], or F_{ROH} [$n=371$], see Table 1 for sample size details). Since genomic estimators of inbreeding (F_{GRM} and F_{ROH}) were only available for recruits (first-year survivors), we tested whether the relationship between TL and F_{PED} varied between survivors (“1”, $n=206$) and non-survivors (“0”, $n=989$) by including an interaction effect between F_{PED} and first-year survival. Tarsus length increases with nestling age, so tarsus length was age-corrected by taking the residuals from a regression of tarsus length on age and age squared. This allowed us to include both tarsus length and age in the models describing variation in TL. Thus, age-standardized tarsus length, fledging age at sampling (in number of days), hatch day (ordinal date mean centered across years), population identity (categorical: Hestmannøy or Træna), and sex (categorical: male or female) were included as fixed effects in all models. We tested whether the effect of inbreeding on TL varied between sexes and populations by including two-way interaction terms between the inbreeding coefficient and sex or population identity. Random intercepts were fitted for year and brood identity to account for the non-independence of nestlings from the same year and brood. This also controls for within-brood effects of inbreeding levels (Olsson et al. 2018). We then tested whether the inclusion of the inbreeding coefficient and interaction terms improved the baseline model (without the inbreeding coefficient) by comparing the resulting 5 candidate models using Akaike’s information criterion corrected for small sample sizes ($AICc$, Akaike 1973; Hurvich and Tsai 1989). Akaike weights (w) and evidence ratios (ER) were calculated to determine the relative fit of models to the data (Burnham and Anderson 2002). Models were validated visually using diagnostic plots of residuals, and model parameters are from models refitted with restricted maximum likelihood (REML). Estimates are reported with standard errors (SE) and 95% confidence intervals (CI). Regression lines were visualized using *ggplot2* (Wickham 2016).

To investigate heterosis effects on TL, we tested if the slopes of the regression between F_{GRM} and TL differed between individuals that were more inbred than on average ($F_{GRM} > \text{mean } F_{GRM}$) and individuals that were less inbred than average ($F_{GRM} < \text{mean } F_{GRM}$). We did this by testing if the inclusion of a regression break point at the mean F_{GRM} improved the models by comparing the resulting 9 candidate models using $AICc$.

RESULTS

Overall, the individual MS pedigree-based inbreeding coefficient (F_{PED}) was not a good predictor of genomic estimators of inbreeding (Fig. S1a,c; Pearson’s $r_p = 0.05$, $n=371$), but its relationships with F_{GRM} and F_{ROH} were improved when including only individuals with at least two generations known (Fig. S1b,d; $r_p > 0.30$, $n=59$). F_{GRM} and F_{ROH} were strongly correlated (Fig. S1e,f; $r_p = 0.7$, $n=371$).

F_{PED} varied from 0.000 to 0.250 (mean 0.007, 16.9% non-zero values). None of the models of F_{PED} provided strong statistical support for a relationship with TL. The highest ranked model explaining variation in TL included a negative effect of F_{PED} , but only slightly improved the fit of the baseline model ($\Delta_{2,1}AICc = 0.8$ [subscripts denote which ranked models are compared], $w_1 = 0.36$, $ER_1 = w_1/w_2 = 1.49$, Table S1 in the supporting information). Thus, there was a tendency for TL to be shorter in more inbred sparrows ($\beta_{F_{PED}} = -0.169 \pm 0.101$, CI = [-0.366, 0.028], $n=1195$, Fig. 1a; Table 2). The model ranked third ($\Delta_{3,1}AICc = 1.3$) indicated that TL was less associated with F_{PED} in males than in females ($\beta_{F_{PED} \times \text{sex}[female]} = -0.167 \pm 0.196$, CI = [-0.549, 0.216]), while the model ranked fourth ($\Delta_{4,1}AICc = 1.9$) indicated that TL was less associated with F_{PED} in the Hestmannøy population than in the Træna population ($\beta_{F_{PED} \times \text{island}[Hestmannøy]} = 0.115 \pm 0.314$, CI = [-0.498, 0.728]). However, due to high uncertainty in these parameter estimates, these effects are not deemed reliable.

When only including individuals with at least 2 full ancestral generations known (33.8% non-zero values), the model with F_{PED} was ranked second ($\Delta_{2,1}AICc = 1.1$, $\beta_{F_{PED}} = -0.205 \pm 0.198$, CI = [-0.588, 0.189], $n=320$, Fig. 1b, Table S2-3) and the baseline model was highest ranked.

There was a tendency for the negative effect of F_{PED} on TL to be weaker in first-year survivors ($n=206$, mean TL = 0.95 ± 0.02 , mean $F_{PED} = 0.010 \pm 0.003$) than in non-survivors ($n=989$, mean TL = 0.97 ± 0.01 , mean $F_{PED} = 0.007 \pm 0.001$, $\beta_{F_{PED} \times \text{first-year survival}} = 0.304 \pm 0.201$, CI = [-0.089, 0.697], $n=1195$, Fig. 1c, Table S4). This effect was uncertain with a CI overlapping zero. This suggests that the following analyses using genomic estimators

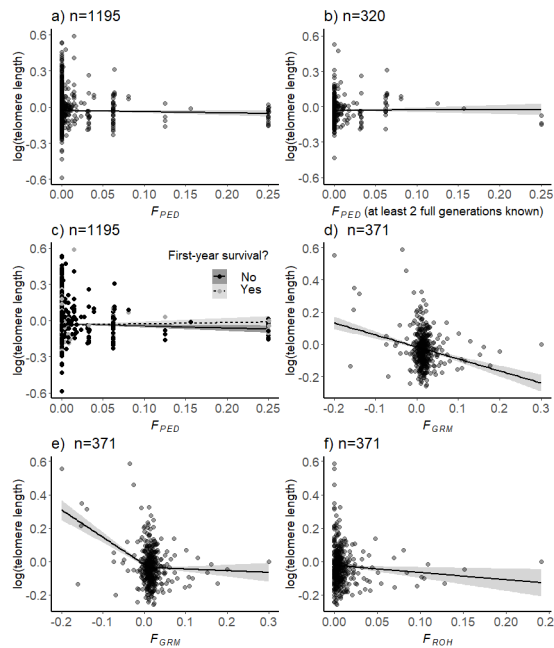


Fig. 1 Associations between early-life telomere length (\log_{10} -transformed) and various individual measures of inbreeding in wild house sparrows: (a) microsatellite pedigree-based inbreeding coefficient (F_{PED}), (b) F_{PED} for individuals with at least two full ancestral generations known, (c) testing for an interaction effect between F_{PED} and first-year survival (survivors: $n=206$ in grey, dotted regression line; non-survivors: $n=989$ in black, solid regression line), (d) genomic inbreeding coefficient F_{GRM} , (e) regression with a break point at the mean F_{GRM} (0.016), and (f) runs-of-homozygosity F_{ROH} . Black lines show the predicted effect of the inbreeding coefficient on TL from LMMs described in the text and the grey area shows 95% confidence intervals. Note that the y-axis is not scaled equally across panels and that color of points are graduated for visibility

of inbreeding in recruits were not biased towards stronger inbreeding effects in recruits.

Genomic inbreeding coefficient (F_{GRM}) estimates varied from -0.200 to 0.300 (mean 0.016, which is different from the expected 0, because F_{GRM} was calculated across the whole metapopulation simultaneously, see Niskanen et al. 2020). The highest ranked model ($\Delta_{2.1}AICc = 2.1$, Table

S5) showed that TL was shorter in more inbred sparrows ($\beta_{F_{GRM}} = -1.517 \pm 0.293$, CI = [-2.150, -0.920], $n=371$, Fig. 1d, and Table 3). In addition, the effect of F_{GRM} on TL was stronger in the Træna population ($\beta_{F_{GRM} * island[Hestmannøy]} = 0.824 \pm 0.339$, CI = [0.142, 1.529], Table 3) and in males ($\beta_{F_{GRM} * sex[female]} = 0.644 \pm 0.314$, CI = [0.034, 1.262], Table 3).

Including a break point at the mean F_{GRM} improved the model compared to a model with no break point (comparing models without interaction terms which were ranked 8 and 5: $\Delta_{8.5}AICc = 4.5$, see Table S6). The highest ranked model ($\Delta_{2.1}AICc = 3.1$, Table S6) revealed a strong negative association between TL and F_{GRM} among individuals with $F_{GRM} < 0.016$ but no association among inbred individuals with $F_{GRM} > 0.016$ (Fig. 1e; Table 4). This indicates that a heterosis effect resulting in longer telomeres in outbred individuals may explain the negative association found between inbreeding and TL. This model also included an interaction term suggesting that this heterosis effect was stronger in the Træna population (Table 4).

The runs-of-homozygosity inbreeding coefficient (F_{ROH}) estimates varied from 0.000 to 0.240 (mean 0.010, 73% non-zero values). The best model provided evidence for a negative effect of F_{ROH} on TL ($\beta_{F_{ROH}} = -1.148 \pm 0.512$, CI = [-2.144, -0.153], $n=371$, Fig. 1f, Table S7 and 5). This model also indicated that the negative effect of F_{ROH} tended to be stronger in males ($\beta_{F_{ROH} * sex[female]} = 0.915 \pm 0.610$, CI = [-0.270, 2.102]).

DISCUSSION

We found evidence using genomic measures of inbreeding that more inbred house sparrow nestlings had shorter telomeres (Fig. 1). Individual differences in TL are established early in life (Entringer et al. 2018), are heritable (Dugdale and Richardson 2018; Pepke et al. 2021a), and are positively associated with fitness in some species (Heidinger

Table 2 Estimates, standard errors (SE), lower and upper 95% confidence intervals (CI) from the highest ranked model of F_{PED} predicting variation in early-life TL ($n=1195$, see Table S2 and Fig. 1a). The model included random intercepts for brood identity (ID) and year. Estimates with CIs not overlapping 0 are shown in italics

Response variable: $\log_{10}(TL)$	Estimate	SE	Lower CI	Upper CI
intercept	-3.1E-4	0.037	-0.072	0.071
inbreeding coefficient (F_{PED})	-0.169	0.101	-0.366	0.028
tarsus length	-0.003	0.002	-0.008	0.001
sex [female]	-0.006	0.006	-0.017	0.005
<i>island identity [Hestmannøy]</i>	<i>0.025</i>	<i>0.012</i>	<i>0.001</i>	<i>0.049</i>
age	-0.003	0.002	-0.007	0.001
hatch day	-1.4E-4	1.6E-4	-4.4E-4	1.7E-4
$\sigma^2_{brood\ ID}$ ($n=500$)	0.002		0.001	0.003
σ^2_{year} ($n=20$)	0.003		0.001	0.006

Marginal R^2 /Conditional R^2 : 0.014/0.393

Table 3 Estimates, standard errors (SE), lower and upper 95% confidence intervals (CI) from the highest ranked model of F_{GRM} predicting variation in early-life TL ($n=371$, see Table S6 and Fig. 1d)

Response variable: $\log_{10}(\text{TL})$	Estimate	SE	Lower CI	Upper CI
intercept	0.069	0.038	-0.004	0.145
inbreeding coefficient (F_{GRM})	-1.517	0.293	-2.150	-0.920
tarsus length	-0.001	0.005	-0.011	0.009
sex [female]	-0.016	0.011	-0.039	0.006
island identity [Hestmannøy]	-0.036	0.016	-0.068	-0.004
age	-0.006	0.003	-0.012	4.6E-4
hatch day	-3.3E-4	2.8E-4	-0.001	2.1E-4
F_{GRM} * island [Hestmannøy]	0.824	0.339	0.142	1.529
F_{GRM} * sex [female]	0.644	0.314	0.034	1.262
$\sigma^2_{\text{brood ID}}$ ($n=273$)	0.004		0.002	0.006
σ^2_{year} ($n=17$)	0.001		0.000	0.003

Marginal R^2 /Conditional R^2 : 0.085/0.512

Table 4 Estimates, standard errors (SE), lower and upper 95% confidence intervals (CI) from the highest ranked model from Table S7 including a break point at $F_{GRM} = 0.016$ ($n=371$, see also Table S1). These effects of F_{GRM} are shown in Fig. 1e

Response variable: $\log_{10}(\text{TL})$	Estimate	SE	Lower CI	Upper CI
intercept	0.021	0.037	-0.051	0.095
inbreeding coefficient (F_{GRM}) < 0.016	-2.177	0.372	-3.051	-1.379
inbreeding coefficient (F_{GRM}) > 0.016	0.189	0.498	-0.780	1.153
tarsus length	-0.001	0.005	-0.011	0.008
sex [female]	-0.006	0.010	-0.027	0.014
island identity [Hestmannøy]	-0.009	0.016	-0.041	0.024
age	-0.005	0.003	-0.011	0.001
hatch day	-3.7E-4	2.7E-4	-0.001	1.5E-4
$F_{GRM} < 0.016$ * island [Hestmannøy]	1.562	0.465	0.610	2.576
$F_{GRM} > 0.016$ * island [Hestmannøy]	-0.026	0.561	-1.114	1.061
$\sigma^2_{\text{brood ID}}$ ($n=273$)	0.003		0.001	0.005
σ^2_{year} ($n=17$)	0.001		0.000	0.003

Marginal R^2 /Conditional R^2 : 0.106/0.458

et al. 2012; Wilbourn et al. 2018). Thus, short telomeres in more inbred individuals may underpin a physiological basis of inbreeding depression in fitness components that has been found in this species (Billing et al. 2012; Jensen et al. 2007; Niskanen et al. 2020) and in other wild animal populations (Keller and Waller 2002).

The effect of inbreeding on TL in house sparrows was negative across all measures of inbreeding, but only statistically significant (i.e. with confidence intervals not overlapping zero) when using genomic levels of inbreeding

(Fig. 1d-f), probably because they are better at capturing homozygosity causing inbreeding depression compared to using a pedigree-based estimator (Fig. 1a-c, Alemu et al. 2021; Huisman et al. 2016; Kardos et al. 2016). For instance, the frequency peak at $F_{PED}=0$ (see histograms in Fig. S1) is better resolved using F_{GRM} , which is expected due to pedigree incompleteness and Mendelian sampling variation in realized inbreeding levels around the pedigree prediction (Huisman et al. 2016). Mating between full siblings or between parent and offspring ($F=0.25$) resulted in a severe reduction in (relative) TL of 58% (F_{GRM}), 48% (F_{ROH}) or 11% (F_{PED}) compared to breeding between unrelated individuals (Tables 2 and 3, and 5). However, such high levels of inbreeding were rare (Fig. 1), and our results may need to be confirmed using larger datasets of highly inbred individuals. TL may be under strong selection in natural populations (Voillemot et al. 2012). Consequently, strong inbreeding depression is expected for fitness components or traits that are under strong selection (Béréanos et al. 2016; DeRose and Roff 1999). The analyses using genomic estimators of inbreeding were limited to recruited individuals, but the negative effect of inbreeding on TL may be even stronger if very inbred individuals, presumably with short telomeres, do not survive their first year and were thus excluded from our analyses (Jensen et al. 2007; Wilbourn et al. 2018). There was a tendency for such an effect when using pedigree-based levels of inbreeding (Fig. 1c and Table S4).

We found some evidence that inbreeding had stronger negative effects on TL in males than females (Tables 3 and 5). Such sex-specific effects of inbreeding are known from other species de Boer et al. 2018a, b; Janicke et al. 2013), but have rarely been observed early in life. There was a weak tendency for longer TL in males than females (Tables 2, 3, 4 and 5), which has been observed in similar house sparrow populations (Pepke et al. 2021b). Thus, males may be better buffered against the effects of inbreeding on TL. However, no sex-specific differences in inbreeding depression were observed in adult sparrows across this study metapopulation (Niskanen et al. 2020).

Increased inbreeding may be accompanied by population decline in small populations (Bozzuto et al. 2019; Chen et al. 2016; Feng et al. 2019), which can drive populations to extinction (O’Grady et al. 2006; Saccheri et al. 1998; Wright et al. 2007; Niskanen et al. 2020) showed that inbreeding depression in adult sparrows in our study system varied little across years or across the different island environments inhabited by these house sparrows. Hence, the strength of inbreeding depression is similar between populations, but due to harboring more inbred individuals, the relative effect is stronger in smaller populations (Niskanen et al. 2020). Small declining populations may be characterized

Table 5 Estimates, standard errors (SE), lower and upper 95% confidence intervals (CI) from the highest ranked model from of F_{ROH} predicting variation in early-life TL ($n = 371$, see Table S8 and Fig. 1f)

Response variable:	Estimate	SE	Lower CI	Upper CI
$\log_{10}(\text{TL})$				
intercept	0.051	0.040	-0.027	0.130
inbreeding coefficient (F_{ROH})	-1.148	0.512	-2.144	-0.153
tarsus length	-0.001	0.005	-0.011	0.010
sex [female]	-0.018	0.012	-0.041	0.005
island identity [Hestmannøy]	-0.020	0.016	-0.052	0.012
age	-0.005	0.003	-0.012	0.001
hatch day	-2.9E-4	3.0E-4	-0.001	2.9E-4
F_{ROH} * sex [female]	0.915	0.610	-0.270	2.102
$\sigma^2_{\text{brood ID}}$ ($n = 273$)	0.006		0.004	0.008
σ^2_{year} ($n = 17$)	0.002		4.6E-4	0.004
Marginal R^2 /Conditional R^2 : 0.029/0.579				

by gradual population-wide and trans-generational telomere erosion. For instance, Dupoué et al. (2017) observed shorter TL along an extinction risk gradient in populations of common lizards (*Zootoca vivipara*) that are disappearing from low altitudes at their southern range limit, presumably due to climate warming (Sinervo et al. 2010). Combined, these results suggest that TL may represent a potential physiological biomarker or molecular tool in conservation genetics addressing the viability of some small animal populations (Bebbington et al. 2016; Bergman et al. 2019; Dupoué et al. 2017; Madliger et al. 2020).

The negative effect of F_{GRM} on TL (Fig. 1d) was stronger among individuals that were less related than the average population (Fig. 1e). This suggests that longer telomeres in outbred individuals may partly be attributed to a general heterosis effect (Charlesworth and Willis 2009) involving mating between immigrants and native individuals (Dickel et al. 2021; Ebert et al. 2002). In our study metapopulation, the proportion of dispersers among recruits can be high among the island populations (0.2 on average ranging from 0.0 to 1.0 across years and islands, Ranke et al. 2021; Saatoglu et al. 2021), and hence most islands are not strongly differentiated (Niskanen et al. 2020). We found that the negative effect of F_{GRM} on TL was stronger in the Træna population (Tables 3 and 4). Træna is known to have a higher proportion of immigrants than Hestmannøy (Ranke et al. 2021), which may contribute to a stronger effect of heterosis in this population (Table 4). Furthermore, the gardens of Træna expose the sparrows to a different environment than the farms on Hestmannøy (Araya-Ajoy et al. 2019; Pärn et al. 2012). Inbreeding depression is expected to have more severe consequences under environmental stress (Armbruster and Reed 2005; Reed et al. 2002), such as harsh weather or competition de Boer et al. 2018a; Fox and Reed 2011; Marr et al. 2006). Telomeres shorten due

to environmental stressors such as harsh abiotic conditions (Chatelain et al. 2020). We speculate that environmental differences between the habitats of the two sparrow populations may explain the exacerbated effects of inbreeding on TL in the Træna population. For instance, in juvenile Seychelles warblers a negative relationship between homozygosity and TL was found only in poor seasons, i.e. when food availability was low (Bebbington et al. 2016). In adult Seychelles warblers, the effect of homozygosity on TL was consistently negative across seasons, suggesting that the negative effects of inbreeding accumulate through life and are reflected in telomere erosion (Bebbington et al. 2016). Here, we showed that inbreeding manifests in TL already at the nestling stage in a similar wild passerine.

We measured TL in blood, thus it is possible that inbreeding or heterosis only affected telomeres in erythrocytes (Manning et al. 2002; Olsson et al. 2020). However, this is unlikely because TLs often correlate well across tissues within the organism (Daniali et al. 2013; Demanelis et al. 2020; Reichert et al. 2013), especially in early-life (Prowse and Greider 1995). Although genomic inbreeding estimates were only available for first-year survivors, we may have avoided confounding effects of selective mortality of inbred individuals at much older ages by measuring TL already at the nestling stage (Hemmings et al. 2012; Sánchez-Montes et al. 2020). Furthermore, since the mutation accumulation theory of senescence predicts that deleterious effects of inbreeding increase with age (Charlesworth and Hughes 1996; Keller et al. 2008), we may expect that the effect on TL is persistent and potentially stronger in adult sparrows. Thus, future studies are required to investigate if inbreeding leads to persistently eroded TL throughout life, and if there are combined fitness consequences of any interaction between TL and inbreeding in wild populations. Even in the absence of a mechanism directly linking inbreeding and TL via the effects of oxidative stress (cf. the introduction), we may find inbred individuals to have short telomeres, because inbreeding impairs other physiological processes that affects both fitness and TL (Bebbington et al. 2016). Thus, the conflicting evidence in the literature of an effect of inbreeding on TL (reviewed in the introduction) suggests that an experimental procedure is needed to further elucidate the mechanisms underlying the correlation reported here (Manning et al. 2002), especially in wild populations.

In conclusion, the negative associations between inbreeding levels and TL found in this study suggest that TL may reveal subtle somatic costs of inbreeding in wild populations, and thereby demonstrates a potential route by which inbreeding negatively impacts the physiological state of an organism in early life. The observation of a potential heterosis effect on TL suggests that maintenance of dispersal

within this metapopulation is important for mitigating the negative effects of inbreeding.

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Authors' contributions MLP measured telomeres, analyzed data, and wrote the manuscript with contributions from all authors. WB supervised telomere measurements. HJ, AKN, and TK contributed to the genotype data processing, pedigree construction, and in designing statistical analyses. THR, BE-S, and HJ initiated the study system. THR, HJ, and TK contributed to the fieldwork.

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Code Availability Not applicable.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethics approval Fieldwork was carried out in accordance with permits from the Ringing Centre at Stavanger Museum and the Norway Norwegian Animal Research Authority.

Consent to participate Not applicable.

Consent for publication Not applicable.

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