

1 **Inbreeding is associated with shorter early-life** 2 **telomere length in a wild passerine**

3 Michael Le Pepke^{1*}, Alina K. Niskanen^{1,2}, Thomas Kvalnes¹, Winnie Boner³, Bernt-Erik
4 Sæther¹, Thor Harald Ringsby^{1§} & Henrik Jensen^{1§}

5 ¹Centre for Biodiversity Dynamics (CBD), Department of Biology, Norwegian University of
6 Science and Technology (NTNU), Trondheim, Norway.

7 ²Ecology and Genetics Research Unit, University of Oulu, Oulu, Finland.

8 ³Institute of Biodiversity, Animal Health and Comparative Medicine (IBAHCM), University
9 of Glasgow, UK.

10 *Correspondence: Michael Le Pepke, email: michael@pepke.dk.

11 §Joint senior authors.

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21 **ABSTRACT**

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

36

37 **INTRODUCTION**

38 Inbreeding may have significant detrimental effects on survival, reproduction, and
39 resistance to disease and other stressors in wild populations (Keller & Waller, 2002). Such
40 decline in fitness resulting from an increase in genome-wide homozygosity is known as
41 inbreeding depression (Charlesworth & Willis, 2009) and is of major concern in small and
42 isolated populations, in particular of endangered species (Bozzuto, Biebach, Muff, Ives, &
43 Keller, 2019; Harrisson et al., 2019; Hedrick & Kalinowski, 2000). Increased homozygosity
44 can lead to reduced fitness due to expression of deleterious recessive alleles (“dominance
45 hypothesis”) or increased homozygosity at loci with heterozygote advantage

46 (“overdominance hypothesis”, Charlesworth & Willis, 2009). Regardless of the genetic basis
47 for inbreeding depression, it is difficult to identify and quantify the physiological
48 mechanisms underlying the fitness costs of inbreeding (Fox & Reed, 2011; Kristensen,
49 Pedersen, Vermeulen, & Loeschcke, 2010; Losdat, Arcese, Sampson, Villar, & Reid, 2016).

50 Telomeres are short DNA tandem repeats that are found at the tips of most eukaryotic
51 chromosomes (Blackburn & Gall, 1978; Červenák, Sepšiová, Nosek, & Tomáška, 2021).
52 Telomeres shorten during cell division (Harley, Futcher, & Greider, 1990), but may also
53 shorten due to several other reasons including physiological processes generating oxidative
54 stress (Barnes, Fouquerel, & Opresko, 2019; Monaghan & Ozanne, 2018; Reichert & Stier,
55 2017; von Zglinicki, 2002). The high guanine content of telomeres (50%) makes them
56 particularly vulnerable to oxidative stress (Kawanishi & Oikawa, 2004). Short telomeres can
57 trigger apoptosis and telomere attrition is considered a hallmark of aging (López-Otín,
58 Blasco, Partridge, Serrano, & Kroemer, 2013), although the causal involvement of telomere
59 shortening in organismal senescence is not well understood (Simons, 2015). However,
60 telomere length (TL) may reflect the cumulative stress experienced by an individual
61 (Bateson, 2016; Monaghan, 2014), and TL or TL shortening are associated with health or
62 fitness in several species (Barrett, Burke, Hammers, Komdeur, & Richardson, 2013;
63 Chatelain, Drobniak, & Szulkin, 2020; Froy et al., 2021; Heidinger, Kucera, Kittilson, &
64 Westneat, 2021; Wilbourn et al., 2018). Thus, TL is increasingly used as a biomarker of
65 somatic integrity in studies of physiological or evolutionary ecology (Bateson & Poirier,
66 2019; Haussmann, 2010; Pepper, Bateson, & Nettle, 2018; Young, 2018).

67 Inbreeding depression can be caused by reduced immune response (Charpentier,
68 Williams, & Drea, 2008; Reid, Arcese, & Keller, 2003) and higher maintenance metabolism
69 (Ketola & Kotiaho, 2009), which increases oxidative stress (de Boer et al., 2018a; Okada,
70 Blount, Sharma, Snook, & Hosken, 2011). Thus, inbred individuals may experience higher

71 levels of oxidative stress (Kristensen, Sørensen, Kruhøffer, Pedersen, & Loeschcke, 2005;
72 Pedersen et al., 2008) and thus have shorter telomeres (von Zglinicki, 2002). We therefore
73 hypothesize that TL could provide an integrative measure of the somatic costs associated
74 with inbreeding depression in wild populations, with inbred individuals having shorter
75 telomeres than outbred individuals. However, the few studies investigating associations
76 between inbreeding and TL have found equivocal results. In line with our expectations,
77 Bebbington et al. (2016) found that homozygosity was negatively associated with TL in wild
78 Seychelles warblers (*Acrocephalus sechellensis*) and Seluanov et al. (2008) reported that
79 telomeres were shorter in inbred laboratory strains of Norway rats (*Rattus norvegicus*) in
80 captivity compared to a single wild-caught rat. Many domesticated species are generally
81 assumed to be more inbred than their wild counterparts (Bosse, Megens, Derks, de Cara, &
82 Groenen, 2018; Moyers, Morrell, & McKay, 2018; Wiener & Wilkinson, 2011). However,
83 several studies have found that telomeres were longer in inbred domesticated strains of
84 laboratory mice (*Mus* spp. and *Peromyscus* spp., Hemann & Greider, 2000; Manning,
85 Crossland, Dewey, & Van Zant, 2002; Seluanov et al., 2008), in domesticated strains of pearl
86 millet (*Pennisetum glaucum*, Sridevi, Uma, Sivaramakrishnan, & Isola, 2002), in
87 domesticated inbred chicken (*Gallus gallus*, O'Hare & Delany, 2009), and across several
88 species of domesticated mammals (Pepke & Eisenberg, 2021) compared to non-domesticated
89 species. However, there were no clear differences in TL between inbred and wild leporid
90 strains (Forsyth, Elder, Shay, & Wright, 2005). Other studies found no association between
91 pedigree-based inbreeding coefficients and TL or telomere attrition in humans (*Homo*
92 *sapiens*, Mansour et al., 2011), wild sand lizards (*Lacerta agilis*, Olsson, Wapstra, & Friesen,
93 2018), or wild natterjack toads (*Epidalea calamita*, Sánchez-Montes et al., 2020). Becker et
94 al. (2015) reported a weak non-significant but positive association between inbreeding and
95 TL in wild white-throated dippers (*Cinclus cinclus*).

96 These contrasting results suggest that the telomere dynamics of captive, domesticated
97 species living in a controlled environment may not be representative of wild, free-living
98 populations (Chatelain et al., 2020; Pepke & Eisenberg, 2021; Weinstein & Cizek, 2002).
99 For instance, captive populations may be less vulnerable to inbreeding because inbreeding
100 depression is greater under stressful environmental conditions (Fox & Reed, 2011; Reed,
101 Briscoe, & Frankham, 2002). Furthermore, captivity may in itself provide conditions that
102 change the telomere dynamics of the populations (Eisenberg, 2011), e.g. Hemann and Greider
103 (2000) attributed the longer telomeres of inbred mice to effects of captive breeding and not
104 inbreeding *per se*. For instance, TL shortening rates may increase during metabolically costly
105 processes such as reproduction (Sudyka, Arct, Drobniak, Gustafsson, & Cichoń, 2019; Wood
106 et al., 2021) and inbreeding may reduce fecundity (Keller & Waller, 2002). Such effects have
107 been suggested to explain the observation of longer adult TL in some inbred domesticated
108 species (Eisenberg, 2011), which could be resolved by measuring TL in early-life.
109 Furthermore, most of the studies of domesticated animals compared TLs of different
110 populations or species and their results may not be extrapolated to natural variation in TL and
111 inbreeding levels within wild populations. Indeed, TL can vary considerably within species
112 (Tricola et al., 2018) and across closely related species (Pepke, Ringsby, & Eisenberg, 2021)
113 in the wild. Finally, it is not known if outbreeding could be accompanied by a heterosis effect
114 (hybrid vigor, e.g. Charlesworth & Willis, 2009) acting on TL. For instance, the observed
115 fitness benefits of outcrossing inbred populations (Frankham, 2015) could be reflected in TL
116 restoration (Nuzhdin & Reiwitch, 2002; Ozawa et al., 2019).

117 In this study, we utilized a long-term metapopulation study to examine how
118 inbreeding affects early-life TL in wild house sparrows (*Passer domesticus*). Inbreeding has
119 been shown to reduce fitness components such as recruitment probability, adult lifespan, and
120 both annual and lifetime reproductive success in this metapopulation (Billing et al., 2012;

121 Jensen, Bremset, Ringsby, & Sæther, 2007; Niskanen et al., 2020), but the physiological
122 effects underlying these phenomena remain unknown. We expect that inbred individuals will
123 have shorter telomeres if TL is a general biomarker of somatic integrity and health (e.g.
124 Bebbington et al., 2016; Boonekamp, Simons, Hemerik, & Verhulst, 2013; Wilbourn et al.,
125 2018). The effects of inbreeding on TL might be sex-specific (Benton et al., 2018; Billing et
126 al., 2012; de Boer et al., 2018a; de Boer, Eens, & Müller, 2018b) or depend on environmental
127 conditions (Armbruster & Reed, 2005; Szulkin & Sheldon, 2007). However, TL is negatively
128 associated with body size or growth rate within many species (Monaghan & Ozanne, 2018;
129 Ringsby et al., 2015) and may change with age (Hall et al., 2004; Remot et al., 2021) or vary
130 between sexes (Barrett & Richardson, 2011; Remot et al., 2020) and habitat quality
131 (Angelier, Vleck, Holberton, & Marra, 2013; McLennan et al., 2021; Wilbourn et al., 2017).
132 We therefore account for body size (measured as tarsus length), age, sex, and habitat type,
133 and test for an interaction between inbreeding levels and sex or habitat type, when
134 investigating the association between TL and inbreeding. We use three different measures of
135 inbreeding; marker-based estimates ($n=371$) which are better at capturing homozygosity and
136 inbreeding caused by distant ancestors not included in a pedigree, and pedigree-based
137 estimates (Kardos, Taylor, Ellegren, Luikart, & Allendorf, 2016) for which larger samples
138 size may be obtained from long-term field studies ($n=1195$). Finally, to investigate a potential
139 heterosis effect on TL, we test if the association between TL and inbreeding is different
140 among outbred and inbred individuals.

141

142 **MATERIAL AND METHODS**

143 *Study system*

144 This study was conducted in two natural populations of house sparrows in northern
145 Norway. On the island of Hestmannøy (66°33'N, 12°50'E), the sparrows live around dairy

146 farms, where they nest inside barns in cavities or nest boxes. The island is characterized by
147 cultivated grassland, mountains, forest, and heathland. On the island of Træna (66°30'N,
148 12°05'E), 34 km further from the mainland, the sparrows live in gardens of a small human
149 settlement and nest in nest boxes. This island is dominated by heathland, sparse forest, and
150 gardens. The natural breeding environment for house sparrows is human habitation (Hanson,
151 Mathews, Hauber, & Martin, 2020) and they have evolved their commensal relationship with
152 humans for millennia (Ravinet et al., 2018). While human presence or farming provide the
153 natural basis of existence for house sparrows (Ringsby, Sæther, Jensen, & Engen, 2006),
154 demographic characteristics, breeding densities, and inbreeding rates are comparable to other
155 small isolated wild animal populations (Araya-Ajoy et al., 2021; Jensen et al., 2007;
156 Niskanen et al., 2020). In the years 1994-2013 (on Hestmannøy) and 2004-2013 (on Træna),
157 nestlings at the age of 5-14 days were ringed with a unique combination of color rings for
158 identification. Nestlings were also blood sampled by brachial venipuncture, and
159 tarsometatarsus (tarsus) was measured with slide calipers to the nearest 0.01 mm. Tarsus
160 length is here used as an index of body size (Rising & Somers, 1989; Senar & Pascual, 1997).
161 Blood samples (25 µL) were stored in 96% ethanol at room temperature in the field and at -
162 20°C in the laboratory until DNA extraction (described in Pepke et al., *submitted 2021b*).
163 Birds that were resighted or recaptured in the year following hatching (i.e. from 1995-2014
164 on Hestmannøy and from 2005-2014 on Træna) were categorized as first-year survivors.

165 *Telomere length measurements*

166 Relative erythrocyte telomere length (TL) was measured in DNA derived from whole
167 blood samples ($n=2746$ nestlings) using the qPCR method (Cawthon, 2002) as described in
168 Pepke et al. (*submitted 2021a*). For this study, we included only individuals with two known
169 parents and at least two known grandparents, or for which genomic inbreeding coefficients
170 could be estimated (described below), resulting in a sample size of $n=1370$ individuals

171 ($n=1161$ from Hestmannøy and $n=209$ from Træna). TL was determined relative to the
172 amount of a non-variable gene (GAPDH) and a reference sample (Criscuolo et al., 2009). All
173 samples were randomized and run in triplicates on 96-well plates. All samples were
174 processed within a few months by the same researcher (MLP) to reduce technical effects.
175 Relative TL was computed using qBASE (Hellemans, Mortier, De Paepe, Speleman, &
176 Vandesompele, 2007) while controlling for inter-run variation. All individual plate
177 efficiencies were within $100\pm 10\%$ (see Pepke et al., *submitted* 2021a). Sex was determined
178 by amplification of the CHD-gene as described in Jensen et al. (2007).

179 *Microsatellite pedigree construction*

180 Microsatellite (MS) pedigrees ($n=1857$ individuals from Hestmannøy and $n=342$ from
181 Træna including non-phenotyped ancestors) were constructed based on 13 polymorphic
182 microsatellite markers using CERVUS 3.0 (Kalinowski, Taper, & Marshall, 2007) as
183 described in Billing et al. (2012). Maximum pedigree depth was 13 generations. We
184 calculated inbreeding coefficients (F_{PED}), which estimate the expected proportion of an
185 individual's genome that is identical by descent (IBD), based on the MS pedigree for
186 individuals with two known parents and at least two known grandparents ($n=1057$ from
187 Hestmannøy and $n=138$ from Træna, Table 1) using the R package *pedigree* (Coster, 2012).
188 We also selected a subset of individuals with at least two full ancestral generations (i.e. four
189 known grandparents) to only include the most robust estimates of F_{PED} ($n=313$ from
190 Hestmannøy and $n=7$ from Træna).

191 *Genomic inbreeding estimation*

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

196 strong linkage disequilibrium, as described in Niskanen et al. (2020). The weighted average
197 homozygosity over all loci from the genomic relationship matrix (F_{GRM}) was estimated for
198 the whole metapopulation simultaneously using the GCTA software (Yang, Lee, Goddard, &
199 Visscher, 2011). F_{GRM} gives more weight to homozygotes of the minor allele than of the
200 major allele, and it is an estimate of the correlation between homologous genes of the two
201 gametes of an individual relative to the current population (Yang et al., 2011). F_{GRM} can be
202 negative if the probability that the two homologous genes of an individual are IBD is smaller
203 than that of two homologous genes being drawn at random from the reference population
204 (Wang, 2014; Yang et al., 2011). Thus, the individuals with the smallest estimates of F_{GRM}
205 are expected to be outbred (hybrids) because of e.g. mating involving immigrants (Wang,
206 2014). The proportion of the genome within runs-of-homozygosity (F_{ROH} ranging from 0 to
207 1, McQuillan et al., 2008) was estimated using the PLINK software (Purcell et al., 2007).
208 ROH arise through mating of individuals that are IBD, and may therefore be used to estimate
209 inbreeding (Curik, Ferenčaković, & Sölkner, 2014).

210 *Statistical analyses*

211 To test whether TL was affected by inbreeding, we fitted linear mixed models
212 (LMMs) using the package *lme4* (Bates, Mächler, Bolker, & Walker, 2015) in R v. 3.6.3 (R
213 Core Team, 2020). TL (response variable) was \log_{10} -transformed to conform to the
214 assumption of normally distributed residuals and the models were fitted with a (continuous)
215 fixed effect of one of the inbreeding coefficients (F_{PED} [$n=1195$], F_{PED} with at least two full
216 generations known [$n=320$], F_{GRM} [$n=371$], or F_{ROH} [$n=371$], see Table 1 for sample size
217 details). Since genomic estimators of inbreeding (F_{GRM} and F_{ROH}) were only available for
218 recruits (first-year survivors), we tested whether the relationship between TL and F_{PED} varied
219 between survivors (“1”, $n=206$) and non-survivors (“0”, $n=989$) by including an interaction
220 effect between F_{PED} and first-year survival. Tarsus length increases with nestling age, so

221 tarsus length was age-corrected by taking the residuals from a regression of tarsus length on
222 age and age squared. This allowed us to include both tarsus length and age in the models
223 describing variation in TL. Thus, age-standardized tarsus length, fledgling age at sampling (in
224 number of days), hatch day (ordinal date mean centered across years), population identity
225 (categorical: Hestmannøy or Træna), and sex (categorical: male or female) were included as
226 fixed effects in all models. We tested whether the effect of inbreeding on TL varied between
227 sexes and populations by including two-way interaction terms between the inbreeding
228 coefficient and sex or population identity. Random intercepts were fitted for year and brood
229 identity to account for the non-independence of nestlings from the same year and brood. This
230 also controls for within-brood effects of inbreeding levels (Olsson et al., 2018). We then
231 tested whether the inclusion of the inbreeding coefficient and interaction terms improved the
232 baseline model (without the inbreeding coefficient) by comparing the resulting 5 candidate
233 models using Akaike's information criterion corrected for small sample sizes ($AICc$, Akaike,
234 1973; Hurvich & Tsai, 1989). Akaike weights (w) and evidence ratios (ER) were calculated to
235 determine the relative fit of models to the data (Burnham & Anderson, 2002). To investigate
236 heterosis effects on TL, we tested if the slopes of the regression between F_{GRM} and TL
237 differed between individuals that were more inbred than on average ($F_{GRM} > \text{mean } F_{GRM}$) and
238 individuals that were less inbred than average ($F_{GRM} < \text{mean } F_{GRM}$). We did this by testing if
239 the inclusion of a regression break point at the mean F_{GRM} improved the models by
240 comparing the resulting 9 candidate models using $AICc$. Models were validated visually
241 using diagnostic plots of residuals, and model parameters are from models refitted with
242 restricted maximum likelihood (REML). Estimates are reported with standard errors (SE) and
243 95% confidence intervals (CI). Regression lines were visualized using *ggplot2* (Wickham,
244 2016).

245

246 RESULTS

247 Individual MS pedigree-based inbreeding coefficients (F_{PED}) varied from 0.000-0.250
248 (mean 0.007, 16.9% non-zero values). The highest ranked model explaining variation in TL
249 included a negative effect of F_{PED} , but only slightly improved the fit of the baseline model
250 ($\Delta_{2:1}AICc=0.8$ [subscripts denote which ranked models are compared], $w_1=0.36$,
251 $ER_1=w_1/w_2=1.49$, Table S1 in the supporting information). Thus, there was a tendency for TL
252 to be shorter in more inbred sparrows ($\beta_{F_{PED}}=-0.169\pm 0.101$, CI=[-0.366, 0.028], $n=1195$,
253 Fig. 1a and Table 2). The model ranked third ($\Delta_{3:1}AICc=1.3$) indicated that TL was less
254 associated with F_{PED} in males than in females ($\beta_{F_{PED}*sex[female]}=-0.167\pm 0.196$, CI=[-0.549,
255 0.216]), while the model ranked fourth ($\Delta_{4:1}AICc=1.9$) indicated that TL was less associated
256 with F_{PED} in the Hestmannøy population than in the Træna population
257 ($\beta_{F_{PED}*island[Hestmannøy]}=0.115\pm 0.314$, CI=[-0.498, 0.728]). However, due to high uncertainty
258 in these parameter estimates, these effects are not deemed reliable.

259 When only including individuals with at least 2 full ancestral generations known
260 (33.8% non-zero values), the model with F_{PED} was ranked second ($\Delta_{2:1}AICc=1.1$, $\beta_{F_{PED}}=-$
261 0.205 ± 0.198 , CI=[-0.588, 0.189], $n=320$, Fig. 1b, Table S2-3) and the baseline model was
262 highest ranked.

263 There was a tendency for the negative effect of F_{PED} on TL to be weaker in first-year
264 survivors ($n=206$, mean TL= 0.95 ± 0.02 , mean $F_{PED}=0.010\pm 0.003$) than in non-survivors
265 ($n=989$, mean TL= 0.97 ± 0.01 , mean $F_{PED}=0.007\pm 0.001$, $\beta_{F_{PED}*first-year\ survival}=-0.304\pm 0.201$,
266 CI=[-0.089, 0.697], $n=1195$, Fig. 1c, Table S4). This effect was uncertain with a CI
267 overlapping zero. This suggests that the following analyses using genomic estimators of
268 inbreeding in recruits were not biased towards stronger inbreeding effects in recruits.

269 Genomic inbreeding coefficient (F_{GRM}) estimates varied from -0.200 to 0.300 (mean
270 0.016). The highest ranked model ($\Delta_{2:1}AICc=2.1$, Table S5) showed that TL was shorter in

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

275 Including a break point at the mean F_{GRM} improved the model compared to a model
276 with no break point (comparing models without interaction terms which were ranked 8 and 5:
277 $\Delta_{8:5}AICc=4.5$, see Table S6). The highest ranked model ($\Delta_{2:1}AICc=3.1$, Table S6) revealed a
278 strong negative association between TL and F_{GRM} among individuals with $F_{GRM}<0.016$ but no
279 significant association among inbred individuals with $F_{GRM}>0.016$ (Fig. 1e and Table 4). This
280 indicates that a heterosis effect resulting in longer telomeres in outbred individuals may
281 explain the negative association found between inbreeding and TL. This model also included
282 an interaction term suggesting that this heterosis effect was stronger in the Træna population
283 (Table 4).

284 The runs-of-homozygosity inbreeding coefficient (F_{ROH}) estimates varied from 0.000-
285 0.240 (mean 0.010, 73% non-zero values). The best model provided evidence for a negative
286 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
287 and 5). This model also indicated that the negative effect of F_{ROH} tended to be stronger in
288 males ($\beta_{F_{ROH}*sex[female]}=0.915\pm 0.610$, $CI=[-0.270, 2.102]$).

289 Overall, F_{PED} was not a good predictor of genomic estimators of inbreeding (Fig.
290 S1a,c; Pearson's $r_p=0.05$, $n=371$), but its relationships with F_{GRM} and F_{ROH} were improved
291 when including only individuals with at least two generations known (Fig. S1b,d; $r_p>0.30$,
292 $n=59$). F_{GRM} and F_{ROH} were strongly correlated (Fig. S1e,f; $r_p=0.7$, $n=371$).

293

294 **DISCUSSION**

295 We found evidence across multiple complementary measures of inbreeding that more
296 inbred house sparrow nestlings had shorter telomeres (Fig. 1). Individual differences in TL
297 are established early in life (Entringer, de Punder, Buss, & Wadhwa, 2018), are heritable
298 (Dugdale & Richardson, 2018; Pepke et al., *submitted* 2021a), and are positively associated
299 with fitness in some species (Heidinger et al., 2012; Wilbourn et al., 2018). Thus, short
300 telomeres in more inbred individuals may therefore underpin a physiological basis of
301 inbreeding depression in fitness components that has been found in this species (Billing et al.,
302 2012; Jensen et al., 2007; Niskanen et al., 2020) and in other wild animal populations (Keller
303 & Waller, 2002).

304 The effect of inbreeding on TL in house sparrows was negative across all measures of
305 inbreeding, but strongest when using genomic levels of inbreeding (Fig. 1d-f), probably
306 because they are better at capturing homozygosity causing inbreeding depression compared
307 to using a pedigree-based estimator (Fig. 1a-c, Alemu et al., 2021; Huisman, Kruuk, Ellis,
308 Clutton-Brock, & Pemberton, 2016; Kardos et al., 2016). Mating between full siblings or
309 between parent and offspring ($F=0.25$) resulted in a severe reduction in (relative) TL of 58%
310 (F_{GRM}), 48% (F_{ROH}) or 11% (F_{PED}) compared to breeding between unrelated individuals
311 (Tables 2, 3, and 5). TL may be under strong selection in natural populations (Voillemot et
312 al., 2012). Consequently, strong inbreeding depression is expected for fitness components or
313 traits that are under strong selection (Bérénos, Ellis, Pilkington, & Pemberton, 2016; DeRose
314 & Roff, 1999). The analyses using genomic estimators of inbreeding were limited to recruited
315 individuals, but the negative effect of inbreeding on TL may be even stronger if very inbred
316 individuals, presumably with short telomeres, do not survive their first year and were thus
317 excluded from our analyses (Jensen et al., 2007; Wilbourn et al., 2018). There was a tendency
318 for such an effect when using pedigree-based levels of inbreeding (Fig. 1c and Table S4). We
319 also found some evidence that inbreeding had stronger negative effects on TL in males than

320 females (Tables 3 and 5). Such sex-specific effects of inbreeding are known from other
321 species (de Boer et al., 2018a; de Boer et al., 2018b; Janicke, Vellnow, Sarda, & David,
322 2013), but have rarely been observed early in life. There was a weak tendency for longer TL
323 in males than females (Tables 2-5), which has been observed in similar house sparrow
324 populations (Pepke et al., *submitted* 2021b). Thus, males may be better buffered against the
325 effects of inbreeding on TL. However, no sex-specific differences in inbreeding depression
326 were observed in adult sparrows across this study metapopulation (Niskanen et al., 2020).

327 Increased inbreeding may be accompanied by population decline in small populations
328 (Bozzuto et al., 2019; Chen, Cosgrove, Bowman, Fitzpatrick, & Clark, 2016; Feng et al.,
329 2019), which can drive populations to extinction (O’Grady et al., 2006; Saccheri et al., 1998;
330 Wright, Tregenza, & Hosken, 2007). Niskanen et al. (2020) showed that inbreeding
331 depression in adult sparrows in our study system varied little across years or across the
332 different island environments inhabited by these house sparrows. Hence, the strength of
333 inbreeding depression is similar between populations, but due to harboring more inbred
334 individuals, the relative effect is stronger in smaller populations (Niskanen et al., 2020).
335 Small declining populations may be characterized by gradual population-wide and trans-
336 generational telomere erosion. For instance, Dupoué et al. (2017) observed shorter TL along
337 an extinction risk gradient in populations of common lizards (*Zootoca vivipara*) that are
338 disappearing from low altitudes at their southern range limit, presumably due to climate
339 warming (Sinervo et al., 2010). Combined, these results suggest that TL may represent a
340 potential physiological biomarker or molecular tool in conservation genetics addressing the
341 viability of some small animal populations (Bebbington et al., 2016; Bergman et al., 2019;
342 Dupoué et al., 2017; Madliger, Franklin, Love, & Cooke, 2020).

343 The negative effect of F_{GRM} on TL (Fig. 1d) was stronger among individuals that were
344 less related than the average population (Fig. 1e). This suggests that longer telomeres in

345 outbred individuals may partly be attributed to a general heterosis effect (Charlesworth &
346 Willis, 2009) involving mating between immigrants and native individuals (Dickel et al.,
347 2021; Ebert et al., 2002). In our study metapopulation, the proportion of dispersers among
348 recruits can be high among the island populations (0.2 on average ranging from 0.0-1.0
349 across years and islands, Ranke et al., 2021; Saatoglu et al., 2021), and hence most islands are
350 not strongly differentiated (Niskanen et al., 2020). We found that the negative effect of F_{GRM}
351 on TL was stronger in the Træna population (Table 3-4). Træna is known to have a higher
352 proportion of immigrants than Hestmannøy (Ranke et al., 2021), which may contribute to a
353 stronger effect of heterosis in this population (Table 4). Furthermore, the gardens of Træna
354 expose the sparrows to a different environment than the farms on Hestmannøy (Araya-Ajoy
355 et al., 2019; Pärn, Ringsby, Jensen, & Sæther, 2012). Inbreeding depression is expected to
356 have more severe consequences under environmental stress (Armbruster & Reed, 2005; Reed
357 et al., 2002), such as harsh weather or competition (de Boer et al., 2018a; Fox & Reed, 2011;
358 Marr, Arcese, Hochachka, Reid, & Keller, 2006). Telomeres shorten due to environmental
359 stressors such as harsh abiotic conditions (Chatelain et al., 2020). We speculate that
360 environmental differences between the habitats of the two sparrow populations may explain
361 the exacerbated effects of inbreeding on TL in the Træna population. For instance, in juvenile
362 Seychelles warblers a negative relationship between homozygosity and TL was found only in
363 poor seasons, i.e. when food availability was low (Bebbington et al., 2016). In adult
364 Seychelles warblers, the effect of homozygosity on TL was consistently negative across
365 seasons, suggesting that the negative effects of inbreeding accumulate through life and are
366 reflected in telomere erosion (Bebbington et al., 2016). Here, we showed that inbreeding
367 manifests in TL already at the nestling stage in a similar wild passerine.

368 We measured TL in blood, thus it is possible that inbreeding or heterosis only affected
369 telomeres in erythrocytes (Manning et al., 2002; Olsson, Geraghty, Wapstra, & Wilson,

370 2020). However, this is unlikely because TLs often correlate well across tissues within the
371 organism (Daniali et al., 2013; Demanelis et al., 2020; Reichert, Criscuolo, Verinaud, Zahn,
372 & Massemin, 2013), especially in early-life (Prowse & Greider, 1995). Although genomic
373 inbreeding estimates were only available for first-year survivors, we may have avoided
374 confounding effects of selective mortality of inbred individuals at much older ages by
375 measuring TL already at the nestling stage (Hemmings, Slate, & Birkhead, 2012; Sánchez-
376 Montes et al., 2020). Furthermore, since the mutation accumulation theory of senescence
377 predicts that deleterious effects of inbreeding increase with age (Charlesworth & Hughes,
378 1996; Keller, Reid, & Arcese, 2008), we may expect that the effect on TL is persistent and
379 potentially stronger in adult sparrows. Thus, future studies are required to investigate if
380 inbreeding leads to persistently eroded TL throughout life, and if there are combined fitness
381 consequences of any interaction between TL and inbreeding in wild populations. Even in the
382 absence of a mechanism directly linking inbreeding and TL via the effects of oxidative stress
383 (cf. the introduction), we may find inbred individuals to have short telomeres, because
384 inbreeding impairs other physiological processes that affects both fitness and TL (Bebbington
385 et al., 2016). Thus, the conflicting evidence in the literature of an effect of inbreeding on TL
386 (reviewed in the introduction) suggests that an experimental procedure is needed to further
387 elucidate the mechanisms underlying the correlation reported here (Manning et al., 2002),
388 especially in wild populations.

389 In conclusion, the negative associations between inbreeding levels and TL found in
390 this study suggest that TL may reveal subtle somatic costs of inbreeding in wild populations,
391 and thereby demonstrates a potential route by which inbreeding negatively impacts the
392 physiological state of an organism in early life. The observation of a potential heterosis effect
393 on TL suggests that maintenance of dispersal within this metapopulation is important for
394 mitigating the negative effects of inbreeding.

395

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400 **Availability of data and material:** Data will be available on Dryad or another open data
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402 **Code availability:** Not applicable.

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

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412

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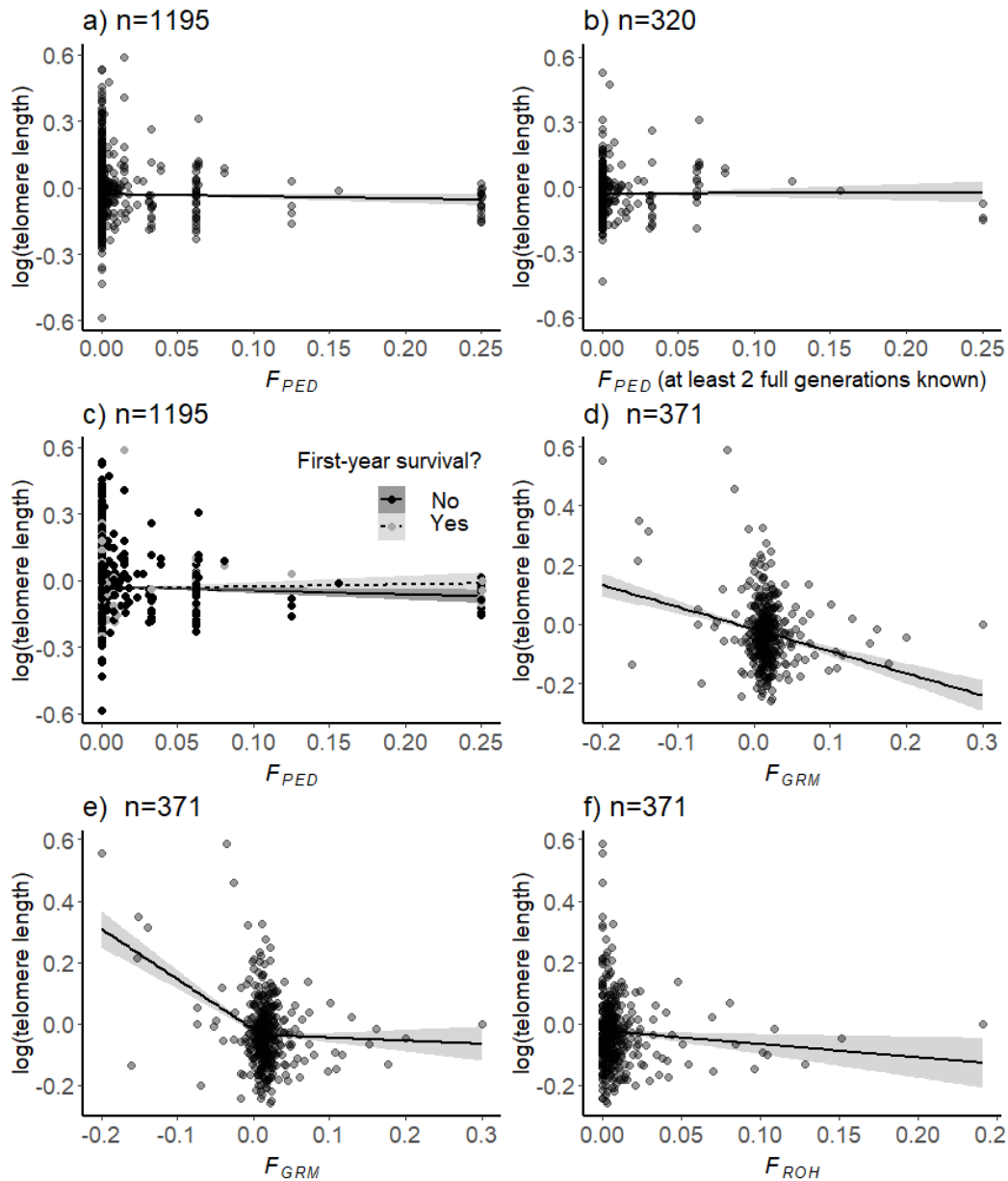
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- 864

865 **TABLES AND FIGURES**

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

Island population:	Hestmannøy			Træna			Sum:
	Males	Females	Sum:	Males	Females	Sum:	
$F_{PED} (\geq 1.5 \text{ gen.})$	511	546	1057	78	60	138	1195
$F_{PED} (\geq 2 \text{ full gen.})$	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

874



875

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

886

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

891

	Response variable: $\log_{10}(\text{TL})$	Estimate	SE	Lower CI	Upper CI
892	intercept	-3.1E-4	0.037	-0.072	0.071
893	inbreeding coefficient (F_{PED})	-0.169	0.101	-0.366	0.028
	tarsus length	-0.003	0.002	-0.008	0.001
894	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>
895	age	-0.003	0.002	-0.007	0.001
896	hatch day	-1.4E-4	1.5E-4	-4.4E-4	1.7E-4
	$\sigma^2_{\text{brood ID}} (n=500)$	0.002		0.001	0.003
897	$\sigma^2_{\text{year}} (n=20)$	0.003		0.001	0.006
898	Marginal R^2 / Conditional R^2 : 0.014 / 0.393				

899

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

903

	Response variable: $\log_{10}(\text{TL})$	Estimate	SE	Lower CI	Upper CI
904	intercept	0.069	0.038	-0.004	0.145
905	<i>inbreeding coefficient (F_{GRM})</i>	<i>-1.517</i>	<i>0.293</i>	<i>-2.150</i>	<i>-0.920</i>
	tarsus length	-0.001	0.005	-0.011	0.009
906	sex [female]	-0.016	0.011	-0.039	0.006
	<i>island identity [Hestmannøy]</i>	<i>-0.036</i>	<i>0.016</i>	<i>-0.068</i>	<i>-0.004</i>
	age	-0.006	0.003	-0.012	4.6E-4
907	hatch day	-3.3E-4	2.8E-4	-0.001	2.1E-4
	<i>F_{GRM} * island [Hestmannøy]</i>	<i>0.824</i>	<i>0.339</i>	<i>0.142</i>	<i>1.529</i>
908	<i>F_{GRM} * sex [female]</i>	<i>0.644</i>	<i>0.314</i>	<i>0.034</i>	<i>1.262</i>
	$\sigma^2_{\text{brood ID}} (n=273)$	0.004		0.002	0.006
	$\sigma^2_{\text{year}} (n=17)$	0.001		0.000	0.003
909	Marginal R^2 / Conditional R^2 : 0.085 / 0.512				

910

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

Response variable: $\log_{10}(TL)$	Estimate	SE	Lower CI	Upper CI
intercept	0.021	0.037	-0.051	0.095
<i>inbreeding coefficient (F_{GRM}) < 0.016</i>	-2.177	0.372	-3.051	-1.379
<i>inbreeding coefficient (F_{GRM}) > 0.016</i>	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
$\sigma^2_{\text{year}} (n=17)$	0.001		0.000	0.003
Marginal R^2 / Conditional R^2 : 0.106 / 0.458				

914

915

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

919

Response variable: $\log_{10}(TL)$	Estimate	SE	Lower CI	Upper CI
intercept	0.051	0.040	-0.027	0.130
<i>inbreeding coefficient (F_{ROH})</i>	-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
$\sigma^2_{\text{year}} (n=17)$	0.002		4.6E-4	0.004
Marginal R^2 / Conditional R^2 : 0.029 / 0.579				