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RESEARCH ARTICLE

Multi-locus homozygosity promotes actuarial senescence in a wild mammal

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Abstract

1. Genome-wide homozygosity, caused for example by inbreeding, is expected to have deleterious effects on survival and/or reproduction. Evolutionary theory predicts that any fitness costs are likely to be detected in late life because natural selection will filter out negative impacts on younger individuals with greater reproductive value.
2. Here we infer associations between multi-locus homozygosity (MLH), sex, disease and age-dependent mortality risks using Bayesian analysis of the life histories of wild European badgers *Meles meles* in a population naturally infected with *Mycobacterium bovis* (the causative agent of bovine tuberculosis [bTB]).
3. We find important effects of MLH on all parameters of the Gompertz–Makeham mortality hazard function, but particularly in later life.
4. Our findings confirm the predicted association between genomic homozygosity and actuarial senescence. Increased homozygosity is particularly associated with an earlier onset, and greater rates of actuarial senescence, regardless of sex. The association between homozygosity and actuarial senescence is further amplified among badgers putatively infected with bTB.
5. These results recommend further investigation into the ecological and behavioural processes that result in genome-wide homozygosity, and focused work on whether homozygosity is harmful or beneficial during early life-stages.

KEYWORDS
Bayesian, inbreeding, mortality trajectory, multi-locus homozygosity, reverse jump Markov Chain Monte Carlo, survival analysis, wildlife disease

1 | INTRODUCTION

Genome-wide homozygosity is commonly considered detrimental to fitness because of increased expression of deleterious recessive alleles, harmful impacts of over dominant alleles and/or a deficit of heterozygote advantage (Charlesworth & Charlesworth, 1987). While various ecological or genetic forces might lead to genome-wide homozygosity (e.g. genetic drift, founder effects, bottlenecks), the usual cause is mating among kin (inbreeding; Charlesworth, 2003). Decreased fitness as a result of inbreeding (inbreeding depression) has been a fundamental premise of evolutionary ecology since the writings of Darwin (1876) and evidence for it is widespread (Bozzuto et al., 2019; Charlesworth & Willis, 2009; Crnokrak & Roff, 1999; Keller & Waller, 2002). However, while genome-wide homozygosity might indeed impose fitness costs, these might be mediated by

the fitness rewards of homozygosity of beneficial alleles (Falconer & Mackay, 1996). Empirical research is required to determine whether genome-wide homozygosity affects fitness in nature.

Studies on the fitness effects of genome-wide homozygosity have tended to focus on captive animals (Bijlsma et al., 2000; Swindell & Bouzat, 2006). However, artificial conditions might affect the strength and genetic architecture of inbreeding depression (Bijlsma et al., 1999), meaning extrapolation of inferences to wild populations can be problematic. Studies of inbreeding depression in the wild have demonstrated its detrimental impact on a variety of traits such as juvenile survival, adult longevity, fecundity, birth weight and egg-hatching rates (for a review, see e.g. Keller & Waller, 2002). However, studies have seldom addressed how the effects of genome-wide homozygosity may vary throughout individual lifetimes (Hedrick & Garcia-Dorado, 2016; Kardos et al., 2016; Stoffel et al., 2021; Trask et al., 2021). Of particular interest is the association between homozygosity and the process of ageing (Brooks & Kemp, 2001; Charlesworth & Hughes, 1996), based on the understanding that fitness often declines in old age, a process known as senescence (Partridge & Mangel, 1999).

Evolutionary theories of senescence assume that the force of selection declines with age and hence will be more efficient at eliminating genetic variants (alleles) that have detrimental effects in early life than those with effects that are manifest in later life (Medawar, 1952; Williams, 1957). Alleles associated with late-life detriments may therefore accrue in populations, causing older individuals to age faster. The two leading genetic explanations for senescence are not mutually exclusive (Charlesworth & Hughes, 1996) but do have differing explanations: *mutation-accumulation* refers to weak selection against late-acting deleterious mutations, while *antagonistic pleiotropy* assumes that genes causing detrimental effects on late-life survival or reproduction are retained in populations if they have pleiotropic effects beneficial in early life (Ungewitter & Scrable, 2009). Both hypotheses predict that harmful effects of homozygosity should only be revealed in late life.

Analyses of associations between inbreeding and fitness have generally relied on pedigree-based measures of inbreeding (e.g. Pemberton, 2004) but the generation of large-scale molecular genetic data offers alternatives and removes the need to conduct parentage analysis over many generations, which can be challenging in natural populations. Large-scale studies tend to use single-nucleotide polymorphisms or microsatellite data to measure multiple-locus *heterozygosity* and then identify statistical associations with specific fitness traits (Acevedo-Whitehouse et al., 2003; Amos et al., 2001; Szulkin et al., 2010). The validity of marker-based measures of genomic homozygosity has been questioned (Nietlisbach et al., 2017; Slate et al., 2004), not least because homozygosity is not a direct measure of the frequency of mating with kin. Marker-based homozygosity does, however, measure directly the main proposed mechanism for inbreeding depression: costs associated with a surfeit of homozygous loci throughout the genome. Any influence of homozygosity on fitness will depend on whether loci generally impose deleterious homozygous costs or confer homozygote advantage.

Many relevant studies have used only small numbers of markers and small sample sizes, although the utility of the approach depends on the number of individuals, the number of loci and their expected heterozygosity (Miller et al., 2013). There has been increasing acknowledgement that molecular genetic measures of inbreeding may be most appropriate when investigating inbreeding depression (Forstmeier et al., 2012; Kardos et al., 2015, 2016; Nietlisbach et al., 2017; Wang, 2016). The use of genomic data has shown inbreeding depression to be more severe and more widespread in natural populations than originally thought, with the potential to be state-dependent and dynamic across lifespans (Bérénos et al., 2016; Chen et al., 2016; Harrisson et al., 2019; Hoffman et al., 2014; Huisman et al., 2016; Niskanen et al., 2020).

Despite an increasing number of information-rich demographic-monitoring projects contributing to our understanding of age-related declines in survival and other fitness-related traits in wild populations (for a review see Beirne et al., 2014, 2016; Nussey et al., 2013), comparatively few have made links with genome-wide homozygosity (but see e.g. Benton et al., 2018; Charmantier et al., 2006; Keller et al., 2008). These studies of wild populations generally focus on changes in a specific fitness-related trait (e.g. fecundity or disease progression) with age, evidence to date has supported both antagonistic pleiotropy and mutation accumulation (Harrison et al., 2011). Here we focus on the actuarial mortality risks experienced by wild mammals that vary naturally in levels of multi-locus homozygosity (MLH).

Survival is a key fitness trait when assessing the demography of animal populations, yet it remains a challenging parameter to estimate in the wild (Delahay et al., 2009; Mccallum, 2008). Some of the issues associated with traditional life-table methods of monitoring survival (e.g. accommodating individual variability in mortality risk, and discretisation of continuous time and age) are overcome by the use of survival and mortality trajectories (Colchero & Clark, 2012; Hudson et al., 2019). Lifetime trajectories can be used to describe survival and mortality patterns across entire lifespans in continuous time and promote deeper understanding of life history (Gaillard et al., 1994; McDonald et al., 2014). Several functions have been used to describe mortality trajectories (e.g. Gompertz—Gompertz, 1825; Gompertz–Makeham—Makeham, 1867; Siler—Siler, 1979), and in humans and laboratory animals the standard shapes are well established (Bebbington et al., 2007; Eberhardt, 1985). For many species, a 'bathtub'-shaped curve is typical, but evidence for bathtub-shaped mortality trajectories in natural populations is relatively uncommon, possibly due to the sampling procedures used to collect data. For example, Capture–Mark–Recapture (CMR) studies will miss individuals that die prior to being first caught and marked, meaning small sample sizes of very young and, for similar reasons, very old individuals (Gilbert et al., 2014), offering limited power to identify all the parameters of the bathtub even if they exist.

In this study, we employ Bayesian statistical techniques to infer the effects of MLH on sex- and infection-specific mortality rates across the life histories of a population of free-living mammals. We use survival and mortality trajectory analysis on data from a long-term monitoring project of a wild population of European badgers *Meles meles*, naturally infected

with the pathogen *Mycobacterium bovis* which causes bovine tuberculosis (bTB). Age-, sex- and infection-specific variations in badger mortality have previously been evidenced (McDonald et al., 2014), including the detection of a senescent increase in disease-related mortality risk in later life (Hudson et al., 2019) but this lacked the consideration of MLH. Benton et al. (2018) demonstrated an age-related increase in the risk of progressed infection in female badgers—this relationship being stronger with increasing MLH. Here we ask whether MLH influences survival during early-, mid- or late-life in badgers. Considering findings that link MLH to sex-specific epidemiology of disease in this species (Benton et al., 2018), we also ask whether any association between MLH and mortality risks is mediated by sex or infection status. We discuss our findings not just as a test of fundamental evolutionary theory, but also regarding the importance of inbreeding for the demography and epidemiology of an important zoonotic reservoir of livestock disease.

2 | MATERIALS AND METHODS

2.1 | Badger sampling

The capture, examination and sampling of live badgers were carried out under Home Office Project Licence PP3493437 and preceding versions of this licence. Data used were collected from a long-term CMR study of a wild population of badgers at Woodchester Park in Gloucestershire (Delahay et al., 2013). Using CMR data introduces biases, since individuals who die prior to being captured or available for capture (i.e. prior to emerging from the sett) are never known. We therefore model survival given at least one capture. Badgers were live-trapped up to four times a year and on the occasion of first capture were given a unique identifying tattoo. On all capture occasions, badgers were anaesthetised and subjected to diagnostic tests for bTB before being released (Delahay et al., 2000). For further information, see Suporting Information. Limitations in the sensitivity of the diagnostic tests are well known (Drewe et al., 2010) but all tests are highly specific, so we assume that test-positive animals are highly likely to be infected and model test-positivity as a proxy for true infection status. We created two distinct infection categories of badger: cub positive (individuals that tested positive to at least one diagnostic test during the first year of their life) and never positive (individuals that never tested positive to any diagnostic test throughout their life). The population monitored consists of 2751 individuals of which 1933 have been genotyped. We retained only known-age individuals ($n = 1793$) and removed the 187 individuals who tested positive after the first year of their lives. Our final dataset consisted of 1606 individuals with year of first capture ranging between 1979 and 2011: 442 classed as 'cub positive' (226 females, 216 males) and 1164 as 'never positive' (625 females, 539 males).

2.2 | Genotyping and measures of inbreeding

A hair sample was taken from each badger at first capture and stored in 80% ethanol prior to DNA extraction and genotyping (Carpenter et al., 2005). Genotyping involved the use of 22 microsatellite markers, each with 4–7 alleles.

We followed the approach used by Benton et al. (2018) to formulate and validate our measures of inbreeding. All data processing and analysis was completed in R version 4.2 (R Core Team, 2019). We used the MicroDrop Programme (Wang & Rosenberg, 2012) to impute missing microsatellite data and tested for deviations from Hardy–Weinberg equilibrium for each of the 22 microsatellite markers using the *hwtest* function in R package ADEGENET (Jombart, 2008) with no deviations found. There has been considerable debate over whether a subset of molecular markers can accurately reflect genome wide homozygosity (DeWoody & DeWoody, 2005) but this uncertainty can be partially addressed through calculation of the parameter g^2 (David et al., 2007) which measures the degree to which a set of markers reflects variation in inbreeding among individuals. We calculated the g^2 parameter using the *g2_microsats* function in R package INBREEDR (Stoffel et al., 2016) and for our set of markers g^2 was statistically significantly different from zero $(g^2 = 0.002, p < 0.001)$ suggesting that the marker set reflects non-zero genome-wide effects of homozygosity (Szulkin et al., 2010).

We calculated three different measures of inbreeding: internal relatedness (IR; Amos et al., 2001) using R package RHH (Alho et al., 2010); an individual inbreeding coefficient (F) calculated using the ADEGENET package in R—(Jombart, 2008); and MLH: the proportion of genotyped loci that are homozygous. We checked the robustness of our analysis by repeating them with each different measure of inbreeding (Figure S2) and found only minor differences: here we present results using MLH. We follow Benton et al. (2018) and Harrison et al. (2013) in checking that the influence of MLH on life-history parameters is not due to the influence of homozygosity at single microsatellite loci. We replaced MLH in our models with a binary homozygosity predictor, for each locus in turn, and judged the importance of locus-specific homozygosity as a rival predictor of the mortality trajectory (Figure S3).

2.3 | Statistical modelling

We initially compared the fit of four different mortality models to the complete dataset using the widely applicable information criterion (WAIC; Watanabe, 2010): (1) the exponential model which assumes constant mortality throughout life independent of age; (2) the Gompertz (Gompertz, 1825) model which describes mortality as exponentially increasing with age; (3) the Gompertz–Makeham (Makeham, 1867) model, which is an extension of Gompertz (1825) with an additional age-independent mortality hazard parameter and (4) the Siler model (Siler, 1979) which describes a 'bathtub' shaped mortality curve with an initial decline in mortality from a high intercept, then near-constant early- to mid-life mortality, followed by exponentially increasing mortality due to actuarial senescence (Table 1).

We jointly estimated survival and recapture probabilities in a similar fashion to Cormack–Jolly–Seber models (Cormack, 1964;

TABLE 1 Mortality functions used as proposal models to fit to the data.

Model	Mortality rate $\mu(x\mid\boldsymbol{\theta})$	Parameters
Exponential	r	$r>0$
Gompertz	ae^{bx}	$a,b>0$
Gompertz–Makeham	$ae^{bx}+c$	$a,b,c>0$
Siler	$a_1e^{-b_1x}+c+a_2e^{b_2x}$	$a_1,a_2,b_1,b_2,c>0$

Jolly, 1965; Seber, 1965), which account for the sampling process and subsequent missing data inherent in CMR studies. We employed a reversible-jump Markov Chain Monte Carlo (Green, 1995; RJ-MCMC) approach to variable selection in the R package NIMBLE (de Valpine et al., 2017) by constructing a maximal model with indicator nodes attached to each parameter. RJ-MCMC is a general framework in which the dimension of the parameter space can vary between iterations of the Markov chain, allowing variables to be included or excluded from the model as the chains progress. After convergence, the proportion of iterations that the MCMC chain spends within a given model space is an estimate of the posterior model weight for that model and can inform model comparisons/choice (Hastie & Green, 2012). Similarly, the proportion of iterations where a variable is present in the model is an estimate of the marginal posterior probability of association for that variable (Hoeting et al., 1999). In models that include many possible combinations of included variables, the posterior model probabilities can quickly become diluted by the volume of possible models, unless the signal within the data is strongly in favour of a small number of models. In these instances, it is more straightforward and interpretable to generate posterior inclusion probabilities for each of the variables and use the posterior model probabilities to inform multi-model inference techniques such as Bayesian model averaging (BMA) to account for the uncertainty in model choice when constructing survival and mortality trajectories.

2.4 | Model specification

We set the core structure of the model such that age-at-death is distributed according to the chosen model from the initial model comparisons—each parameter then allowing for combinations of sex-, infection- and MLH-specific variations. The survival time distribution can be defined by its hazard function, for example, the Gompertz–Makeham hazard function is:

$$h(tD_i) = a_i e^{b_i t} + c_i, \tag{1}$$

where tD_i is age-at-death of individual i. We specify a log-linear relationship between the parameters of the model and the sex-, infection- and MLH-specific covariates (and all interactions), e.g.

$$\begin{aligned}\log(a_i) = \log(a) &+ \beta_1^a \times \text{sex}_i \times z_1^a \\ &+ \beta_2^a \times \text{infection}_i \times z_2^a \\ &+ \beta_3^a \times \text{MLH}_i \times z_3^a \\ &+ \beta_4^a \times \text{MLH}_i \times \text{infection}_i \times z_4^a \\ &+ \beta_5^a \times \text{MLH}_i \times \text{sex}_i \times z_5^a \\ &+ \beta_6^a \times \text{sex}_i \times \text{infection}_i \times z_6^a \\ &+ \beta_7^a \times \text{MLH}_i \times \text{sex}_i \times \text{infection}_i \times z_7^a \\ &+ \gamma_{S_i}\end{aligned} \tag{2}$$

Here γ_{S_i} denotes the random intercept for social group S_i ($S_i=1, \ldots, 40$) of individual i ($i=1, \ldots, N$). Similar forms are placed on the b_i and c_i terms (except for the random intercept terms—see discussion below). We place 'slab-and-spike' prior distributions on the regression parameters in (2). NIMBLE does this by augmenting the parameter space with an additional set of binary indicator variables to capture inclusion (e.g. $z_k^a, z_k^b, z_k^c;\ k = 1, \ldots, 7$). For full details, please see the model code in Supporting Information.

We also ensured that interaction terms could not be included in the model unless each associated main effect was included using the *constraint* function in NIMBLE. Badgers live in territorial social groups with individual infection status related to group membership, individuals can and do move between social groups although this is generally after they reach sexual maturity. In our analyses, we chose to use an individual's modal social group included as a random effect (γ) in our model on parameters a and c which both act similarly to raise or lower the overall mortality trajectory. With 40 different social groups present in the data, we chose to share the effect of each across the two parameters (in a similar style to a random-intercepts model). We ran the same analyses with social group included on b but with negligible differences in the resulting model-averaged trajectories we present the more parsimonious model here.

2.5 | Priors

We used weakly informative exponential distributions (rate = 1) for the priors of the model parameters. We specified normal prior distributions (mean = 0, SD = 1) for all of the sex-, infection- and inbreeding-specific coefficients and used Bernoulli distributions (with prior probability of success $p=0.5$) for the inclusion probabilities, giving each variable an equal prior probability of being included. Social group was specified as a random effect with normal distribution (standard deviation given a Uniform (0,10) prior). Bayes' Factors are sometimes criticised for their sensitivity to the priors used so we repeated the analysis using more diffuse exponential (rate = 0.1) and normal (mean = 0, SD = 10) distributions; this had negligible effects on any outcomes of the model comparisons, so we present the Exp(1)/N(0, 1) results here. We ran two chains for 500,000 iterations with a burn-in of 24,000 (see Supporting Information for diagnostics).

2.6 | Analysis

To judge the importance of each parameter, we used the inclusion probability thresholds as described in Viallefont et al. (2001), who consider anything with a posterior inclusion probability over 0.5 to be informative (0.5–0.75 is described as evidence of a weak association, 0.75–0.9 as positive, 0.95–0.99 as strong and >0.99 as very strong). When estimating the effects of inbreeding depression, the consensus has been to perform a regression analysis with a fitness component as the response (Keller & Waller, 2002; Morton et al., 1956) and MLH as a continuous predictor. Here we model parameters of the Gompertz–Makeham function as regressions against MLH. We check the robustness of this assumption of a linear association between parameters and predictor, and hence of our inference, by repeating the analysis using MLH as a categorical variable (Figures S4 and S5). Although the posterior inclusion probabilities for MLH (and the MLH × infection interaction) are reduced below 0.5 the pattern is broadly similar with the largest effect on *b*. The model averaged trajectories describe similar patterns of survival and mortality although the effects are reduced. We also used bespoke model validation approaches to check the linear regression assumption (Figure S6). Here we present results using MLH as a continuous predictor.

In summary, our mortality trajectory models treat sex and infection status as categorical predictors, and MLH as a continuous predictor, and implements a log-linear relationship between each Gompertz–Makeham parameter and the covariates. Indicator variables allowed MCMC chains to switch each predictor on or off and we judge the importance of parameters and predictors using inclusion probabilities and BMA.

3 | RESULTS

In the Woodchester badger population, MLH ranged from 0.045 to 0.64 (Figure 1), with a median MLH score of 0.32, which is similar to other reported populations (Supporting Information). There were strong positive correlations between the three different measures of inbreeding MLH:IR = 0.96, MLH:F = 0.91, F:IR = 0.90 suggesting our chosen metric of MLH was representative of other genomic-based measures of inbreeding. The badger age distribution was typical of CMR data with lower proportions of very young and very old individuals although the never-positive category had a higher proportion of young individuals compared to the cub-positive group (Figure S7). MLH scores were distributed evenly across the different badger categories and through time (Figure S1). The initial model comparison identified that the Gompertz-Makeham model best described the dataset (Table 2), this model was used for the remainder of the analysis presented here. The posterior distribution of sigma which represents the variance in the effect of social group was credibly different from zero (Figure S17) suggesting it should be included in the model.

With over 9000 different models visited by the RJ-MCMC algorithm and no single model having a posterior probability greater than 0.01, it is appropriate to look at the proportion of models that include each predictor for each parameter and calculate posterior inclusion probabilities across *all* the possible models (Figure 2). MLH has an informative impact on each of the three Gompertz–Makeham parameters indicating influence on mortality rates across the lifespan of badgers (inclusion probabilities of MLH on: $a = 0.59$; $b = 0.95$; $c = 0.70$). Only one interaction term was considered informative, inclusion probability of 0.77 for an interaction between MLH and infection status on *b* (Figure 2). Despite the inclusion probabilities suggesting informative effects of MLH on all parameters, the strength of some of these effects is weak. The model-averaged posterior density plots (Figure 3) show the associations between MLH and parameters *a* and *c* are not credibly different from zero, although it is possible these parameters compete to describe the signal of MLH affecting early- and mid-life mortality risks as we have shown previously (Hudson et al., 2019). The association between MLH and *b*, among putatively infected cubs, is credibly distributed away from zero (Figure 3) confirming that for this group of badgers increasing MLH steepens the senescent increase in mortality.

The combined effects of MLH on all parameters are revealed in the model-averaged posterior-predictive trajectories (Figure 4) which account for uncertainty in the choice of model. Figure 4b

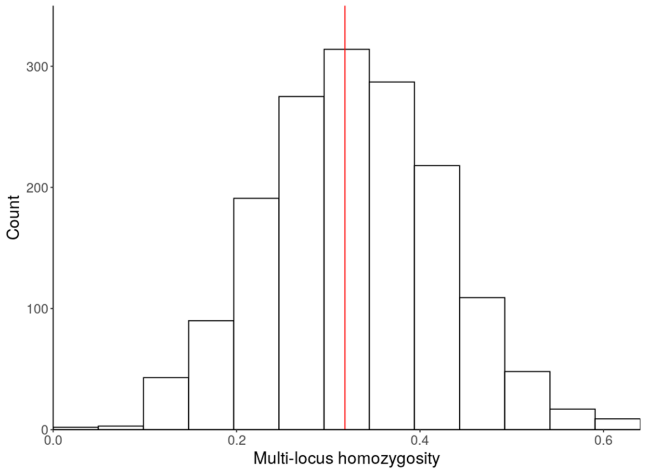

FIGURE 1 Multi-locus homozygosity (MLH) scores of European badgers *Meles meles*. Data from a long-term capture–mark–recapture study of a wild population of badgers at Woodchester Park in Gloucestershire. Median score (0.318) indicated by vertical red line.

TABLE 2 WAIC Scores for initial model comparisons on the complete dataset. ΔWAIC indicates the difference in WAIC score to the next best model.

Mortality model	WAIC	ΔWAIC	Rank
Gompertz–Makeham	32045.73	3.79	1
Siler	32049.52	12.53	2
Exponential	32062.05	5.02	3
Gompertz	32067.07	—	4

Abbreviation: WAIC: widely applicable information criterion.

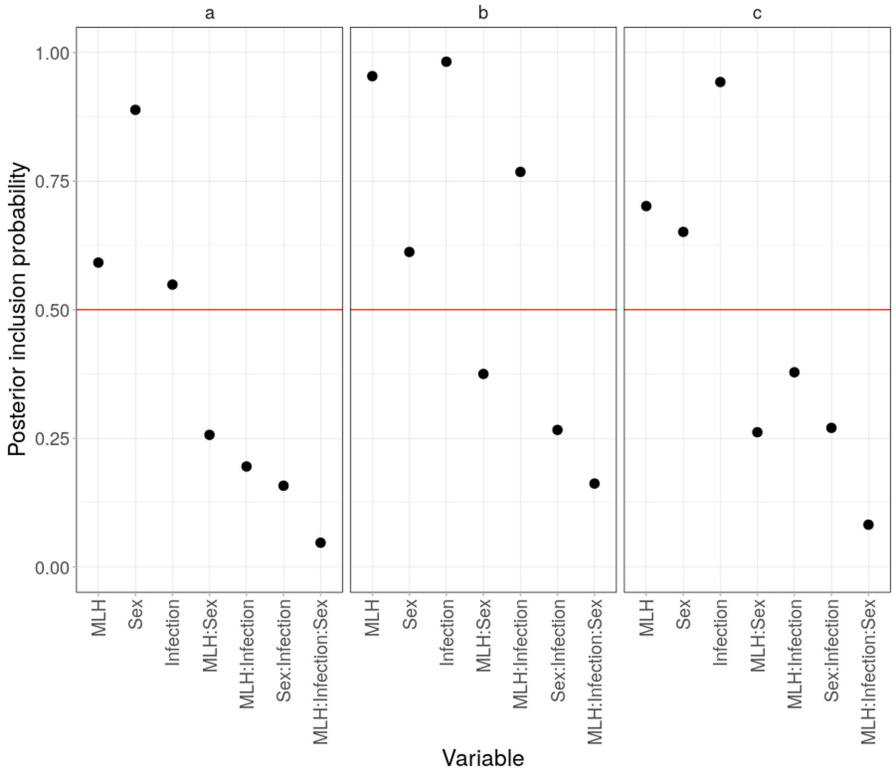

FIGURE 2 Posterior inclusion probabilities for each variable on each parameter of the Gompertz–Makeham model (panels a, b and c). Values generated from the posterior samples of a RJ-MCMC analysis using a model allowing sex-, infection- and multi-locus homozygosity (MLH) specific variation. Sex and infection fitted as categorical variables, MLH fitted as a continuous variable.

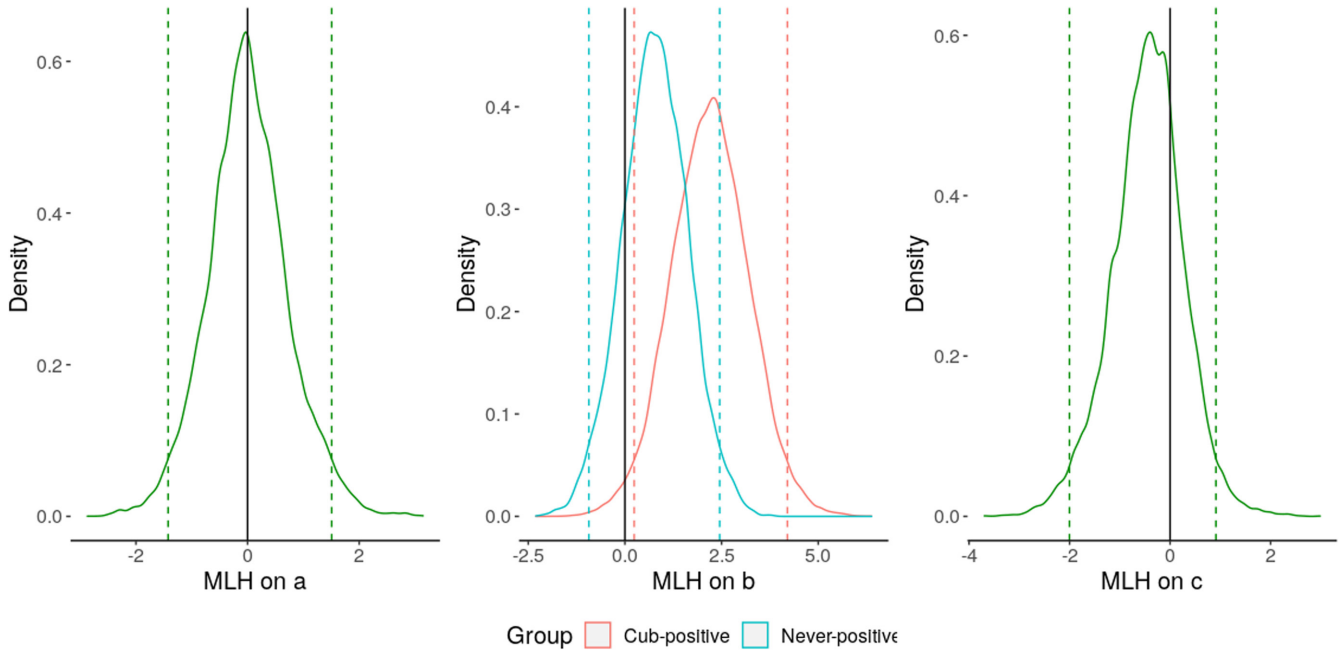

FIGURE 3 Model-averaged posterior distributions of inbreeding coefficients. The coefficient estimates refer to the additional effect of a single unit increase in multi-locus homozygosity (MLH) on each of the Gompertz–Makeham parameters, dashed lines represent 95% credible intervals.

indicates reduced survival with increased MLH throughout life for all badgers. The mortality trajectories (Figure 4a) confirm this relationship and show the effect is most pronounced for males and those identified as bTB positive as cubs. These relationships are supported by the bivariate posterior density coefficient plots (Figure 5) which diverge most credibly from zero when they include the influence of the senescent mortality parameter *b*.

4 | DISCUSSION

Several studies have linked genome-wide homozygosity with fitness-related traits in wild animal populations but few have investigated impacts across lifespans (although see Keller, 1998; Slate et al., 2000; Szulkin et al., 2007). Here we provide evidence for impacts of inbreeding on age-, sex- and infection-specific mortality in

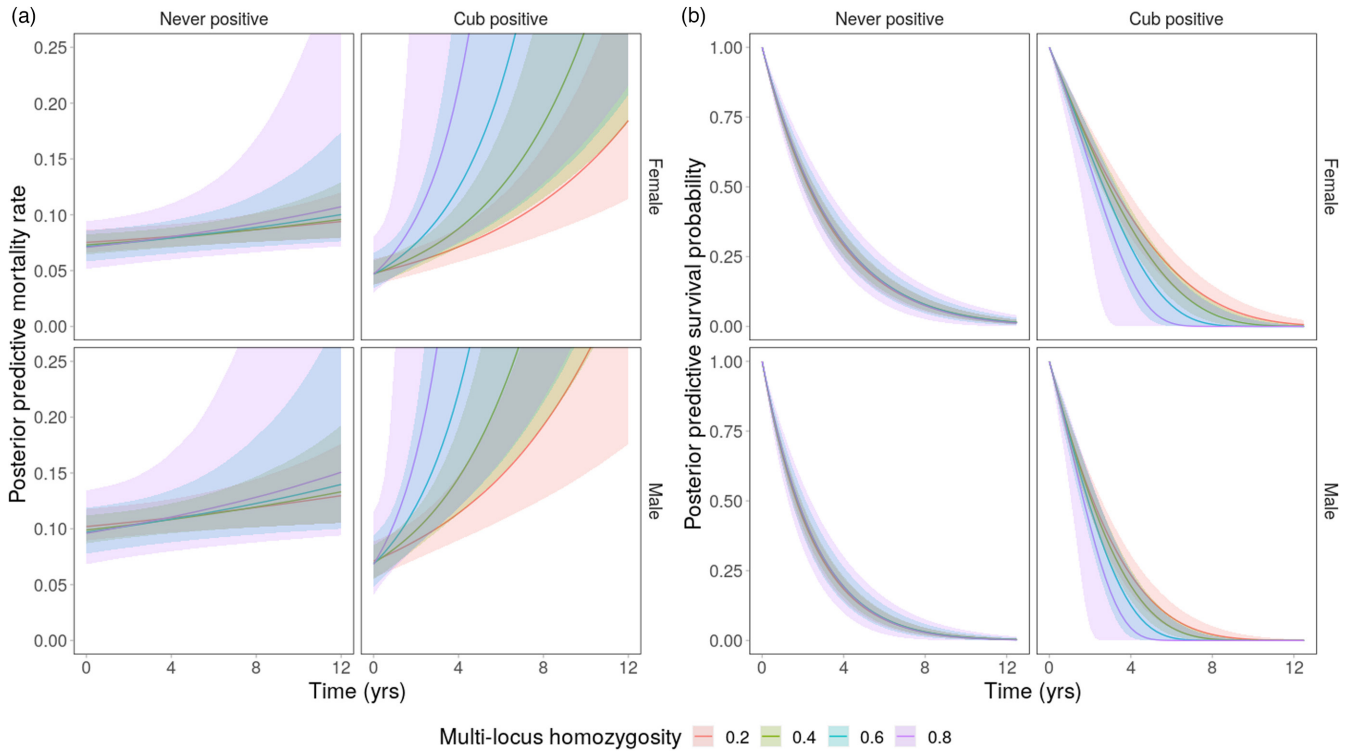

FIGURE 4 Model-averaged, posterior-predictive mortality (a) and survival trajectories (b) of a population of European badgers naturally infected with *Mycobacterium bovis*. Trajectories drawn at four levels of increasing multi-locus homozygosity. Shaded areas represent 95% credible intervals.

a population of wild badgers using a measure of inbreeding derived from multi-locus data.

Our analysis generated posterior inclusion probabilities that indicated a non-negligible effect of MLH on all parameters of the lifetime mortality trajectory, suggesting both age-dependent and age-independent effects on survival and mortality. The strongest effect was seen in the positive association between MLH and the rate of increase of late-life mortality, that is the intensity of actuarial senescence. Although independent interpretation of the parameters can help suggest where in an individual badger's lifetime the impacts of being inbred may be felt, we feel it is safer to accommodate model uncertainty (Raftery et al., 1994) and covariances among parameters by producing model-averaged survival and mortality trajectories. We focus on the mortality trajectories which are better able to capture the combined effects of MLH on the shape of the lifetime mortality trajectory itself. The model averaged mortality trajectories reflect the posterior inclusion probabilities and describe an earlier onset, and steeper senescent increase in mortality with increasing MLH.

Ageing in badgers has previously been shown to differ between sexes and infection categories (Hudson et al., 2019; McDonald et al., 2014) but our analysis here suggests that the majority of MLH effects are independent of sex and infection status. We found positive support for one interaction term, between MLH and infection status, on the rate of increase in senescent mortality. Putatively infected individuals suffered steeper senescent increases in mortality compared to their never-positive counterparts, this further amplified by increasing MLH. Our findings here support predictions from mutation accumulation theory which suggest an age-dependent increase in inbreeding depression (Charlesworth & Hughes, 1996; Hughes et al., 2002; Moorad & Promislow, 2009), although this pattern has also been shown to be consistent with antagonistic pleiotropy (Moorad & Promislow, 2009).

Previous research in other species has found evidence for interactions between sex and inbreeding although analyses were confined to older individuals (Fox et al., 2006; Reid et al., 2007). Harrisson et al. (2019) analysed lifetime fitness costs of inbreeding in the helmeted honeyeater *Lichenostomus melanops cassidix* and found, as we have, negligible variation in mortality from the interacting effects of homozygosity and sex. Research has generally focused on the impact of inbreeding on a fitness-related trait such as susceptibility to disease or progression of infection (Benton et al., 2018; Queirós et al., 2016; Trinkel et al., 2011) as opposed to investigating links with mortality. We chose to categorise badgers into distinct 'infection' groups so complete lifetime trajectories (conditional on first capture) could be compared but this meant we filtered out badgers that tested positive after their first year of life ($n = 187$) leaving unanswered questions regarding the mortality trajectories of these individuals. Including this group of badgers in this framework would introduce an inherent bias—to be a member of this group is conditional on having lived beyond their first year, thus forcing early survival estimates for this group to be artificially high.

Working with CMR data from wild populations comes with some inherent problems and potential bias. We cannot model

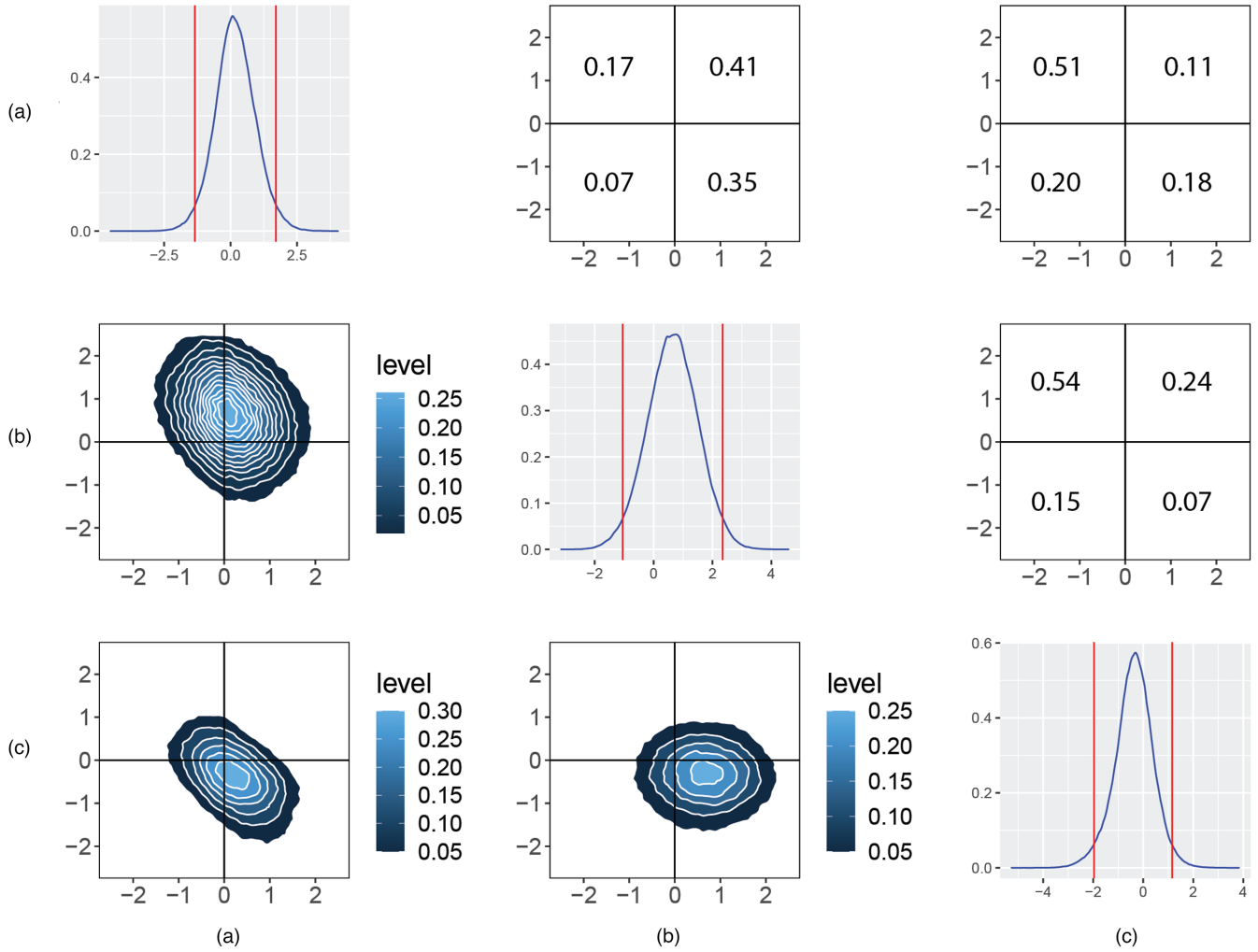

FIGURE 5 Model-averaged posterior distributions of multi-locus homozygosity (MLH) coefficient estimates from a RJ-MCMC analysis of a wild population of European badgers using the Gompertz-Makehmam mortality function with parameters a, b and c lower triangle: model-averaged bivariate posterior density distributions of MLH coefficient estimates. Centre diagonal: model-averaged univariate posterior density distributions of MLH coefficient estimates. Upper triangle: numbers representing the proportion of each corresponding bivariate distribution from the lower triangle that lies within each quadrant. Coefficient estimates refer to the maximum possible effect of MLH on the Gompertz–Makeham parameters (i.e. moving from MLH = 0 to MLH = 1).

survival or mortality from birth as we only have information on captured individuals: it is almost certain that some individuals will die prior to being available for capture. Rogers et al. (1997) estimated pre-capture mortality in this population at 24% but we are unable to determine whether this rate varies with different levels of inbreeding or infection status. We are working on methods to include this type of information in such analyses but without any adjustment we are likely under-estimating initial/'at-birth' mortality and reducing our ability to detect bathtub shaped mortality patterns in our analyses. In our initial model comparison, the WAIC score of the Siler model was only 3.79 points higher than the Gompertz–Makeham model suggesting it provided a similarly good fit to the data. The difference between the two models lies in the description of very early life mortality changes—the Gompertz–Makeham model effectively ignores them whilst the Siler models them with a declining Gompertz function to allow initially high mortality to decrease as individuals reach maturity. The mortality trajectories of never-positive individuals do hint at some variation in early life with reduced mortality for individuals with higher MLH which, if confirmed, would provide support for Antagonistic Pleiotropy, or the disposable soma theory (Kirkwood, 1977) which describes a trade-off between committing energy to reproduction vs investing in maintenance of body tissues. We ran our full RJ-MCMC analysis using the Siler model (see Supporting information) and the resulting mortality trajectories provide some support for early-life survival benefits associated with increased MLH. This raises an important question: is MLH beneficial for cub survival, or are the surviving, emerging cubs a biased subset of cubs? As a result of poor information on pre-emergent cubs in setts, it remains possible that inbreeding negatively affects 'at-birth' survival rates which we are unable to detect. Alternatively, the pattern we observe may arise from a reduction in the number of offspring (pre-emergence from the sett) allowing greater investment in those cubs that do survive (Rabon & Waddell, 2010)

long enough to be captured. This may also help explain the lower initial mortality rates of putatively-infected cubs as we found here and previously (Hudson et al., 2019)—higher mortality of infected cubs prior to emergence from burrows would bias our inference of initial mortality rates.

Further complications relevant to studies of bTB are the limitations of diagnostic tests and changes in the prevailing tests employed in studies over time (Clifton-Hadley et al., 1995; Dalley et al., 2008; Delahay et al., 2013). False-positive diagnosis would potentially weaken the signal of mortality in 'cub-positive' badgers, whereas the more likely false negatives could strengthen the signal in the 'never-positive' individuals. Our results may therefore be more conservative for 'cub-positive' yet potentially overstated for 'never-positive' individuals. We are confident that any impact is minimal due to tests being highly specific and recapture being common.

Our data originate from a study of a natural free-living population of badgers, with no experimental manipulation of their breeding system or disease status; hence, the patterns we infer are associations rather than deductions of cause and effect. Our results provide evidence for an association between genome-wide homozygosity and the lifetime mortality of a free-living mammal, the strongest effect describing both an earlier onset and faster senescent decline in survival with increasing levels of MLH across both sexes. There is some indication that the magnitude of the effect on senescence is mediated by the infection status of the individual as putatively infected individuals suffered worse. Our findings are relevant to the conservation of small and fragmented populations in the wild because they highlight credible life-history impacts of MLH caused by inbreeding or genetic drift. Our findings are also relevant to our understanding of how the impacts of disease can be mediated by host genetics: in the badger-bTB system, infection and MLH combine to amplify actuarial senescence, with inevitable consequences for host demography. One avenue for further research is to consider how population management strategies, designed to reduce the transmission of bTB between wildlife and livestock, might influence the genetic structure of the wild host population.

Our findings confirm a positive association between genome-wide homozygosity and the intensity of actuarial senescence in a wild mammal. This association amplified among putatively infected individuals, highlighting the importance of links between life history, population genetics and disease.

AUTHOR CONTRIBUTIONS

Conceptualisation—Dave W. Hudson, Trevelyan J. McKinley and Dave J. Hodgson; methodology—Dave W. Hudson, Trevelyan J. McKinley, Richard Delahay and Dave J. Hodgson; writing—original draft preparation—Dave W. Hudson; writing—review and editing—Dave W. Hudson, Trevelyan J. McKinley, Clare H. Benton, Richard Delahay, Robbie A. McDonald and Dave J. Hodgson; funding acquisition—Trevelyan J. McKinley, Richard Delahay, Robbie A. McDonald and Dave J. Hodgson.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. The funders had no role in the design of the study; collection, analyses or interpretation of data; in the writing of the manuscript; and in the decision to publish the results.

DATA AVAILABILITY STATEMENT

Data available from the Dryad Digital Repository https://doi.org/10.5061/dryad.bk3j9kdg6 (Hudson, 2023).

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REFERENCES

Acevedo-Whitehouse, K., Gulland, F., Greig, D., & Amos, W. (2003). Disease susceptibility in California Sea lions. *Nature*, *422*(6927), 35. https://doi.org/10.1038/422035a

Alho, J. S., Välimäki, K., & Merilä, J. (2010). Rhh: An R extension for estimating multilocus heterozygosity and heterozygosity–heterozygosity correlation. *Molecular Ecology Resources*, *10*(4), 720–722. https://doi.org/10.1111/J.1755-0998.2010.02830.X

Amos, W., Worthington Wilmer, J., Fullard, K., Burg, T. M., Croxall, J. P., Bloch, D., & Coulson, T. (2001). The influence of parental relatedness on reproductive success. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, *268*(1480), 2021–2027. https://doi.org/10.1098/RSPB.2001.1751

Bebbington, M., Lai, C.-D., & Zitikis, R. (2007). Modeling human mortality using mixtures of bathtub shaped failure distributions. *Journal of Theoretical Biology*, *245*(3), 528–538. https://doi.org/10.1016/J.JTBI.2006.11.011

Beirne, C., Delahay, R., Hares, M., & Young, A. (2014). Age-related declines and disease-associated variation in immune cell telomere length in a wild mammal. *PLoS ONE*, *9*, e108964. https://doi.org/10.1371/journal.pone.0108964

Beirne, C., Waring, L., McDonald, R. A., Delahay, R., & Young, A. (2016). Age-related declines in immune response in a wild mammal are unrelated to immune cell telomere length. *Proceedings of the Royal Society B: Biological Sciences*, *283*(1825), 20152949. https://doi.org/10.1098/rspb.2015.2949

Benton, C. H., Delahay, R. J., Smith, F. A. P., Robertson, A., McDonald, R. A., Young, A. J., Burke, T. A., & Hodgson, D. (2018). Inbreeding intensifies sex- and age-dependent disease in a wild

mammal. *Journal of Animal Ecology*, *87*(6), 1500–1511. https://doi.org/10.1111/1365-2656.12878

Bérénos, C., Ellis, P. A., Pilkington, J. G., & Pemberton, J. M. (2016). Genomic analysis reveals depression due to both individual and maternal inbreeding in a free-living mammal population. *Molecular Ecology*, *25*(13), 3152–3168. https://doi.org/10.1111/MEC.13681

Bijlsma, R., Bundgaard, J., & Boerema, A. C. (2000). Does inbreeding affect the extinction risk of small populations? Predictions from Drosophila. *Journal of Evolutionary Biology*, *13*(3), 502–514. https://doi.org/10.1046/J.1420-9101.2000.00177.X

Bijlsma, R., Bundgaard, J., & Van Putten, W. F. (1999). Environmental dependence of inbreeding depression and purging in Drosophila melanogaster. *Journal of Evolutionary Biology*, *12*(6), 1125–1137. https://doi.org/10.1046/J.1420-9101.1999.00113.X

Bozzuto, C., Biebach, I., Muff, S., Ives, A. R., & Keller, L. F. (2019). Inbreeding reduces long-term growth of Alpine ibex populations. *Nature Ecology & Evolution*, *3*(9), 1359–1364. https://doi.org/10.1038/s41559-019-0968-1

Brooks, R., & Kemp, D. J. (2001). Can older males deliver the good genes? *Trends in Ecology & Evolution*, *16*(6), 308–313. https://doi.org/10.1016/S0169-5347(01)02147-4

Carpenter, P. J., Pope, L. C., Greig, C., Dawson, D. A., Rogers, L. M., Erven, K., Wilson, G. J., Delahay, R. J., Cheesman, C. L., & Burke, T. (2005). Mating system of the Eurasian badger, Meles meles, in a high density population. *Molecular Ecology*, *14*(1), 273–284. https://doi.org/10.1111/J.1365-294X.2004.02401.X

Charlesworth, B., & Hughes, K. A. (1996). Age-specific inbreeding depression and components of genetic variance in relation to the evolution of senescence (mutation accumulation/antagonistic pleiotropy/aging).

Charlesworth, D. (2003). Effects of inbreeding on the genetic diversity of populations. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *358*(1434), 1051–1070. https://doi.org/10.1098/RSTB.2003.1296

Charlesworth, D., & Charlesworth, B. (1987). Inbreeding depression and its evolutionary consequences. *Annual Review of Ecology and Systematics*, *18*, 237–268.

Charlesworth, D., & Willis, J. H. (2009). The genetics of inbreeding depression. *Nature Reviews Genetics*, *10*(11), 783–796. https://doi.org/10.1038/nrg2664

Charmantier, A., Perrins, C., McCleery, R. H., & Sheldon, B. C. (2006). Quantitative genetics of age at reproduction in wild swans: Support for antagonistic pleiotropy models of senescence. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(17), 6587–6592. https://doi.org/10.1073/PNAS.0511123103

Chen, N., Cosgrove, E. J., Bowman, R., Fitzpatrick, J. W., & Clark, A. G. (2016). Genomic consequences of population decline in the endangered Florida Scrub-Jay. *Current Biology*, *26*(21), 2974–2979. https://doi.org/10.1016/J.CUB.2016.08.062

Clifton-Hadley, R. S., Sayers, A. R., & Stock, M. P. (1995). Evaluation of an ELISA for *Mycobacterium bovis* infection in badgers (*Meles meles*). *The Veterinary Record*, *137*, 555–558. https://doi.org/10.1136/vr.137.22.555

Colchero, F., & Clark, J. S. (2012). Bayesian inference on age-specific survival for censored and truncated data. *Journal of Animal Ecology*, *81*(1), 139–149. https://doi.org/10.1111/j.1365-2656.2011.01898.x

Cormack, R. M. (1964). Estimates of survival from the sighting of marked animals. *Biometrika*, *51*, 429. https://doi.org/10.2307/2334149

Crnokrak, P., & Roff, D. A. (1999). Inbreeding depression in the wild. *Heredity*, *83*(3), 260–270. https://doi.org/10.1038/sj.hdy.6885530

Dalley, D., Davé, D., Lesellier, S., Palmer, S., Crawshaw, T., Hewinson, R. G., & Chambers, M. (2008). Development and evaluation of a gamma-interferon assay for tuberculosis in badgers (*Meles meles*). *Tuberculosis*, *88*, 235–243. https://doi.org/10.1016/j.tube.2007.11.001

Darwin, C. (1876). *The effect of cross and self fertilization in the vegetable kingdom*. John Murray. https://www.jstor.org/stable/43236582

David, P., Pujol, B., Viard, F., Castella, V., & Goudet, J. (2007). Reliable selfing rate estimates from imperfect population genetic data. *Molecular Ecology*, *16*(12), 2474–2487. https://doi.org/10.1111/J.1365-294X.2007.03330.X

de Valpine, P., Turek, D., Paciorek, C. J., Anderson-Bergman, C., Lang, D. T., & Bodik, R. (2017). Programming with models: Writing statistical algorithms for general model structures with NIMBLE. *Journal of Computational and Graphical Statistics*, *26*(2), 403–413. https://doi.org/10.1080/10618600.2016.1172487

Delahay, R. J., Langton, S., Smith, G. C., Clifton-Hadley, R. S., & Cheeseman, C. L. (2000). The spatio-temporal distribution of *Mycobacterium bovis* (bovine tuberculosis) infection in a high-density badger population. *Journal of Animal Ecology*, *69*(3), 428–441. https://doi.org/10.1046/j.1365-2656.2000.00406.x

Delahay, R. J., Smith, G. C., & Hutchings, M. R. (2009). The science of wildlife disease management. In *Management of disease in wild mammals* (pp. 1–8). Springer. https://doi.org/10.1007/978-4-431-77134-0_1

Delahay, R. J., Walker, N., Smith, G. S., Wilkinson, D., Clifton-Hadley, R. S., Cheeseman, C. L., Tomlinson, A. J., & Chambers, M. A. (2013). Long-term temporal trends and estimated transmission rates for *Mycobacterium bovis* infection in an undisturbed high-density badger (*Meles meles*) population. *Epidemiology and Infection*, *141*(7), 1445–1456. https://doi.org/10.1017/S0950268813000721

DeWoody, Y. D., & DeWoody, J. A. (2005). On the estimation of genome-wide heterozygosity using molecular markers. *Journal of Heredity*, *96*(2), 85–88. https://doi.org/10.1093/JHERED/ESI017

Drewe, J. A., Tomlinson, A. J., Walker, N. J., & Delahay, R. J. (2010). Diagnostic accuracy and optimal use of three tests for tuberculosis in live badgers. *PLoS ONE*, *5*, e11196. https://doi.org/10.1371/journal.pone.0011196

Eberhardt, L. L. (1985). Assessing the dynamics of wild populations. *The Journal of Wildlife Management*, *49*(4), 997. https://doi.org/10.2307/3801386

Falconer, D. S., & Mackay, T. F. C. (1996). *Introduction to quantitative genetics* (4th ed.). Longman.

Forstmeier, W., Schielzeth, H., Mueller, J. C., Ellegren, H., & Kempenaers, B. (2012). Heterozygosity–fitness correlations in zebra finches: Microsatellite markers can be better than their reputation. *Molecular Ecology*, *21*(13), 3237–3249. https://doi.org/10.1111/J.1365-294X.2012.05593.X

Fox, C. W., Scheibly, K. L., Wallin, W. G., Hitchcock, L. J., Stillwell, R. C., & Smith, B. P. (2006). The genetic architecture of life span and mortality rates: Gender and species differences in inbreeding load of two seed-feeding beetles. *Genetics*, *174*(2), 763–773. https://doi.org/10.1534/GENETICS.106.060392

Gaillard, J.-M., Allaine, D., Pontier, D., Yoccoz, N. G., & Promislow, D. E. L. (1994). Senescence in natural populations of mammals: A reanalysis. *Evolution*, *48*(2), 509–516. https://doi.org/10.2307/2410110

Gilbert, S. L., Lindberg, M. S., Hundertmark, K. J., & Person, D. K. (2014). Dead before detection: Addressing the effects of left truncation on survival estimation and ecological inference for neonates. *Methods in Ecology and Evolution*, *5*(10), 992–1001. https://doi.org/10.1111/2041-210X.12234

Gompertz, B. (1825). On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *182*, 513–585.

Green, P. J. (1995). Reversible jump Markov Chain Monte Carlo computation and Bayesian model determination. *Biometrika*, *82*, 711–732. https://doi.org/10.1093/biomet/82.4.711

Harrison, X., Bearhop, S., Inger, R., Colhoun, K., Gudmundsson, G. A., Hodgson, D., McElwaine, G., & Tregenza, T. (2011). Heterozygosity–fitness correlations in a migratory bird: An analysis of inbreeding and single-locus effects. *Molecular Ecology*, *20*(22), 4786–4795. https://doi.org/10.1111/J.1365-294X.2011.05283.X

Harrison, X. A., York, J. E., Cram, D. L., & Young, A. J. (2013). Extra-group mating increases inbreeding risk in a cooperatively breeding bird. *Molecular Ecology*, *22*(22), 5700–5715. https://doi.org/10.1111/MEC.12505

Harrisson, K. A., Magrath, M. J. L., Yen, J. D. L., Pavlova, A., Murray, N., Quin, B., Menkhorst, P., Miller, K. A., Cartwright, K., & Sunnucks, P. (2019). Lifetime fitness costs of inbreeding and being inbred in a critically endangered bird. *Current Biology*, *29*(16), 2711–2717.e4. https://doi.org/10.1016/J.CUB.2019.06.064

Hastie, D. I., & Green, P. J. (2012). Model choice using reversible jump Markov Chain Monte Carlo. *Statistica Neerlandica*, *66*(3), 309–338. https://doi.org/10.1111/J.1467-9574.2012.00516.X

Hedrick, P. W., & Garcia-Dorado, A. (2016). Understanding inbreeding depression, purging, and genetic rescue. *Trends in Ecology & Evolution*, *31*(12), 940–952. https://doi.org/10.1016/J.TREE.2016.09.005

Hoeting, J. A., Madigan, D., Raftery, A. E., & Volinsky, C. T. (1999). Bayesian model averaging: A tutorial. *Statistical Science*, *14*, 382–401. https://doi.org/10.1214/ss/1009212519

Hoffman, J. I., Simpson, F., David, P., Rijks, J. M., Kuiken, T., Thorne, M. A. S., Lacy, R. C., & Dasmahapatra, K. K. (2014). High-throughput sequencing reveals inbreeding depression in a natural population. *Proceedings of the National Academy of Sciences of the United States of America*, *111*, 3775–3780. https://doi.org/10.1073/pnas.1318945111

Hudson, D. W. (2023). Data from: Multi-locus homozygosity promotes actuarial senescence in a wild mammal. *Dryad Digital Repository*. https://doi.org/10.5061/dryad.bk3j9kdg6

Hudson, D. W., Delahay, R., McDonald, R. A., McKinley, T. J., & Hodgson, D. J. (2019). Analysis of lifetime mortality trajectories in wildlife disease research: BaSTA and beyond. *Diversity*, *11*(10), 182. https://doi.org/10.3390/D11100182

Hughes, K. A., Alipaz, J. A., Drnevich, J. M., & Reynolds, R. M. (2002). A test of evolutionary theories of aging. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(22), 14286–14291. https://doi.org/10.1073/PNAS.222326199

Huisman, J., Kruuk, L. E. B., Ellisa, P. A., Clutton-Brock, T., & Pemberton, J. M. (2016). Inbreeding depression across the lifespan in a wild mammal population. *Proceedings of the National Academy of Sciences of the United States of America*, *113*, 3585–3590. https://doi.org/10.1073/pnas.1518046113

Jolly, G. M. (1965). Explicit estimates from capture-recapture data with both death and immigration-stochastic model. *Biometrika*, *52*, 225–248. https://doi.org/10.2307/2333826

Jombart, T. (2008). adegenet: A R package for the multivariate analysis of genetic markers. *Bioinformatics*, *24*(11), 1403–1405. https://doi.org/10.1093/BIOINFORMATICS/BTN129

Kardos, M., Luikart, G., & Allendorf, F. W. (2015). Measuring individual inbreeding in the age of genomics: Marker-based measures are better than pedigrees. *Heredity*, *115*(1), 63–72. https://doi.org/10.1038/hdy.2015.17

Kardos, M., Taylor, H. R., Ellegren, H., Luikart, G., & Allendorf, F. W. (2016). Genomics advances the study of inbreeding depression in the wild. *Evolutionary Applications*, *9*(10), 1205–1218. https://doi.org/10.1111/EVA.12414

Keller, L. F. (1998). Inbreeding and its effects in an insular population of song sparrows (*Melospiza melodia*). *Evolution*, *52*(1), 240–250. https://doi.org/10.1111/J.1558-5646.1998.TB05157.X

Keller, L. F., Reid, J. M., & Arcese, P. (2008). Testing evolutionary models of senescence in a natural population: Age and inbreeding effects on fitness components in song sparrows. *Proceedings of the Royal Society B: Biological Sciences*, *275*, 597–604. https://doi.org/10.1098/rspb.2007.0961

Keller, L. F., & Waller, D. M. (2002). Inbreeding effects in the wild. *Trends in Ecology & Evolution*, *17*, 230–241.

Kirkwood, T. B. L. (1977). Evolution of ageing. *Nature*, *270*, 301–304. https://doi.org/10.1038/270301a0

Makeham, W. M. (1867). On the law of mortality. *Journal of the Institute of Actuaries*, *13*(6), 325–358. https://doi.org/10.1017/s2046166600003238

Mccallum, H. (2008). Population parameters: Estimation for ecological models. In *Population parameters: Estimation for ecological models*. Wiley. https://doi.org/10.1002/9780470757468

McDonald, J. L., Smith, G. C., McDonald, R. A., Delahay, R. J., & Hodgson, D. (2014). Mortality trajectory analysis reveals the drivers of sex-specific epidemiology in natural wildlife-disease interactions. *Proceedings of the Royal Society B: Biological Sciences*, *281*(1790), 20140526. https://doi.org/10.1098/rspb.2014.0526

Medawar, P. B. (1952). An unsolved problem of biology. In H. K. Lewis (Ed.), *An unsolved problem of biology* (pp. 467–506). Yale University Press. https://doi.org/10.2307/j.ctt2250w9n.16

Miller, J. M., Malenfant, R. M., David, P., Davis, C. S., Poissant, J., Hogg, J. T., Festa-Bianchet, M., & Coltman, D. W. (2013). Estimating genome-wide heterozygosity: Effects of demographic history and marker type. *Heredity 2014 112:3*, *112*(3), 240–247. https://doi.org/10.1038/hdy.2013.99

Moorad, J. A., & Promislow, D. E. L. (2009). What can genetic variation tell us about the evolution of senescence? *Proceedings of the Royal Society B: Biological Sciences*, *276*, 2271–2278. https://doi.org/10.1098/rspb.2009.0183

Morton, N. E., Crow, J. F., & Muller, H. J. (1956). An estimate of the mutational damage in man from data on consanguineous marriages. *Proceedings of the National Academy of Sciences of the United States of America*, *42*(11), 855. https://doi.org/10.1073/PNAS.42.11.855

Nietlisbach, P., Keller, L. F., Camenisch, G., Guillaume, F., Arcese, P., Reid, J. M., & Postma, E. (2017). Pedigree-based inbreeding coefficient explains more variation in fitness than heterozygosity at 160 microsatellites in a wild bird population. *Proceedings of the Royal Society B: Biological Sciences*, *284*(1850), 20162763. https://doi.org/10.1098/RSPB.2016.2763

Niskanen, A. K., Billing, A. M., Holand, H., Hagen, I. J., Araya-Ajoy, Y. G., Husby, A., Rønning, B., Myhre, A. M., Ranke, P. S., Kvalnes, T., Pärn, H., Ringsby, T. H., Lien, S., Sæther, B.-E., Muff, S., & Jensen, H. (2020). Consistent scaling of inbreeding depression in space and time in a house sparrow metapopulation. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(25), 14584–14592. https://doi.org/10.1073/PNAS.1909599117

Nussey, D. H., Froy, H., Lemaitre, J.-F., Gaillard, J.-M., & Austad, S. N. (2013). Senescence in natural populations of animals: Widespread evidence and its implications for bio-gerontology. *Ageing Research Reviews*, *12*(1), 214–225. https://doi.org/10.1016/J.ARR.2012.07.004

Partridge, L., & Mangel, M. (1999). Messages from mortality: The evolution of death rates in the old. *Trends in Ecology & Evolution*, *14*(11), 438–442. https://doi.org/10.1016/S0169-5347(99)01646-8

Pemberton, J. (2004). Measuring inbreeding depression in the wild: The old ways are the best. *Trends in Ecology & Evolution*, *19*(12), 613–615. https://doi.org/10.1016/J.TREE.2004.09.010

Queirós, J., Vicente, J., Alves, P. C., de la Fuente, J., & Gortazar, C. (2016). Tuberculosis, genetic diversity and fitness in the red deer, Cervus elaphus. *Infection, Genetics and Evolution*, *43*, 203–212. https://doi.org/10.1016/J.MEEGID.2016.05.031

R Core Team. (2019). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing.

Rabon, D. R., & Waddell, W. (2010). Effects of inbreeding on reproductive success, performance, litter size, and survival in captive red wolves (*Canis rufus*). *Zoo Biology*, *29*(1), 36–49. https://doi.org/10.1002/ZOO.20262

Raftery, A. E., Madigan, D., & Volinsky, C. T. (1994). *Accounting for model uncertainty in survival analysis improves predictive performance*.

Reid, J. M., Arcese, P., Keller, L. F., Elliott, K. H., Sampson, L., & Hasselquist, D. (2007). Inbreeding effects on immune response in free-living song sparrows (*Melospiza melodia*). *Proceedings of the Royal Society B: Biological Sciences*, *274*(1610), 697–706. https://doi.org/10.1098/rspb.2006.0092

Rogers, L. M., Cheeseman, C. L., Mallinson, P. J., & Clifton-hadley, A. N. D. R. (1997). The demography of a high-density badger (Meles meles) population in the west of England. *Journal of Zoology*, *242*, 705–728. https://doi.org/10.1111/j.1469-7998.1997.tb05821.x

Seber, G. A. F. (1965). A note on the multiple-recapture census. *Biometrika*, *52*, 249–260. https://doi.org/10.2307/2333827

Siler, W. (1979). A competing-risk model for animal mortality. *Ecology*, *60*, 750–757. https://doi.org/10.2307/1936612

Slate, J., David, P., Dodds, K. G., Veenvliet, B. A., Glass, B. C., Broad, T. E., & McEwan, J. C. (2004). Understanding the relationship between the inbreeding coefficient and multilocus heterozygosity: Theoretical expectations and empirical data. *Heredity*, *93*, 255–265. https://doi.org/10.1038/sj.hdy.6800485

Slate, J., Kruuk, L. E. B., Marshall, T. C., Pemberton, J. M., & Clutton-Brock, T. H. (2000). Inbreeding depression influences lifetime breeding success in a wild population of red deer (*Cervus elaphus*). *Proceedings of the Royal Society of London. Series B: Biological Sciences*, *267*(1453), 1657–1662. https://doi.org/10.1098/RSPB.2000.1192

Stoffel, M. A., Esser, M., Kardos, M., Humble, E., Nichols, H., David, P., & Hoffman, J. I. (2016). inbreedR: An R package for the analysis of inbreeding based on genetic markers. *Methods in Ecology and Evolution*, *7*(11), 1331–1339. https://doi.org/10.1111/2041-210X.12588

Stoffel, M. A., Johnston, S. E., Pilkington, J. G., & Pemberton, J. M. (2021). Genetic architecture and lifetime dynamics of inbreeding depression in a wild mammal. *Nature Communications*, *12*(1), 1–10. https://doi.org/10.1038/s41467-021-23222-9

Swindell, W. R., & Bouzat, J. L. (2006). Reduced inbreeding depression due to historical inbreeding in Drosophila melanogaster: Evidence for purging. *Journal of Evolutionary Biology*, *19*(4), 1257–1264. https://doi.org/10.1111/J.1420-9101.2005.01074.X

Szulkin, M., Bierne, N., & David, P. (2010). Heterozygosity-fitness correlations: A time for reappraisal. *Evolution*, *64*(5), 1202–1217. https://doi.org/10.1111/J.1558-5646.2010.00966.X

Szulkin, M., Garant, D., Mccleery, R. H., & Sheldon, B. C. (2007). Inbreeding depression along a life-history continuum in the great tit. *Journal of Evolutionary Biology*, *20*, 1531–1543. https://doi.org/10.1111/j.1420-9101.2007.01325.x

Trask, A. E., Ferrie, G. M., Wang, J., Newland, S., Canessa, S., Moehrenschlager, A., Laut, M., Duenas, L. B., & Ewen, J. G. (2021). Multiple life-stage inbreeding depression impacts demography and extinction risk in an extinct-in-the-wild species. *Scientific Reports*, *11*(1), 1–10. https://doi.org/10.1038/s41598-020-79979-4

Trinkel, M., Cooper, D., Packer, C., & Slotow, R. (2011). Inbreeding depression increases susceptibility to bovine tuberculosis in lions: An experimental test using an inbred-outbred contrast through translocation. *Journal of Wildlife Diseases*, *47*(3), 494–500. https://doi.org/10.7589/0090-3558-47.3.494

Ungewitter, E., & Scrable, H. (2009). Antagonistic pleiotropy and p53. *Mechanisms of Ageing and Development*, *130*(1–2), 10–17. https://doi.org/10.1016/J.MAD.2008.06.002

Viallefont, V., Raftery, A. E., & Richardson, S. (2001). Variable selection and Bayesian model averaging in case-control studies. *Statistics in Medicine*, *20*(21), 3215–3230. https://doi.org/10.1002/SIM.976

Wang, C., & Rosenberg, N. A. (2012). *MicroDrop: A program for estimating and correcting for allelic dropout in nonreplicated microsatellite genotypes version 1.01*. http://rosenberglab.stanford.edu/software.html

Wang, J. (2016). Pedigrees or markers: Which are better in estimating relatedness and inbreeding coefficient? *Theoretical Population Biology*, *107*, 4–13. https://doi.org/10.1016/J.TPB.2015.08.006

Watanabe, S. (2010). Asymptotic equivalence of Bayes cross validation and widely applicable information criterion in singular learning theory. *Journal of Machine Learning Research*, *11*(12), 3571–3594.

Williams, G. C. (1957). Pleiotropy, natural-selection, and the evolution of senescence. *Evolution*, *11*, 398.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Figure S1. Distribution of MLH scores across different badger groups and through time.

Figure S2. Inclusion probabilities comparison of different inbreeding measures.

Figure S3. Posterior inclusion probabilities using individual locus homozygosity as a categorical measure of inbreeding.

Figure S4. Posterior inclusion probabilities from categorical inbreeding analysis.

Figure S5. Model averaged survival and mortality trajectories from categorical inbreeding analysis.

Figure S6. Plot of inferred age at death against multi-locus homozygosity.

Figure S7. Density distributions of model-averaged predicted age-at-death of the European badgers (Meles meles) used in this study split by infection category.

Figure S8. Violin plots of posterior parameter densities from 'important' model (No RJ-MCMC).

Figure S9. Trace plots for the 5 Siler parameters.

Figure S10. Trace plots for the inbreeding coefficients.

Figure S11. Trace plots for the inbreeding:sex coefficients.

Figure S12. Trace plots for the inbreeding:infection coefficiants.

Figure S13. Trace plots for the inbreeding:infection:sex coefficients.

Figure S14. Trace plots for the infection:sex coefficients.

Figure S15. Inclusion probabilities from Siler analysis.

Figure S16. Model-averaged, posterior-predictive survival and mortality trajectories generated using the Siler model.

Figure S17. Posterior density plot of sigma.

Table S1. Diagnostic summary from the RJMCMC analysis.

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