



CHICAGO JOURNALS



The University of Chicago

The Size—Life Span Trade-Off Decomposed: Why Large Dogs Die Young

Author(s): Cornelia Kraus, Samuel Pavard and Daniel E. L. Promislow,

Reviewed work(s):

Source: *The American Naturalist*, (-Not available-), p. 000

Published by: [The University of Chicago Press](#) for [The American Society of Naturalists](#)

Stable URL: <http://www.jstor.org/stable/10.1086/669665>

Accessed: 26/02/2013 12:37

Your use of the JSTOR archive indicates your acceptance of the Terms & Conditions of Use, available at <http://www.jstor.org/page/info/about/policies/terms.jsp>

JSTOR is a not-for-profit service that helps scholars, researchers, and students discover, use, and build upon a wide range of content in a trusted digital archive. We use information technology and tools to increase productivity and facilitate new forms of scholarship. For more information about JSTOR, please contact support@jstor.org.



The University of Chicago Press, The American Society of Naturalists, The University of Chicago are collaborating with JSTOR to digitize, preserve and extend access to *The American Naturalist*.

<http://www.jstor.org>

The Size–Life Span Trade-Off Decomposed: Why Large Dogs Die Young

Cornelia Kraus,^{1,2,*} Samuel Pavard,^{1,3} and Daniel E. L. Promislow⁴

1. Laboratory of Survival and Longevity, Max Planck Institute for Demographic Research, Rostock, Germany; 2. Department of Sociobiology/Anthropology, University of Göttingen, Göttingen, Germany; 3. Eco-Anthropologie et Ethnobiologie, Unité Mixte de Recherche 7206, Centre National de la Recherche Scientifique, Muséum National d'Histoire Naturelle, Université Paris Diderot, Sorbonne Paris Cité, F-75005 Paris, France; 4. Department of Genetics, University of Georgia, Athens, Georgia 30602

Submitted July 7, 2011; Accepted November 7, 2012; Electronically published February 21, 2013

Online enhancements: PDF appendixes.

ABSTRACT: Large body size is one of the best predictors of long life span across species of mammals. In marked contrast, there is considerable evidence that, within species, larger individuals are actually shorter lived. This apparent cost of larger size is especially evident in the domestic dog, where artificial selection has led to breeds that vary in body size by almost two orders of magnitude and in average life expectancy by a factor of two. Survival costs of large size might be paid at different stages of the life cycle: a higher early mortality, an early onset of senescence, an elevated baseline mortality, or an increased rate of aging. After fitting different mortality hazard models to death data from 74 breeds of dogs, we describe the relationship between size and several mortality components. We did not find a clear correlation between body size and the onset of senescence. The baseline hazard is slightly higher in large dogs, but the driving force behind the trade-off between size and life span is apparently a strong positive relationship between size and aging rate. We conclude that large dogs die young mainly because they age quickly.

Keywords: size, life span, baseline hazard, aging rate, onset of senescence, dogs.

Introduction

You can't have it all. Organisms cannot allocate unlimited resources to growth, maintenance (repair), and reproduction throughout life. Trade-offs between these traits are inevitable. Although large size can increase short-term survival and fecundity, growing large rapidly and maintaining a large body size might come at the cost of reduced survival later in life. There is considerable evidence that growing fast can compromise an individual's life span (Metcalf and Monaghan 2003; Austad 2010). Mice, rats, and dogs selected for a high growth rate and/or a large body size exhibit reduced longevity (Patronek et al. 1997; Miller et

al. 2000, 2002; Bartke et al. 2001a; Rollo 2002), and there is some evidence that increased weight and height might be detrimental to human health (Samaras 2009). The relationship between growth and longevity also holds across species. Even though a strong positive relationship between body size and life span exists in mammals (Gaillard et al. 1989; Promislow and Harvey 1990), postnatal growth rate and adult life span are inversely correlated when controlling for body size (de Magalhaes et al. 2007).

The domestic dog, *Canis lupus familiaris*, provides us with an ideal opportunity to understand how the shape of age-specific mortality curves has evolved under strong directional selection for body size. Body size varies by almost two orders of magnitude (from Chihuahuas to mastiffs; Moody et al. 2006; Sutter et al. 2008) and longevity by a factor of two: small breeds are expected to live about 10–14 years, whereas large breeds die at a median age of 5–8 years (Michell 1999; Proschowsky et al. 2003). Large dogs grow considerably faster and also take longer to reach adult weight (Kirkwood 1985; Favier et al. 2001; Hawthorne et al. 2004; Galis et al. 2007). Having exchanged natural selection for artificial selection some 9,000 generations ago (Lindblad-Toh et al. 2005), dogs might seem a rather unsuitable species to help us answer evolutionary questions. But one can envision the making of the roughly 400 dog breeds known today as a large-scale selection experiment for a wide variety of traits, ranging from body size to complex behavioral traits. Domestication and selective breeding have produced earth's most phenotypically variable mammal (Austad 2005; Moody et al. 2006). This provides a unique chance to identify and characterize trade-offs between life-history traits. Often, such trade-offs are difficult to measure in observational data. Across species, negative correlations can be masked by correlated responses of other traits such as fecundity. Within species, trade-offs are often obscured by a high positive covariance due to

* Corresponding author; e-mail: ckraus1@gwdg.de.

variation in individual quality (Reznick et al. 2000; Metcalfe and Monaghan 2003). At the level of single strains or breeds within a species, the size-longevity relationship is inconsistent (mice: Anisimov et al. 2004; *Drosophila*: Khazaeli et al. 2005; dogs: Galis et al. 2007), perhaps because of lack of variation. Under natural conditions, where extrinsic mortality factors play a large role, increased body size often improves survival prospects (e.g., ungulates: Gaillard et al. 2000; rodents: Sauer and Slade 1987). Covariation of life-history traits across dog breeds directly selected for certain trait values, such as a standard body size, can provide a valuable addition to experimental studies of trade-off functions.

Why do large dogs die young? Life span is often used as a proxy for aging (Monaghan et al. 2008). However, life span is the outcome of several components of the mortality trajectory: the early mortality decline, the onset of senescence, the baseline mortality (i.e., the lowest point in the hazard curve, sometimes also called level of mortality, initial mortality, or age-independent mortality), and/or the rate of aging, which is determined by age-related changes in intrinsic susceptibility (fig. 1). Artificial selection for large size in yellow dung flies resulted in increased juvenile mortality, but only in stressful environments (Teuschl et al. 2006). In dwarf mice, it has been suggested that the increased longevity is a consequence of a delayed onset of senescence (Bartke et al. 2001*b*). Fast growth in natural populations of perch and lizards resulted in increased adult mortality (Olsson and Shine 2002; Metcalfe and Monaghan 2003). The costs of rapid growth might also be paid late in life: comparative analyses have linked pre- as well as postnatal growth rate to senescence rates in mammals and birds (Ricklefs and Scheuerlein 2001; Ricklefs 2006).

Here our aim is to decompose the size–adult life expectancy trade-off by comparing mortality trajectories across 74 dog breeds. We attempt to test three specific—nonexclusive—hypotheses. The decreased life expectancy of large dogs compared to their smaller conspecifics might be due to (1) an earlier onset of senescence (fig. 1*B*), (2) a higher minimum mortality hazard (fig. 1*C*), and/or (3) an increased rate of aging (fig. 1*D*).

Methods

Data

Mortality curves were derived from age at death data for dogs from the Veterinary Medical Database (VMDB).¹ These data include dogs seen at veterinary teaching hos-

pitals throughout North America and have been used to study mortality in dogs previously (Li et al. 1996; Patronek et al. 1997; Galis et al. 2007). Among other variables, this data set includes information on breed, sex, age at death, and body mass. The data set covers the years 1984–2004. We selected all breeds for which at least 120 individuals were available. Because very early mortality is likely to be highly biased (stillbirth, neonatal, and early mortality are presumably much less likely to be seen at a teaching hospital), we excluded animals that died during the first 2 months of life. In contrast to some earlier studies using the VMDB (e.g., Galis et al. 2007), we did not exclude any causes of death, such as accidents. We consider them an integral part of the (likely largely age-independent) general level of mortality. In total, 56,637 individuals from 74 breeds were included in the final data set (see supplementary material, table A1, available online).

In the VMDB, age at death is recorded as a categorical variable (0–15 days, 15–60 days, 2–6 months, 6 months–1 year, 1–2 years, 2–4 years, 4–7 years, 7–10 years, 10–15 years, >15 years). These interval-censored data were used to estimate age-specific mortality for each breed. Data on breed weight were obtained from Sutter et al. (2007, supplementary material). We decided not to use the weight at death recorded in the database for several reasons. (1) As with age at death data, body weight data are interval censored (weight categories in pounds: 0–1, 1–5, 5–15, 15–30, 30–50, etc.). As a result, resolution in body weight, especially for the larger breeds for which the last weight interval is “>100 pounds” (>45.5 kg), would be poor. (2) Individual weight is unknown in 16,453 cases (~30%). (3) For the young ages, individuals are not fully grown, and hence the weight category given in the database is not representative of size/growth. (4) Especially at older ages, diseases leading to death might cause substantial weight loss, such that weight recorded did not reflect normal adult weight in that individual. A recent study suggested that the relatively small variation within most breeds makes average breed values a suitable surrogate for individual measures (Sutter et al. 2008).

We assume here that our data set, based on observed deaths of patients in teaching hospitals, will be subject to certain biases. First, our models assume that the distribution of ages at death is the same as the distribution of age structure in the population at large. However, it is likely that individuals dying at a teaching hospital represent a nonrandom sample of diseases, ages, and breeds. Dogs with rare or difficult-to-treat diseases are probably more likely to be brought to a teaching hospital than dogs with more common or untreatable disorders (see also discussion in Patronek et al. 1997). Additionally, the relative frequency of mixed-breed versus purebred dogs might be lower at teaching hospitals than neighborhood

¹ Veterinary Medical Database (VMDB), <http://www.vmdb.org/>; VMDB does not make any implicit or implied opinion on the subject of the article or study.

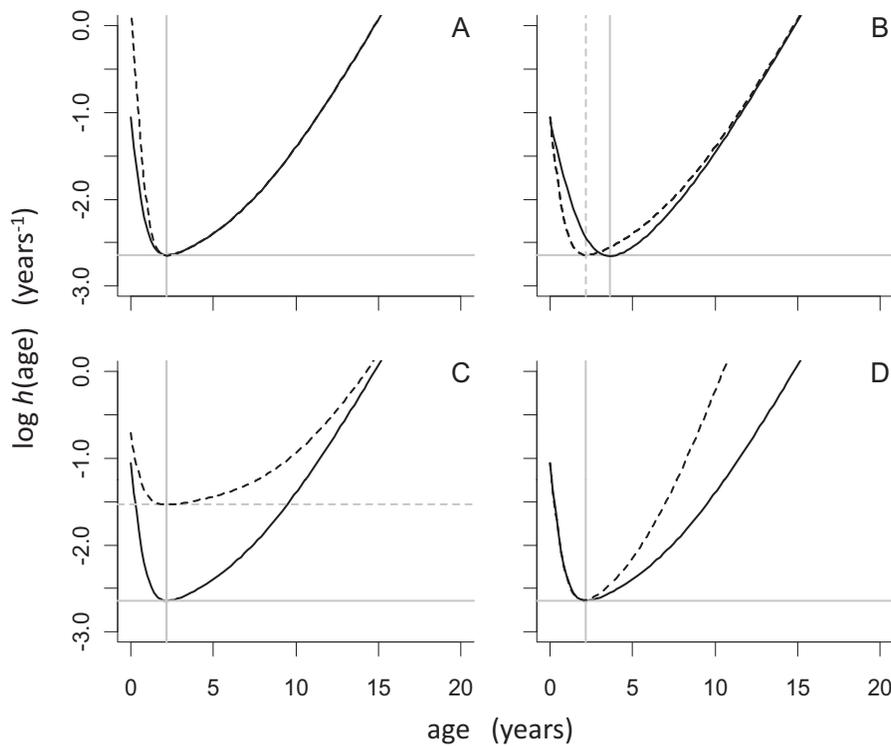


Figure 1: A decline in life expectancy can be due to changes (solid line to dashed line) in different components of the mortality hazard trajectory $h(\text{age})$: A, increased early mortality; B, an earlier onset of senescence, age α ; C, an increased minimum hazard $h(\alpha)$; and D, an increased rate of aging. Vertical gray lines mark age α , horizontal gray lines mark $h(\alpha)$. Here we investigate scenarios B–D.

clinics. Because mixed-breed dogs live longer than pure-bred dogs (Patronek et al. 1997), this could alter observed mortality dynamics. These or other biases in our data set could account for the fact that mean life expectancy estimates are lower in this data set than those from other sources. However, they do show the same pattern of size dependence as seen previously (Patronek et al. 1997; Michell 1999; Proschowsky et al. 2003; Galis et al. 2007). Second, data quality may be particularly low for early mortality because it is often sudden and therefore not likely to be seen at a teaching hospital. Third, the lower sample sizes at the oldest ages mean that the uncertainty of the estimates of mortality rates at older ages increases. Finally, we do not know the size of the “at risk” population for each breed and age class (i.e., the healthy dogs in each age class). We therefore assume that the population of each breed was stationary during the 20-year period analyzed here (i.e., constant population size and stable age distribution). Thus, while this is the most extensive analysis of age-specific mortality dynamics in dogs undertaken to date, we need to bear these caveats in mind as we interpret our findings.

Mortality Hazard Functions

Because exact ages at death were not available, and because we excluded mortality until 2 months of age, we used survival analysis for interval-censored data (Klein and Moeschberger 2005). Failure time T_i (i.e., the age at death of dog i), is known to occur within a given age interval, $[L_i, R_i]$, with L_i denoting the lower and R_i the upper age limits of an interval. Each individual is defined by a set of three binary operators $\delta_{1,i}$, $\delta_{2,i}$ and $\delta_{3,i}$ defining three possibilities: (1) the failure time T_i occurred before the first observation time ($T_i \leq R_{\text{first},i}$), so $\delta_{1,i} = 1$, $\delta_{2,i} = 0$, and $\delta_{3,i} = 0$; (2) the failure time T_i occurred within a given interval ($L_{t,i} < T_i \leq R_{t,i}$), so $\delta_{1,i} = 0$, $\delta_{2,i} = 1$, and $\delta_{3,i} = 0$; or (3) the failure time T_i was not observed because death occurred within the last open interval ($T_i > L_{\text{last},i}$), so $\delta_{1,i} = 0$, $\delta_{2,i} = 0$, and $\delta_{3,i} = 1$. For each dog, the effective observations are $(L_p, R_p, \delta_{1,p}, \delta_{2,p}, \delta_{3,p})$. The likelihood function over the N individuals is of the form $L \propto \prod_{i=0}^N [1 - S(R_i)]^{\delta_{1,i}} [S(L_i) - S(R_i)]^{\delta_{2,i}} S(L_i)^{\delta_{3,i}}$, where $S(L_i)$ and $S(R_i)$ are the survival probabilities at the beginning and the end of each interval.

Hazard Models Considered

We fitted several parametric survival models. In mammals, the mortality hazard first decreases throughout the juvenile period until an age, α , at which the hazard reaches its minimum, $h(\alpha)$ (note that for our purposes, α is defined only by the hazard, not by sexual maturity). Mortality then increases continuously from age α onward. We therefore fitted a set of common hazard models following this general pattern. The general structure of the models fitted differs by the number of terms incorporated (two or three). Each term stands for an additive mortality hazard that together constitute a competitive risk model. These general structures were $h(t) = h_1(t) + h_3(t)$ and $h(t) = h_1(t) + h_2 + h_3(t)$, where $h_1(t)$ is a negative exponential- or power-based function capturing the decrease in mortality with age during early life; $h_2 = a_2$ is a constant scaling up or down of the entire hazard function; and $h_3(t)$ is a positive exponential- or power-based function capturing the senescent mortality. The constant h_2 , when incorporated, allows the hazard to almost plateau (slow increase) for young adults, by decoupling the early and late rapid mortality changes to some extent.

We fitted the general structure above for all possible combinations of $h_1(t)$ and $h_3(t)$ corresponding to either a Weibull function (i.e., $h_1(t) = \beta_1 \lambda_1 t^{\beta_1 - 1}$ with $0 < \beta_1 < 1$ and $h_3(t) = \beta_3 \lambda_3 t^{\beta_3 - 1}$ with $\beta_3 > 1$; Weibull 1951) or a Gompertz function (i.e., $h_1(t) = a_1 e^{-b_1 t}$ and $h_3(t) = a_3 e^{b_3 t}$; Gompertz 1825). We have chosen the Gompertz and the Weibull functions because they are the most commonly used ones for human and animal mortality and have been found to fit a variety of species (e.g., Siler 1979; Juckett and Rosenberg 1993; Wilson 1994; Ricklefs and Scheuerlein 2001; Moorad et al. 2012). In particular, the Weibull function (power function) is very flexible and can accommodate a large range of shapes for the hazard increase with age: from accelerating to constant (linear hazard increase) and decelerating hazards. Other potential candidate models such as the Kannisto or the logistic survival model require the estimation of even more parameters (for a comparison, see Thatcher et al. 1998). However, even the five-parameter models failed to reach a convergent likelihood solution for some breeds (likely due to the interval-censored nature of the age at death data). Models with even more parameters exacerbate this problem. For each breed, we therefore fitted eight models. If we denote W- and W+ the decreasing and increasing Weibull functions, respectively, h the constant second term, and G- and G+ the decreasing and increasing Gompertz functions, these eight models can be denoted: G-G+, G-hG+, G-W+, G-hW+, W-G+, W-hG+, W-W+, W-hW+. Model G-hG+ is also known as the Siler model for animal mortality (Siler 1979).

Model Fitting and Selection

All models were fitted using the Nelder-Mead algorithm implemented in the “optim” function of the Stats package in the statistical program R (ver. 2.9.2; Nelder and Mead 1965; R Development Core Team 2011). For each model, the corrected Akaike Information Criterion (AIC_c) for small sample sizes was computed (Burnham and Anderson 2002). The model with the lowest AIC_c was selected as the best-supported model in our candidate set of models. In 32 out of 74 cases, the ΔAIC_c (here, AIC_c of the second-best model minus the AIC_c of the top model) was below 2. This suggests that the second-best model was almost equally well supported by the data. Nonetheless, including the second-best model for these breeds in the regression analyses (see below) yielded quantitatively very similar results. In four cases, only one model converged. For each breed, the selected model, the model parameters, and select derived parameters are listed in supplementary table A1.

Key Parameters for Analyzing Age-Specific Mortality

Because of the interval-censored nature of the data and because the covariate of interest, body size, was available only as a breed average, we could not use an individual-based approach for analyzing the relationship between breed size and mortality. Rather, the mortality parameters of interest (table 1) were analyzed as a function of body size using linear regression at the breed level.

Comparing the mortality hazard across populations at a given chronological age t can confound the effects of size on baseline mortality with the effects of size on aging. If two populations differ in the onset of senescence, at a given age, one population will be further along their hazard trajectory than the other. Hence, for the population that starts aging earlier, aging will have already contributed more to the hazard level at this age relative to the population that just started aging. Therefore, we analyzed the mortality-size relationships as a function of τ (hereafter called “relative age”) such that chronological age $t = \alpha + \tau$. Rooting the hazard functions at age α allows us to describe the speed at which mortality hazard is changing τ years after α .

In case our estimates of α are biased, given that the location of the minimum of a bathtub-like function can only be estimated with substantial uncertainty, and due to the data quality problems mentioned above, we also analyzed how size affects baseline mortality and the age-specific increase in the mortality hazard using chronological age. Thus, we can ask whether, at a given chronological age, large dogs exhibit a higher mortality hazard than small dogs and whether mortality rates increase faster with age

Table 1: Parameters describing mortality patterns at the breed level

Parameter	Notation	Description
Onset of senescence	α	Age at which the mortality hazard is at its lowest point
Adult life expectancy	$e(\alpha)$	Remaining life expectancy at age α
Baseline hazard	$h(\alpha)$	Mortality hazard at age α ; estimates the minimum hazard
Absolute rate of aging	$h'(\alpha + \tau)$	Describes the speed at which the mortality hazard is increasing at the relative age τ (τ years after α)
Relative rate of aging	$h'(\alpha + \tau)/h(\alpha + \tau)$	Describes the speed at which the mortality hazard is increasing at the relative age τ (τ years after α), relative to the hazard at this age

in large dogs. We chose 4 years as the starting point for these analyses because mortality has begun to increase for all breeds at this age (see table A1 and fig. A1, available online). As a consequence, however, the effects of size on the baseline hazard will be slightly overestimated. Because the results of these analyses largely parallel those for relative age, we present them in the supplementary material (tables B1, B2; figs. B1–B4, available online).

To make sure that the results obtained in the parametric analyses were robust and not simply a result of the hazard functions imposed, we also used nonparametric survival analysis to estimate a piecewise (per interval) constant hazard function. The results of the nonparametric hazard functions match those using the parametric mortality models, albeit with higher uncertainty levels, and hence are only presented in the supplementary material (tables C1, C2; figs. C1–C4, available online).

Onset of Senescence. We did not use our estimates of the early mortality decline for inference because of data quality issues discussed above. We used these data (from the age of 2 months onward), however, to be able to estimate the onset of senescence. To investigate whether body size affects the onset of senescence, we calculated the age α that separates the phase of decreasing mortality during early life from the phase of increasing mortality later in life (i.e., senescent mortality). It does not necessarily coincide with the age of sexual maturity or the end of the growth period. For mortality hazard functions incorporating only Gompertz terms, age α at which mortality is the lowest can be calculated analytically by solving the equation $h'(t) = 0$. In this case, $\alpha = [\log(a_1 b_1) - \log(a_3 b_3)] / (b_1 + b_3)$. For hazard models that include a Weibull component, we solved the equation $h'(t) = 0$ numerically using the function “uniroot” in R (R Development Core Team 2011).

Adult Life Expectancy. We first examine the relationship between body size and the life expectancy estimates derived from the best-fitting mortality functions. We estimated remaining life expectancy at age α by numerical integration. Remaining life expectancy $e(\alpha)$ represents “adult life

expectancy” (i.e., mean years to death after α , throughout the complete period of increasing mortality).

Baseline Hazard. To investigate whether the trade-off between life span and size across dog breeds is driven mainly by an increase in the overall level of mortality, we compared the baseline hazard $h(\alpha)$ across breeds.

Absolute and Relative Rate of Aging. Demographic senescence is usually defined as an increase of mortality with age. Still, measuring the rate of aging is far from straightforward and many different measures have been proposed and debated (e.g., Promislow 1991; Partridge and Barton 1996; Ricklefs and Scheuerlein 2002; Williams et al. 2006; Moorad et al. 2012). Here we quantify the speed of aging and its relationship to size on two levels: an absolute and a proportional one. First, we calculated the absolute increase in mortality simply as the first derivative of the hazard function $h'(t)$, which we hereafter call the “absolute rate of aging.” To us, this seems the most direct translation of the definition of aging as an “increase in mortality rate over age” into mathematics. Because h_2 is independent of age, $h'(t) = h'_1(t) + h'_3(t)$, where the derivatives of the negative and the positive Gompertz are $-a_1 b_1 e^{-b_1 t}$ and $a_3 b_3 e^{b_3 t}$, respectively, and the derivative of the Weibull term is $\lambda(\beta - 1)\beta t^{\beta-2}$. Second, we calculated the increase in mortality relative to the level of mortality at this age as the ratio $h'(t)/h(t)$, which we hereafter call the “relative rate of aging.” This is comparable to the commonly used actuarial rate of aging. For the Gompertz function, this ratio equals the parameter b (i.e., the actuarial rate of aging; Gompertz 1825). For the Weibull function, this ratio is itself a function of age t , $h'(t)/h(t) = (\beta - 1)/t$. With increasing age, $h_1(t)$ approaches 0, and hence the relative rate of aging converges to $h'_3(t)/h_3(t)$ or $h'_3(t)/[h_2 + h_3(t)]$.

This approach has the advantage that we can compare aging rates even if populations differ in their type of hazard function. Additionally, it allows us to investigate how the rate of aging itself changes with age, as suggested by Williams et al. (2006). On the other hand, this can be seen as a drawback because we cannot derive one neat summary

measure such as the Gompertz b and simply compare this statistic across populations. Therefore, we estimated the relationship between size and aging rate at three points in time during the senescent period—ages $\alpha + 2$, $\alpha + 4$, and $\alpha + 7$ years.

Statistical Analyses

To test whether body size or sample size affected which model provided the best fit for the mortality data of the given breeds, we employed one-way ANOVAs with model type as a categorical variable. We used simple linear regression to estimate the slope of the relationships between breed size and the single mortality components. For most parameters, we had to log-transform the response variable to linearize the relationship and to meet standard linear model assumptions, which we checked using diagnostic plots. In some cases, there were some outliers (between 1 and 3), but removing these did not change the estimated coefficients substantially and only increased R^2 by a few percent; therefore we retained all data in the final analyses and graphs presented. Our focus here is on describing the shape and the strength of the relationships between size and components of the mortality trajectory. We still do report F and P values, even though we are well aware that they are necessarily not exact, because we could not easily integrate the uncertainty about our model parameters in the regression analyses. Still, to test how sensitive our results are to this problem, we repeated the analyses with a weighted linear regression using the square root of sample size as weight. As with model selection uncertainty, results were quantitatively very similar, and hence here we present only the regression with equal weight for all breeds. We also do multiple tests on different derived parameters based on the same directly estimated parameters. Still, these values should allow a rough evaluation of the relative support for the different relationships we estimate.

Breeds differ in their degree of genetic relatedness. In a statistical analysis, breeds that are genetically similar are expected to be relatively similar to one another in phenotypic traits as well. As such, each breed value does not represent a fully independent point, as is generally assumed in statistical analysis. There are a variety of methods for correcting for this among species (Harvey and Pagel 1991), as well as among genotypes within species (Kang et al. 2008). Models among species assume that species are not a product of hybrids (clearly not true for dog breeds; Parker et al. 2004), and models to correct for relatedness, allowing for reticulate evolution, have been designed primarily for genome-wide association studies (Kang et al. 2008). In the present case, P values may be somewhat smaller than the true P values because we will have slightly overestimated the biologically true degrees of freedom.

Results

Size and the Best-Fitting Model

Most of the 74 breeds showed a Gompertz-like increase in the mortality hazard ($n_{G-G+} = 37$, $n_{G-hG+} = 21$, $n_{G-W+} = 13$, $n_{G-hW+} = 3$; see table A1 for more details). Body size affected which of the candidate models provided the best fit for the mortality data of a breed (one-way ANOVA, response: size, factor: “model”: $F_{3,70} = 3.52$, $P = .019$). Breeds for which the model $G-hG+$ fits best were on average smallest and those for which the model $G-W+$ fits best were on average largest. An inclusion of the constant hazard h_2 was linked to a 10-kg difference in weight, although only three breeds were fitted best by model $G-hW+$ (mean size \pm SD: size $_{G-G+} = 26 \pm 18$ kg, size $_{G-hG+} = 17 \pm 12$ kg, size $_{G-W+} = 35 \pm 18$ kg, size $_{G-hW+} = 26 \pm 2$ kg). The model that fit best did not depend on sample size (ANOVA, response: n , factor “model”: $F_{3,70} = 0.544$, $P = .65$).

Size and Mortality Components

Table 2 provides a summary of the linear regression estimates and statistics describing the relationship between size and all mortality components considered. In the following paragraphs, we describe these relationships in more detail.

The results for chronological age and the nonparametric analyses parallel those of the parametric ones for relative age to a large degree and are therefore presented in the supplementary material (app. B and app. C).

Size and the Onset of Aging

The mean age at the onset of senescence among dog breeds was 2.15 years (± 0.77 SD). We found no statistically significant relationship between body size and the onset of aging (fig. 2A; table 2). The only conspicuous feature of this relationship is that the largest dogs (“giant” breeds, >50 kg) all start aging rather early—in fact, before they are fully grown.

Size and Life Expectancy

Reaching α , dogs could expect to live on average for 6.47 ± 1.12 more years. Our analyses revealed a strong negative relationship between adult life expectancy and size: size explained 44% of the variance in life expectancy at α (table 2; fig. 2B).

Table 2: Linear regression estimates and statistics for the relationship between size and several components of mortality

Parameter	β	SE(β)	R^2	$F_{1,72}$	P
α	-.0006	.0053	$\ll .001$.013	.909
$e(\alpha)$	-.0431	.0058	.438	56.04	$\ll .001$
$\log(h(\alpha))$.0074	.0032	.071	5.49	.022
$\log(h'(\alpha + 2))$.0251	.0037	.385	44.99	$\ll .001$
$\log(h'(\alpha + 4))$.0240	.0029	.491	69.46	$\ll .001$
$\log(h'(\alpha + 7))$.0198	.0025	.467	62.97	$\ll .001$
$\log(h'(\alpha + 2)/h(\alpha + 2))$.0144	.0040	.151	12.79	.004
$\log(h'(\alpha + 4)/h(\alpha + 4))$.0094	.0026	.156	13.30	<.001
$\log(h'(\alpha + 7)/h(\alpha + 7))$.0021	.0021	.143	1.046	<.001

Note: The parameter notation is explained in table 1.

Size and the Baseline Hazard

Large dogs did have a somewhat higher hazard at age α compared to their smaller counterparts, with the hazard increasing with size (fig. 2C; table 2). However, the relationship is not very strong: size explained only 7% of the variance in the baseline hazard across breeds. The modest explanatory power of size regarding the baseline hazard suggests that this effect is not the main mechanism by which size affects life expectancy. At the chronological age of 4 the relationship is stronger, explaining 15% of the variance in the mortality hazard across breeds (see supplementary material, table B1; fig. B2), suggesting that, by this age, aging has already started to drive the hazard curves of small and large dogs further apart.

Size and the Rate of Aging

The absolute rate of aging (measured as the first derivative of the hazard function) showed a strong positive correlation with size (table 2; fig. 3); that is, the speed at which the mortality hazard increases following the onset of senescence increases with body size. Likewise, given that a dog has reached a certain age (chronological age perspective), the absolute rate of aging increases with body size (see table B2; fig. B3). A clustering of breeds according to the best mortality model fitted is evident (fig. 3): breeds that aged according to the Weibull function had higher aging rates than those fit by the Siler model ($G-hG+$). The slope of the relationship between size and aging rate remained rather stable over age, but the variance in aging rate explained by body size increased from 39% to ~48% from age $\alpha + 2$ to later ages (table 2). The latter effect occurs because on a log scale, the first derivative of the Weibull function increases more slowly with age ($\log(t)$) than the Gompertz function, decreasing the variance in aging rates between Gompertz and Weibull breeds.

The relative rate of aging—that is, the increase in the hazard relative to the hazard level at this age—also in-

creases with size. However, the effect is clearly smaller than for the absolute rate of aging; its slope decreases with age and is not significantly different from 0 for $\alpha + 7$ (table 2; fig. 4). This is mainly because the smaller breeds fitted best by the Siler model and have a lower relative aging rate than the Weibull-fitted breeds, which are on average larger. For the Gompertz-fitted breeds, the size relationship should stabilize with age because the relative rate of aging converges to b_3 , whereas for the Weibull-fitted breeds it declines with age. The same pattern is shown for chronological age (table B2; fig. B4).

Size and Life Expectancy Revisited

After describing how size is related to the single components of the hazard trajectory, here we set out to quantify how much of the variation in life expectancy can be explained by size when acting through the baseline hazard versus the rate of aging (table 3). The baseline hazard and the absolute rate of aging at age $\alpha + 4$ together explain (not surprisingly) 96% of the variance in life expectancy among breeds (note that they are not correlated, $r_{h(\alpha), h'(\alpha+4)} = 0.06$; moreover, the relative rate of aging does not correlate with life expectancy, $r_{e(\alpha), h'(\alpha+4)/h(\alpha+4)} = -0.06$, and hence cannot explain the trade-off between size and life expectancy). Adding size to the two hazard components does not improve the fit of the model (R^2 remains at 96%). Replacing the rate of aging with size increases the variance explained by only the baseline hazard by 25% (from 48% to 73%), whereas it improves R^2 by only 5% when replacing the baseline hazard with size (from 51% to 56%). This suggests that the size effect on life expectancy is driven by its effect on the rate of aging rather than by its effect on the baseline hazard.

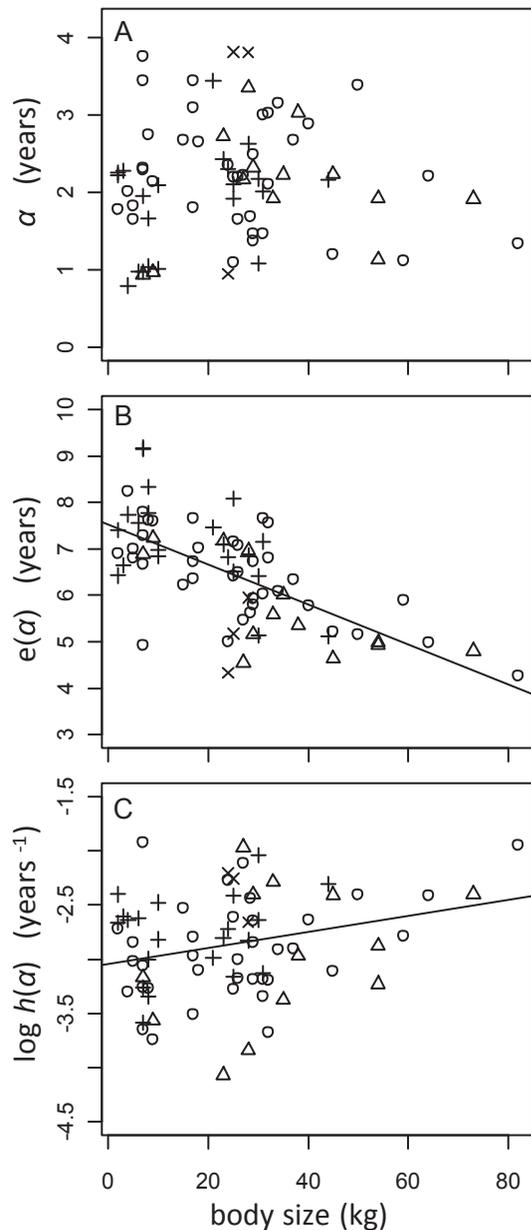


Figure 2: Body size shows no significant correlation with the onset of senescence α (A), it decreases with life expectancy at age α , $e(\alpha)$ (B), and it increases with the baseline hazard $h(\alpha)$ (C). The different symbols denote the best-fitting model for each breed (circles: G-G+, triangles: G-W+, plus: G-hG+, cross: G-hW+).

Discussion

Large dogs die young because they age quickly. Across breeds, body size is strongly positively linked to the absolute speed at which the mortality hazard increases. This

relationship was still evident when looking at the aging rate relative to the current level of the mortality hazard (proportional scale); that is, large dogs age at an accelerated pace, suggesting that their adult life unwinds in fast motion. Additionally, size was connected to the baseline hazard, which was higher in large dogs compared to small ones. We found no clear relationship between the age at the onset of senescence and size.

Growing Large and Growing Old

The breed-specific hazard trajectories we fitted follow the familiar bathtub-shaped hazard curve and clearly captured the size–life span trade-off documented in earlier studies that used age at death data directly (Patronek et al. 1997; Michell 1999; Greer et al. 2007). Body size explained 44% of the variance among breeds in life expectancy at age α and 47% at age 4 years. Among breeds, an increase of 2 kg in body mass leads to a loss of approximately 1 month of life expectancy. As expected, our estimates based on data from veterinary teaching hospitals were somewhat lower than those based on more representative pet populations (Michell 1999; Proschowsky et al. 2003; Greer et al. 2007). Our results suggest that in dogs, this trade-off is mainly driven by the effect of size on aging rate rather than on baseline mortality. The baseline hazard and the absolute aging rate each explained about 50% of the variation in life expectancy across breeds. Half (25%) of the explanatory power of aging rate, but only 5% of that of the baseline hazard, can be replaced by size as a predictor (table 3). Depending on age, size explained 38%–49% of the variation in absolute aging rates.

We see clear differences in the mortality trajectory between short- and long-lived dogs. Our challenge now is to determine how these mortality trajectories are shaped by the underlying diseases that dogs die of. Smaller, longer-lived dogs show a comparatively slow increase after age α , suggesting that the onset of age-related diseases is delayed in these breeds. Another possible explanation is that small and large dogs do not die of the same causes. Fleming et al. (2011) showed that deaths due to neoplastic processes tend to be more common in large dogs than in their smaller counterparts. This could be due to the fact that selection for large size in these breeds leads to greater cell division. Interestingly, compared to other causes of death by pathophysiological processes, neoplasia shows a steep increase in frequency with age (Fleming et al. 2011), which could contribute to the observed high aging rate in large dogs. Additionally, cause-specific hazard curves for breeds of different sizes could shed further light on this phenomenon.

In addition to large breeds being less likely than small breeds to show a constant hazard component, large

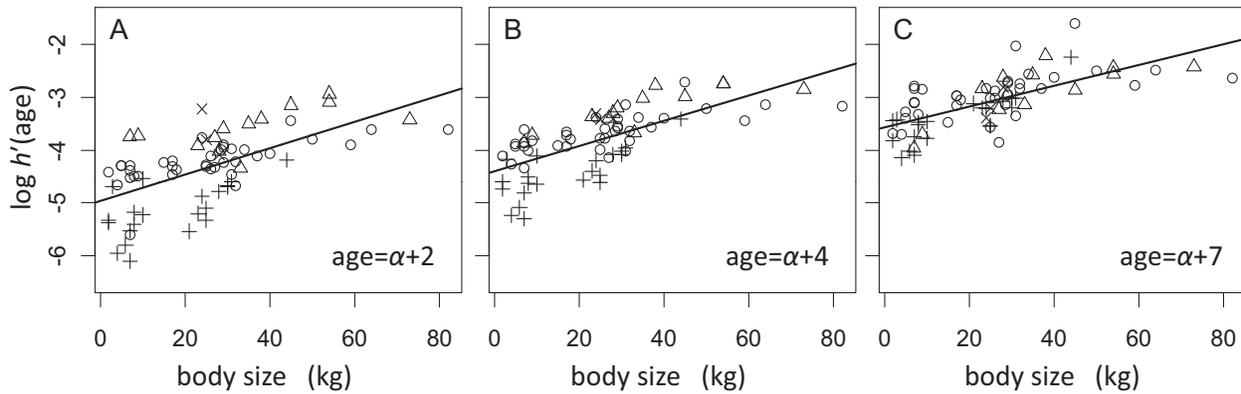


Figure 3: The absolute rate of aging increases with body size when measured as the first derivative of the hazard function (h'). Depicted are h' at the relative age of (A) $\alpha + 2$, (B) $\alpha + 4$, and (C) $\alpha + 7$ years. The different symbols denote the best-fitting model for each breed (circles: G-G+, triangles: G-W+, plus: G-hG+, cross: G-hW+).

breeds were more likely than small ones to age according to the Weibull model. Again, one possible explanation is that the different distributions of causes of death in small and large dogs described by Fleming et al. (2011) add up to hazard profiles of different shape. Another speculative idea is that populations of large breeds are more heterogeneous compared to smaller ones. Whereas in the Gompertz function the mortality increase always accelerates ($f''(t) = f(a, b)e^{bt}$), the Weibull function can accommodate accelerating as well as decelerating mortality hazards ($f''(t) = f(\beta, \lambda)t^{(\beta-3)}$). Indeed, most of the Weibull-fitted breeds had an estimated $\beta_3 < 3$, leading to a slowing down in the hazard increase with age. As Vaupel and Yashin (1985) showed, population stratification with regard to frailty can strongly affect the overall mortality patterns. With frailer subpopulations being selected out, the mortality hazard becomes increasingly dominated by more robust individuals. As a consequence, the hazard increase can slow down or even reach the much-debated mortality plateau (Vaupel and Yashin 1985; Pletcher and Curtsinger 1998; Drapeau et al. 2000). Some have suggested that rapid growth may lead to a “jerry-built” body, due, for example, to a higher probability of developmental errors (Blanckenhorn 2000; Metcalfe and Monaghan 2003). This, in turn, could lead to a larger variance in quality. Even if large bodies expire on average more quickly, there will be some with few errors, reaching a life span comparable to their small counterparts. In a cohort study on exceptionally old rottweilers ($\beta_3 = 2.2$), Cooley et al. (2003) showed that the majority of the oldest old dogs had a late onset of all major diseases, suggesting a robust physiology. Another case in point is the only two small breeds whose death data were best fit with a Weibull model, the chondrodystrophic dachshund and miniature dachshund. Their long backs render them es-

pecially prone to degenerative disc disease, which usually has an age of onset between 3 and 7 years of age (~15% of all deaths; Proschowsky et al. 2003; Fleming et al. 2011). Otherwise, dachshunds are known to be rather robust and long-lived dogs (e.g., Michell 1999; Proschowsky et al. 2003; Bonnett et al. 2005). It is intuitive that with individuals of the high-risk subpopulation dying off more quickly, aging will decelerate.

The Baseline Hazard

Compared to the effect of size on aging rate, its effect on the baseline hazard was small ($R^2 = 0.07$). Translating the baseline hazard into annual mortality probabilities (assuming a constant hazard) reveals that an increase in size from 10 to 25 kg increases mortality probability from 0.050 to 0.056, and a further increase to 50 kg leads to a slight increase in mortality probability to 0.066. Orthopedic diseases such as hip dysplasia are a frequent cause of death at young adult ages in dogs and are much more prevalent in large dogs (e.g., Proschowsky et al. 2003; Bonnett et al. 2005; Fleming et al. 2011). They are also thought to be negatively influenced by fast growth (Dammrich 1991). Hence they might contribute to the size effect on early adult mortality, as well as to age-related mortality, because they are usually degenerative. Recently, van der Most et al. (2011) reported compromised immune function in poultry strains selected for fast growth, which might render them more susceptible to infectious disease throughout life. However, there is currently no evidence for a size effect on either infectious or inflammatory disease in dogs (Fleming et al. 2011). The variability in the estimates of the baseline hazard among breeds is high. In part this is due to the inevitably smaller number of deaths available for estimation at this point of the hazard trajectory. More-

over, due to founder effects and breeding practices (e.g., popular sire effects) influencing effective population size, inbreeding levels differ substantially among breeds (Parker et al. 2004), and these could be linked to different levels of vulnerability independent of size. Breed idiosyncrasies certainly add to the high variance among breeds (e.g., Sutter and Ostrander 2004; Fleming et al. 2011).

The Onset of Senescence

Veterinarians recommend starting geriatric checkups for small dogs around age 11, for medium-sized ones at age 9–10, and for large dogs at age 7–8, indicating that age-related diseases appear later in small dogs. Still, we could not identify a clear correlation between the onset of senescence and body size, even though the low α values of the few giant dog breeds included in the analysis are suggestive. Across mammals and birds, the age of onset and the rate of senescence are both tightly linked to generation time and, hence, should be correlated (Promislow 1991; Jones et al. 2008; Peron et al. 2010).

One interesting explanation for why we did not find the expected effect of size on the onset of senescence could be that two opposing processes are at play. On the one hand, deleterious effects of growth might shift α toward earlier ages in large dogs. On the other hand, larger dogs might undergo a longer mortality decline as a result of a longer developmental period. We know that size and age at maturity (first heat in female dogs) are positively correlated; however, the relationship is not as strong as the one between size and life span ($R^2 = 0.16$; C. Kraus, un-

Table 3: Linear regression estimates and statistics showing that the size affects life expectancy mainly via aging rate

Model	β	SE(β)	R^2	$F_{1,72/71}$	P
$e(\alpha) \sim \log(h(\alpha))$	-1.630	.120	.481	66.59	$\ll .001$
$e(\alpha) \sim \log(H(\alpha+4))$	-1.367	.157	.514	76.23	$\ll .001$
$e(\alpha) \sim \log(h(\alpha)) + \log(H(\alpha+4))$	-1.563	.058	.956	715.7	$\ll .001$
$e(\alpha) \sim \text{size} + \log(H(\alpha+4))$	-1.316	.047		770.4	$\ll .001$
$e(\alpha) \sim \text{size} + \log(h(\alpha))$	-.020	.007	.564	8.09	.006
$e(\alpha) \sim \text{size} + \log(H(\alpha+4))$	-.949	.209		20.57	$\ll .001$
$e(\alpha) \sim \text{size} + \log(h(\alpha))$	-.033	.004	.725	63.35	$\ll .001$
$e(\alpha) \sim \text{size} + \log(H(\alpha+4))$	-1.308	.152		74.42	$\ll .001$
$e(\alpha) \sim \text{size} + \log(h(\alpha)) + \log(H(\alpha+4))$	-.0001	.002		.003	.960
$e(\alpha) \sim \text{size} + \log(H(\alpha+4))$	-1.563	.062	.956	626.24	$\ll .001$
$e(\alpha) \sim \text{size} + \log(h(\alpha)) + \log(H(\alpha+4))$	-1.313	.068		368.4	$\ll .001$

Note: The parameter notation is explained in table 1.

published data), consistent with the notion that large dogs have been selected artificially for fast growth. The less interesting explanation is that the lack of a relationship between α and size is simply due to sample size and data quality problems. It turns out to be extremely challenging to distinguish a delay in the onset of aging (a rightward shift in the Gompertz curve) from a downward shift in the mortality trajectory, because of a constant proportional decline at all ages (Promislow et al. 1999). The flat profile of the hazard trajectory at young adult ages especially in small dogs also renders it more difficult to estimate the exact age of onset of senescence. Higher-resolution age data from a more representative population are clearly needed.

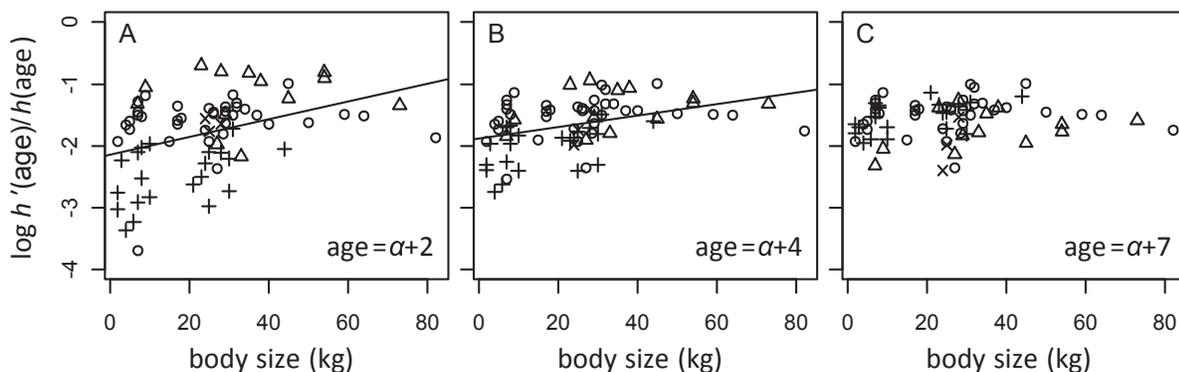


Figure 4: Relative rate of aging increases with body size when measured as the first derivative of the hazard function (h') divided by the hazard at the same age. The effect declines with age. Depicted are h'/h at the relative age of (A) $\alpha + 2$, (B) $\alpha + 4$, and (C) $\alpha + 7$ years. The different symbols denote the best-fitting model for each breed (circles: G-G+, triangles: G-W+, plus: G-hG+, cross: G-hW+).

Potential Proximate Factors

Theoretical and empirical aging research supports the idea that development and aging are intricately connected (e.g., Cichon 1997; Desai and Hales 1997; Morgan et al. 2000; Finch and Crimmins 2004; Kirkwood 2005; Ricklefs 2006; Chen et al. 2007; Kaplan and Robson 2009; Austad 2010), but the exact nature of these links is not yet fully understood. Potential candidates involved in mediating a trade-off between growth and senescence rate include IGF-1, telomere dynamics, and oxidative stress (Metcalf and Monaghan 2003; Bonsall 2006). The growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis might be a pivotal pathway mediating the trade-off between growth and survival, with a dampening of IGF-1 signaling generally delaying or slowing down aging and thus extending life span in a wide range of organisms (Tatar et al. 2003; Kenyon 2005; Berryman et al. 2008). Not many genetic changes are necessary to reduce the size of a dog (Boyko et al. 2010), and indeed, according to Sutter et al. (2007), a single *IGF1* allele is an important determinant of body size in dogs. Consistently, IGF-1 serum levels of small dogs are lower than those of large ones (Eigenmann et al. 1988; Sutter et al. 2007; Greer et al. 2011). Additionally, Favier et al. (2001) report excessive juvenile secretion of GH in a giant breed (Great Dane) compared to a medium-sized breed (beagle), leading to a prolonged phase of rapid growth in young large-breed dogs. This circumstantial evidence renders it plausible that the GH/IGF-1 axis contributes to the life span/aging benefits of small size in dogs. There is not much yet known about telomere dynamics or oxidative stress in dogs (but see Nasir et al. 2001; Speakman et al. 2003; Davis and Kipling 2005). Still, all of the three (and additional) potential mechanisms might interact and together shape the observed trade-off between size/aging and life span.

Outlook

Despite some problems inherent in the data set used and the large residual variance in mortality components among breeds, the size signal in patterns of aging was strong. These results point to the clear need for a long-term, longitudinal study of growth and mortality in a large cohort of companion dogs tracked from birth to death. More exact death data representative of the general dog population would help to remove the bias in our hazard and life expectancy estimates. This would allow us to also investigate the relationship between size and mortality within breeds (see also Galis et al. 2007) as well as direct effects of growth on mortality, by including the early decline in mortality, a stage that often encompasses a large fraction of deaths and yet has rarely been studied (Levitis 2011).

In this study, we had to use size as a proxy for growth, but size is the outcome of a process involving many factors such as neonatal weight and the speed and duration of growth (Metcalf and Monaghan 2003). In large dogs, especially growth rate, but also the duration of body growth, is increased (Kirkwood 1985). It is well known that large dogs take longer to reach physical and behavioral maturity, and dogs reaching a similar adult size might differ in growth patterns. Given the apparent importance of growth patterns in the evolution of life-history strategies (e.g., Charnov and Berrigan 1991; Charnov 1993), dogs seem an excellent model to investigate evolutionary, genetic, and physiological links between growth and mortality and in great detail.

Acknowledgments

We thank the Veterinary Medical Database (VMDB) for making available their data, and we are grateful to S. Austad, who assisted with procurement of the data from the VMDB. We would also like to thank J. Gampe, A. Scheuerlein, and J. Vaupel for stimulating discussions. We are grateful to P. Kappeler, T. Kirkwood, S. Verhulst, Franz J. Weissing, and an anonymous reviewer for helpful comments on the manuscript. C.K. would like to thank her dogs Flaca and Chacka for thought-provoking walks. This work was supported in part by a Breakthroughs in Gerontology grant to D.E.L.P. from the American Federation of Aging Research.

Literature Cited

- Anisimov, V. N., K. G. Arbeev, I. G. Popovic, M. A. Zabezhinski, S. V. Rosenfeld, T. S. Piskunova, L. S. Arbeeve, A. V. Semenchenko, and A. I. Yashin. 2004. Body weight is not always a good predictor of longevity in mice. *Experimental Gerontology* 39:305–319.
- Austad, S. N. 2005. Diverse aging rates in metazoans: targets for functional genomics. *Mechanisms of Ageing and Development* 126:43–49.
- . 2010. Animal size, metabolic rate, and survival, among and within species. Pp. 27–41 in N. S. Wolf, ed. *The comparative biology of aging*. Springer, Dordrecht.
- Bartke, A., K. Coshigano, J. Kopchick, V. Chandrashekar, J. Mattison, B. Kinney, and S. Hauck. 2001a. Genes that prolong life: relationships of growth hormone and growth to aging and life span. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 56:B340–B349.
- Bartke, A., J. C. Wright, J. A. Mattison, D. K. Ingram, R. A. Miller, and G. S. Roth. 2001b. Longevity: extending the lifespan of long-lived mice. *Nature* 414:412.
- Berryman, D. E., J. S. Christiansen, G. Johannsson, M. O. Thorner, and J. J. Kopchick. 2008. Role of the GH/IGF-1 axis in lifespan and healthspan: lessons from animal models. *Growth Hormone and IGF Research* 18:455–471.

- Blanckenhorn, W. U. 2000. The evolution of body size: what keeps organisms small? *Quarterly Review of Biology* 75:385–407.
- Bonnett, B. N., A. Egenvall, A. Hedhammar, and P. Olson. 2005. Mortality in over 350,000 insured Swedish dogs from 1995–2000. I. Breed-, gender-, age- and cause-specific rates. *Acta Veterinaria Scandinavica* 46:105–120.
- Bonsall, M. B. 2006. Longevity and ageing: appraising the evolutionary consequences of growing old. *Philosophical Transactions of the Royal Society B: Biological Sciences* 361:119–135.
- Boyko, A. R., P. Quignon, L. Li, J. J. Schoenebeck, J. D. Degenhardt, K. E. Lohmueller, K. Y. Zhao, et al. 2010. A simple genetic architecture underlies morphological variation in dogs. *PLoS Biology* 8:e1000451.
- Burnham, K. P., and D. R. Anderson. 2002. *Model selection and multimodel inference: a practical information-theoretic approach*. Springer, New York.
- Charnov, E. L. 1993. *Life history invariants*. Oxford University Press, New York.
- Charnov, E. L., and D. Berrigan. 1991. Dimensionless numbers and the assembly rules for life histories. *Philosophical Transactions of the Royal Society B: Biological Sciences* 332:41–48.
- Chen, D., K. Z. Pan, J. E. Palter, and P. Kapahi. 2007. Longevity determined by developmental arrest genes in *Caenorhabditis elegans*. *Aging Cell* 6:525–533.
- Cichon, M. 1997. Evolution of longevity through optimal resource allocation. *Proceedings of the Royal Society B: Biological Sciences* 264:1383–1388.
- Cooley, D. M., D. L. Schlittler, L. T. Glickman, M. Hayek, and D. J. Waters. 2003. Exceptional longevity in pet dogs is accompanied by cancer resistance and delayed onset of major diseases. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 58:1078–1084.
- Dammrich, K. 1991. Relationship between nutrition and bone-growth in large and giant dogs. *Journal of Nutrition* 121:S114–S121.
- Davis, T., and D. Kipling. 2005. Telomeres and telomerase biology in vertebrates: progress towards a non-human model for replicative senescence and ageing. *Biogerontology* 6:371–385.
- de Magalhaes, J. P., J. Costa, and G. M. Church. 2007. An analysis of the relationship between metabolism, developmental schedules, and longevity using phylogenetic independent contrasts. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 62:149–160.
- Desai, M., and C. N. Hales. 1997. Role of fetal and infant growth in programming metabolism in later life. *Biological Reviews of the Cambridge Philosophical Society* 72:329–348.
- Drapeau, M. D., E. K. Gass, M. D. Simison, L. D. Mueller, and M. R. Rose. 2000. Testing the heterogeneity theory of late-life mortality plateaus by using cohorts of *Drosophila melanogaster*. *Experimental Gerontology* 35:71–84.
- Eigenmann, J. E., A. Amador, and D. F. Patterson. 1988. Insulin-like growth factor-1 levels in proportionate dogs, chondrodystrophic dogs and giant dogs. *Acta Endocrinologica* 118:105–108.
- Favier, R. P., J. A. Mol, H. S. Kooistra, and A. Rijnberk. 2001. Large body size in the dog is associated with transient GH excess at a young age. *Journal of Endocrinology* 170:479–484.
- Finch, C. E., and E. M. Crimmins. 2004. Inflammatory exposure and historical changes in human life-spans. *Science* 305:1736–1739.
- Fleming, J. M., K. E. Creevy, and D. E. L. Promislow. 2011. Mortality in North American dogs from 1984 to 2004: an investigation into age-, size-, and breed-related causes of death. *Journal of Veterinary Internal Medicine* 25:187–198.
- Gaillard J.-M., M. Festa-Bianchet, D. Delorme, and J. Jorgenson. 2000. Body mass and individual fitness in female ungulates: bigger is not always better. *Proceedings of the Royal Society B: Biological Sciences* 267:471–477.
- Gaillard, J.-M., D. Pontier, D. Allainé, J. D. Lebreton, J. Trouvilliez, and J. Clobert. 1989. An analysis of demographic tactics in birds and mammals. *Oikos* 56:59–76.
- Galis, F., I. Van Der Sluijs, T. J. M. Van Dooren, J. A. J. Metz, and M. Nussbaumer. 2007. Do large dogs die young? *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution* 308B:119–126.
- Gompertz, B. 1825. On the nature of the function expressive of the law of human mortality, and on the mode of determining the value of life contingencies. *Philosophical Transactions of the Royal Society* 115:513–585.
- Greer, K., L. Hughes, and M. Masternak. 2011. Connecting serum IGF-1, body size, and age in the domestic dog. *Age* 33:475–483.
- Greer, K. A., S. C. Canterbury, and K. E. Murphy. 2007. Statistical analysis regarding the effects of height and weight on life span of the domestic dog. *Research in Veterinary Science* 82:208–214.
- Harvey, P. H., and M. D. Pagel. 1991. *The comparative method in evolutionary biology*. Oxford University Press, Oxford.
- Hawthorne, A. J., D. Booles, P. A. Nugent, G. Gettinby, and J. Wilkinson. 2004. Body-weight changes during growth in puppies of different breeds. *Journal of Nutrition* 134:2027S–2030S.
- Jones, O. R., J. M. Gaillard, S. Tuljapurkar, J. S. Alho, K. B. Armitage, P. H. Becker, and P. Bize, et al. 2008. Senescence rates are determined by ranking on the fast-slow life-history continuum. *Ecology Letters* 11:664–673.
- Juckett, D. A., and B. Rosenberg. 1993. Comparison of the Gompertz and Weibull functions as descriptors for human mortality distributions and their intersections. *Mechanisms of Ageing and Development* 69:1–31.
- Kang, H. M., N. A. Zaitlen, C. M. Wade, A. Kirby, D. Heckerman, M. J. Daly, and E. Eskin. 2008. Efficient control of population structure in model organism association mapping. *Genetics* 178:1709–1723.
- Kaplan, H. S., and A. J. Robson. 2009. We age because we grow. *Proceedings of the Royal Society B: Biological Sciences* 276:1837–1844.
- Kenyon, C. 2005. The plasticity of aging: insights from long-lived mutants. *Cell* 120:449–460.
- Khazaeli, A. A., W. J. Van Voorhies, and W. Curtsinger. 2005. The relationship between life span and adult body size is highly strain-specific in *Drosophila melanogaster*. *Experimental Gerontology* 40:377–385.
- Kirkwood, J. K. 1985. The influence of size on the biology of the dog. *Journal of Small Animal Practice* 26:97–110.
- Kirkwood, T. B. L. 2005. Understanding the odd science of aging. *Cell* 120:437–447.
- Klein, J. P., and M. L. Moeschberger. 2005. *Survival analysis: techniques for censored and truncated data*. Springer, Berlin.
- Levitits, D. A. 2011. Before senescence: the evolutionary demography of ontogenesis. *Proceedings of the Royal Society B: Biological Sciences* 278:801–809.
- Li, Y., B. Deeb, W. Pendergrass, and N. Wolf. 1996. Cellular proliferative capacity and life span in small and large dogs. *Journals of*

- Gerontology Series A: Biological Sciences and Medical Sciences 51: B403–B408.
- Lindblad-Toh, K., C. M. Wade, T. S. Mikkelsen, E. K. Karlsson, D. B. Jaffe, M. Kamal, M. Clamp, et al. 2005. Genome sequence, comparative analysis and haplotype structure of the domestic dog. *Nature* 438:803–819.
- Metcalfe, N. B., and P. Monaghan. 2003. Growth versus lifespan: perspectives from evolutionary ecology. *Experimental Gerontology* 38:935–940.
- Michell, A. R. 1999. Longevity of British breeds of dog and its relationships with sex, size, cardiovascular variables and disease. *Veterinary Record* 145:625–629.
- Miller, R. A., C. Chrisp, and W. Atchley. 2000. Differential longevity in mouse stocks selected for early life growth trajectory. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 55:B455–B461.
- Miller, R. A., J. M. Harper, A. Galecki, and D. T. Burke. 2002. Big mice die young: early life body weight predicts longevity in genetically heterogeneous mice. *Aging Cell* 1:22–29.
- Monaghan, P., A. Charmanier, D. H. Nussey, and R. E. Ricklefs. 2008. The evolutionary ecology of senescence. *Functional Ecology* 22:371–378.
- Moody, J. A., L. A. Clark, and K. E. Murphy. 2006. Canine history and breed clubs. Pages 1–18 *in* E. A. Ostrander and F. Galibert, eds. *The dog and its genome*. CSHL, New York.
- Moorad, J. A., D. E. L. Promislow, N. Flesness, and R. A. Miller. 2012. A comparative assessment of univariate longevity measures using zoological animal records. *Aging Cell* 11:940–948, doi: 10.1111/j.1474-9726.2012.00861.x.
- Morgan, I. J., I. D. McCarthy, and N. B. Metcalfe. 2000. Life-history strategies and protein metabolism in overwintering juvenile Atlantic salmon: growth is enhanced in early migrants through lower protein turnover. *Journal of Fish Biology* 56:637–647.
- Nasir, L., P. Devlin, T. McKevitt, G. Rutteman, and D. J. Argyle. 2001. Telomere lengths and telomerase activity in dog tissues: a potential model system to study human telomere and telomerase biology. *Neoplasia* 3:351–359.
- Nelder, J. A., and R. Mead. 1965. A simplex algorithm for function minimization. *Computer Journal* 7:308–313.
- Olsson, M., and R. Shine. 2002. Growth to death in lizards. *Evolution* 56:1867–1870.
- Parker, H. G., L. V. Kim, N. B. Sutter, S. Carlson, T. D. Lorentzen, T. B. Malek, G. S. Johnson, et al. 2004. Genetic structure of the purebred domestic dog. *Science* 304:1160–1164.
- Partridge, L., and N. H. Barton. 1996. On measuring the rate of ageing. *Proceedings of the Royal Society B: Biological Sciences* 263: 1365–1371.
- Patronek, G. J., D. J. Waters, and L. T. Glickman. 1997. Comparative longevity of pet dogs and humans: implications for gerontology research. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 52:B171–B178.
- Peron, G., O. Gimenez, A. Charmanier, J. M. Gaillard, and P. A. Crochet. 2010. Age at the onset of senescence in birds and mammals is predicted by early-life performance. *Proceedings of the Royal Society B: Biological Sciences* 277:2849–2856.
- Pletcher, S. D., and J. W. Curtsinger. 1998. Mortality plateaus and the evolution of senescence: why are old-age mortality rates so low? *Evolution* 52:454–464.
- Promislow, D. E. L. 1991. Senescence in natural populations of mammals: a comparative study. *Evolution* 45:1869–1887.
- Promislow, D. E. L., and P. H. Harvey. 1990. Living fast and dying young: a comparative analysis of life-history variation among mammals. *Journal of Zoology (London)* 220:417–437.
- Promislow, D. E. L., M. Tatar, S. Pletcher, and J. R. Carey. 1999. Below-threshold mortality: implications for studies in evolution, ecology and demography. *Journal of Evolutionary Biology* 12:314–328.
- Proschowsky, H. F., H. Rugbjerg, and A. K. Ersboll. 2003. Mortality of purebred and mixed-breed dogs in Denmark. *Preventive Veterinary Medicine* 58:63–74.
- R Development Core Team. 2011. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna.
- Reznick, D., L. Nunney, and A. Tessier. 2000. Big houses, big cars, superfleas and the costs of reproduction. *Trends in Ecology and Evolution* 15:421–425.
- Ricklefs, R. E. 2006. Embryo development and ageing in birds and mammals. *Proceedings of the Royal Society B: Biological Sciences* 273:2077–2082.
- Ricklefs, R. E., and A. Scheuerlein. 2001. Comparison of aging-related mortality among birds and mammals. *Experimental Gerontology* 36:845–857.
- . 2002. Biological implications of the Weibull and Gompertz models of aging. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 57:B69–B76.
- Rollo, C. D. 2002. Growth negatively impacts the life span of mammals. *Evolution and Development* 4:55–61.
- Samaras, T. J. 2009. Should we be concerned over increasing body height and weight? *Experimental Gerontology* 44:83–92.
- Sauer, J. R., and N. A. Slade. 1987. Uinta ground squirrel demography: is body mass a better categorical variable than age? *Ecology* 68:642–650.
- Siler, W. 1979. A competing-risk model for animal mortality. *Ecology* 60:750–757.
- Speakman, J. R., A. van Acker, and E. J. Harper. 2003. Age-related changes in the metabolism and body composition of three dog breeds and their relationship to life expectancy. *Aging Cell* 2:265–275.
- Sutter, N., D. Mosher, M. Gray, and E. Ostrander. 2008. Morphometrics within dog breeds are highly reproducible and dispute Rensch's rule. *Mammalian Genome* 19:713–723.
- Sutter, N. B., C. D. Bustamante, K. Chase, M. M. Gray, K. Y. Zhao, L. Zhu, B. Padhukasahasram, et al. 2007. A single IGF1 allele is a major determinant of small size in dogs. *Science* 316:112–115.
- Sutter, N. B., and E. A. Ostrander. 2004. Dog star rising: the canine genetic system. *Nature Reviews Genetics* 5:900–910.
- Tatar, M., A. Bartke, and A. Antebi. 2003. The endocrine regulation of aging by insulin-like signals. *Science* 299:1346–1351.
- Teuschl, Y., C. Reim, and W. U. Blanckenhorn. 2006. Correlated response to artificial selection in growth, development, phenotypic plasticity and juvenile viability in yellow dung flies. *Journal of Evolutionary Biology* 20:87–103.
- Thatcher, A. R., V. Kannisto, and J. W. Vaupel. 1998. The force of mortality at ages 80 to 120. *Odense Monographs on Population Aging* 5. Odense University Press, Odense.
- van der Most, P. J., B. de Jong, H. K. Parmentier, and S. Verhulst. 2011. Trade-off between growth and immune function: a meta-analysis of selection experiments. *Functional Ecology* 25:74–80.
- Vaupel, J. W., and A. I. Yashin. 1985. Heterogeneity ruses: some

- surprising effects of selection on population dynamics. *American Statistician* 39:176–185.
- Weibull, W. 1951. A statistical distribution function of wide applicability. *Journal of Applied Mechanics* 18:293–297.
- Williams, P. D., T. Day, Q. Fletcher, and L. Rowe. 2006. The shaping of senescence in the wild. *Trends in Ecology and Evolution* 21: 458–463.
- Wilson, D. L. 1994. The analysis of survival (mortality) data: fitting Gompertz, Weibull, and logistic functions. *Mechanisms of Ageing and Development* 74:15–33.

Associate Editor: Franz J. Weissing
Editor: Mark A. McPeck



Large dogs die young because they age fast. Photograph by Thomas Köllner.