E-Article

Dog Life Spans and the Evolution of Aging

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Submitted July 20, 2022; Accepted November 15, 2022; Electronically published April 4, 2023
Online enhancements: supplemental PDF.

ABSTRACT: The basic tenets of the evolutionary theories of senescence are well supported. However, there has been little progress in determining the relative influences of mutation accumulation and life history optimization. The causes of the well-established inverse relationship between life span and body size across dog breeds are used here to test these two classes of theories. The life span–body size relationship is confirmed for the first time after controlling for breed phylogeny. The life span–body size relationship cannot be explained by evolutionary responses to differences in extrinsic mortality either of contemporary breeds or of breeds at their establishment. The development of breeds larger and smaller than ancestral gray wolves has occurred through changes in early growth rate. This may explain the increase in the minimum age-dependent mortality rate with breed body size and thus higher age-dependent mortality throughout adult life. The main cause of this mortality is cancer. These patterns are consistent with the optimization of life history as described by the disposable soma theory of the evolution of aging. The dog breed life span–body size relationship may be the result of the evolution of greater defense against cancer lagging behind the rapid increase in body size during recent breed establishment.

Keywords: domestic dog, *Canis familiaris*, aging, senescence, life span, cancer.

Introduction

The basic tenet of evolutionary theories of aging—that natural selection is weaker on mutations acting at older ages (Medawar 1952; Williams 1957; Hamilton 1966)—is well supported by comparative and experimental studies (Finch 1990; Rose 1991). However, little progress seems to have been made in testing the individual theories (Charlesworth 2000; Stearns 2011; Robins and Conneely 2014). This appears to be partly due to the fact that both deleterious mutation accumulation and life history optimization are expected to contribute to the evolution of aging (Partridge and Barton 1993) and partly because details of the mechanisms of life history evolution have generally not been used to test theory (Stearns 2011). Recent studies of genome-wide association, mutation accumulation, and gene expression have provided evidence for and against both classes of theory (e.g., Durham et al. 2014; Robins and Conneely 2014; Kaya et al. 2015; Robins et al. 2017; Rodríguez et al. 2017; Everman and Morgan 2018; Turan et al. 2019).

The two main theories based on genetic mechanisms are the mutation accumulation theory and the antagonistic pleiotropy theory (Medawar 1952; Williams 1957). The mutation accumulation theory posits that because selection weakens with age, deleterious mutations acting at late ages will tend to accumulate in germ lines through mutation-selection balance (Charlesworth 1994). The antagonistic pleiotropy theory, as originally conceived, posits that some mutations that are beneficial at early ages may be incidentally deleterious at late ages but will nevertheless be favored because selection is stronger at early ages. These were originally considered essentially the same theory since any mutation that has an age-specific deleterious effect is either neutral or beneficial at other ages and thus antagonistically pleiotropic (Hamilton 1966). As such, these theories predicted that the cause of aging is small-effect mutations at many diverse loci that differ between species and individuals (Medawar 1952; Williams 1957). This was the prevailing wisdom up until quite recently (Partridge and Barton 1993).

A more modern interpretation of the theories classifies explanations for the evolution of aging as maladaptive mutation accumulation or as a consequence of life history optimization (Partridge and Barton 1993). Optimization theories include the original antagonistic pleiotropy theory and the disposable soma theory. Under the disposable soma theory, aging evolves because an optimal life history typically requires the allocation of resources to growth and reproduction early in life, which trades off against the allocation of resources toward somatic maintenance (Kirkwood 1977; Kirkwood and Rose 1991). Hence, damage to macromolecules and tissues accumulates over the lifetime of the

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individual, causing the physiological deterioration with age we call aging. The antagonistic pleiotropy and disposable soma theories are generally considered different versions of the same optimization theory since the disposable soma theory is based on assumed pleiotropic effects of mutations that direct resources to growth and reproduction early in life, reducing late-life survival and fertility.

However, the recent discoveries of single mutations that extend life span by considerable amounts and are conserved across yeast, nematodes, fruit flies, and mice (Kenyon 2010) called into question the assumed mechanisms of the mutation accumulation and antagonistic pleiotropy theories (Partridge and Gems 2002; Partridge and Gems 2006). Indeed, the relevance of these mutations to the evolution of aging is still questioned (Reznick 2005; Flatt and Schmidt 2009; Flatt and Partridge 2018), although they are now usually seen as consistent with the general principle of the antagonistic pleiotropy theory (Austad and Hoffman 2018). These mutations occur at loci involved in nutrient-sensing endocrine signaling pathways, and low signaling levels in these pathways—either due to mutation or as a plastic response to stress—appear to shunt resources from growth and reproduction to somatic maintenance, in accordance with the disposable soma theory. This molecular genetic basis of aging helps explain the plasticity of senescence, a topic that had previously received little attention (Partridge and Gems 2006; Flatt et al. 2013; da Silva 2019). Reduced signaling in the insulin/insulin-like growth factor 1 (IGF-1) signaling (IIS) pathway reduces growth rate and body size and increases life span in mice (Bartke 2021). The apparent primary causes of the increased life span are greater DNA repair and stress resistance and a reduced incidence of cancers, a leading cause of death in laboratory mice.

The development of domestic dog (*Canis familiaris*) breeds of different sizes provides an unintended test of the evolutionary theories of aging. It is well established that larger breeds have shorter life spans (Miller and Austad 2006). This inverse relationship between body size and life span also exists for other domesticated animals and for humans but is best documented in dogs. The apparent evolutionary response of life span to selection on body size in dogs is seen as a paradox because across species of mammals and other vertebrates, larger species typically live longer (Austad 2010). Here, published data pertaining to the causes of the life span–body size relationship in dogs are analyzed to test the evolutionary theories of aging. The life span–body size relationship is confirmed for the first time while controlling for breed phylogeny. The decrease in life span with breed size is associated with (1) an increase in the minimum age-dependent mortality rate, (2) an increase in growth rate, and (3) an increase in the risk of dying from cancer. It appears that indirect selection for a higher growth rate in larger breeds has resulted in reduced somatic maintenance, leading to lower life-long robustness and a higher risk of cancer. These hypothesized causal connections are supported by evidence linking greater signaling in the IIS pathway to larger size, increased tumor formation, and a shorter life span in dogs. These results are consistent with the life history optimization theories of the evolution of aging and, in particular, the life history trade-offs specified by the disposable soma theory. The life span–body size relationship of dogs may be the result of the evolution of greater defense against cancer lagging behind the rapid increase in body size during recent breed establishment.

Methods

Life History Data

Adult body weights are midpoints of breed standards from the American Kennel Club (American Kennel Club 2020). Breed median life spans are based on ages of death for 169 breeds (Adams et al. 2010). Breed mean litter sizes are from Borge et al. (2011). Early growth rate was calculated using the time to reach 50% of breed adult body weight (Hawthorne et al. 2004; Posada et al. 2014) and breed mean birth weights (Fan et al. 2016). Frequencies of causes of death are from Fleming et al. (2011), who tabulated these data from the Veterinarian Medical Database for breeds with 100 or more reported deaths.

Phylogenetic Comparative Analyses

Phylogenetic comparative analyses were based on a recently published phylogram of 164 dog breeds plus the gray wolf (*Canis lupus*) and the golden jackal (*Canis aureus*), inferred from whole genome single-nucleotide polymorphism data (Parker et al. 2017; fig. 1). The effect of phylogeny on statistical relationships was controlled using phylogenetic generalized least squares regression (Pagel 1999), as implemented by the R package caper (Orme et al. 2018; R Development Core Team 2022). As part of a separate analysis, rates of evolution for terminal branches leading to extant breeds were estimated from the ages of the internal nodes of these branches. Node ages were calculated by subtracting the year of the node from 2017, the year in which the phylogeny was published. Node years from various sources (table S1) were available for 34 breeds for which body weights were also available (fig. 1).

Life Table Analyses

Mortality rate components were estimated from published life tables compiled for weight classes of insured dogs in Japan (Inoue et al. 2015): toy (<5 kg), small (5–10 kg),

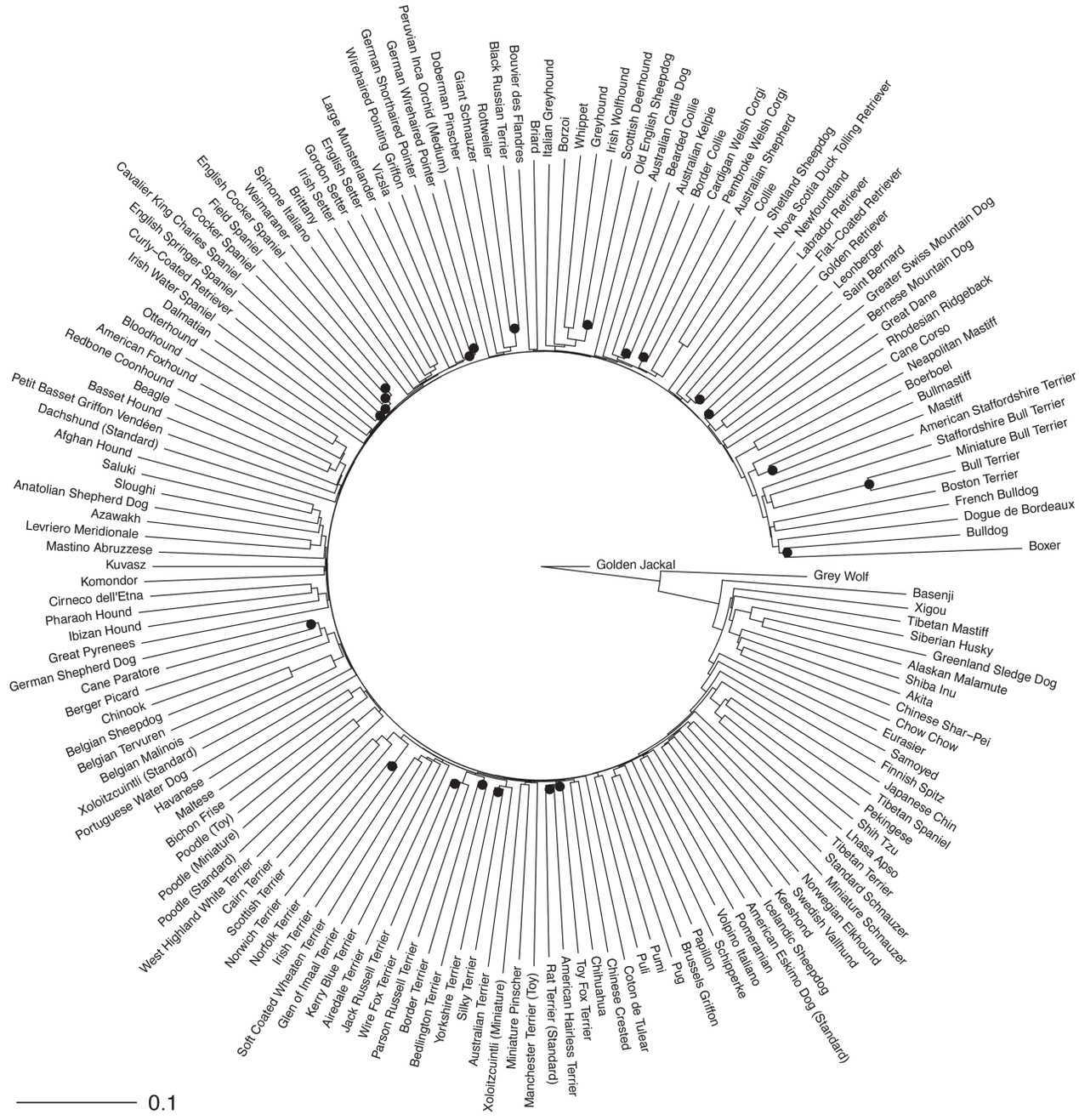

Figure 1: Phylogram of 164 dog breeds modified from Parker et al. (2017) to show a single branch for each breed. Circles indicate nodes for which dates are available. Branch lengths are in units of substitutions per site.

medium (10–20 kg), large (20–40 kg), and giant (40–80 kg). These data are at a higher adult age resolution (at increments of 1 year) than data used in previous analyses (Kraus et al. 2013; Yordy et al. 2019) and therefore are expected to provide more accurate estimates of model parameters. Rates of age-dependent and age-independent mortality were estimated by fitting a model of the instantaneous mortality rate as a function of age to life table data. The model used is the Gompertz-Makeham: $\mu_x = ae^{bx} + c$, where x is age, a is the minimum age-dependent mortality rate, b is the exponential increase in the age-dependent mortality rate, and c is the age-independent mortality rate. The Gompertz

model fits parameters a and b only and has previously been used to study the components of the mortality rate of dog breeds (Kraus et al. 2013; Yordy et al. 2019). The Gompertz-Makeham model additionally accounts for age-independent mortality and is used here because it increases the explanatory power of the model and reduces biases in estimating the age-dependent parameters (Golubev 2004; Pietrzak et al. 2015). The age-independent mortality rate is generally thought to capture extrinsic mortality that is not age dependent. Instantaneous mortality rates were estimated by fitting the model to observed values, Y_x, by optimizing the error-minimizing function $L = (1 - \mu_x/Y_x)^2$ using the R package MortalityLaws.

Data and code have been deposited in the Dryad Digital Repository (https://doi.org/10.5061/dryad.wwpzgmsn6; da Silva and Cross 2023).

Results

The Life Span–Body Size Relationship

The negative relationship between life span and breed size and the positive relationship between litter size and breed size (Miller and Austad 2006) are confirmed after controlling for phylogeny with phylogenetic generalized least squares regression. Regressing median life span (from breeds with sample size $n \geq 50$ individuals) on adult body weight gives a strong negative linear relationship (fig. 2*A*; $\lambda = 0.55$, $\delta = 0.54$, $\kappa = 0.53$; $r^2 = 0.4260$, $F_{1,67} = 49.73$, $P = 1.224 \times 10^{-9}$): increasing body weight by 10 kg decreases median life span by 0.88 years on average. And regressing $\log_{10}$-transformed litter size (from breeds with $n \geq 20$) on $\log_{10}$-transformed body weight gives a strong positive linear relationship ($\lambda = 1.00, \delta = 0.99, \kappa = 0.66$; $r^2 = 0.6952$, $F_{1,72} = 164.2$, $P < 2.2 \times 10^{-16}$). Litter size increases as a power function of body weight with allometric exponent $b = 0.3224$ (fig. 2*B*).

Phylogenetic signal in the residuals of the regression for life span, indicated by $\lambda > 0$ and δ and $\kappa < 1$, is consistent with life span changing rapidly at first and then remaining stable, as might occur during an adaptive radiation (Pagel 1999). Although a bifurcating tree is an imperfect representation of the evolutionary history of breeds, which have often been crossed (vonHoldt et al. 2010; Parker et al. 2017), the phylogeny nevertheless captures a substantial amount of the shared history of breeds and the tempo of their evolution.

Body Size and Evolutionary Rate

It has been suggested that the breed life span–body size relationship is due to very recent strong selection for larger size in the largest breeds, resulting in growth abnormalities

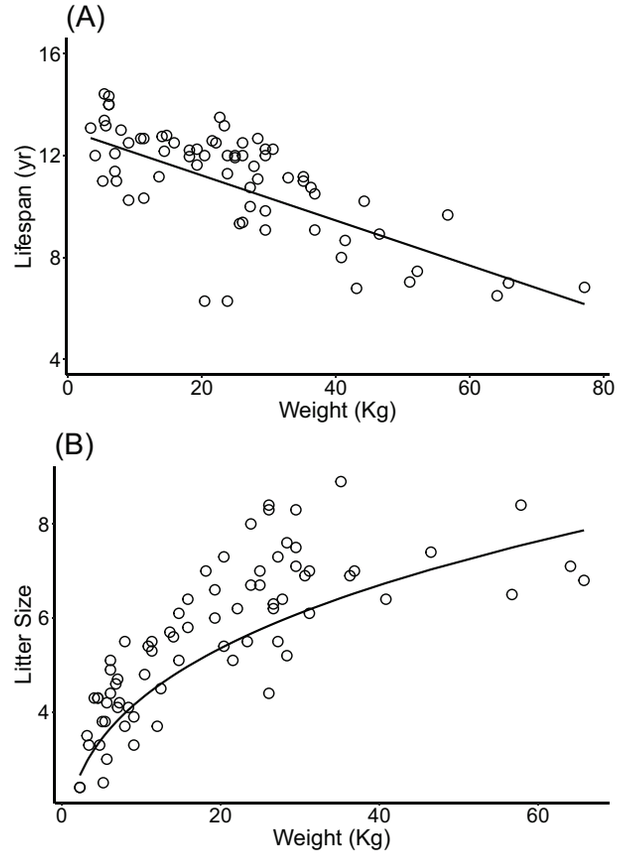

Figure 2: Phylogenetic generalized least squares regressions of breed median life span on adult weight, $y = 12.99–0.08842x$ (*A*), and breed litter size on adult weight, $y = 2.0399x^{0.3224}$ (*B*).

(Galis et al. 2007). This may be tested by estimating rates of evolution for terminal branches of the phylogeny, leading to individual extant breeds. These rates were calculated from the ages of internal nodes of terminal branches of the phylogeny (fig. 1). All the nodes for which data were available date to the nineteenth and twentieth centuries and therefore involve modern breeds. Body weights for these breeds range from 2.4 to 77.1 kg, spanning all breed size categories (toy to giant). The mean (±SE) rate of evolution for the terminal branches for these breeds is 0.0015 ± 0.0001 substitutions per site per year. By comparison, the terminal branch leading to the gray wolf, assuming a node of age 25,000 years for the shared ancestor of wolves and dogs (Freedman and Wayne 2017), represents a rate of evolution of 4.9×10^{-6} substitutions per site per year, nearly three orders of magnitude lower. This comparison supports the view that modern dog breeds have experienced intense selective breeding. However, rates of evolution are not higher for larger breeds; there is no relationship between evolutionary rate and body weight ($\lambda = 1.0$, $\delta = 0.78$,

$\kappa = 0$; $r^2 = 0.01766$, $F_{1,32} = 0.5752$, $P = .4538$), and small breeds have the highest rates estimated (fig. 3). Therefore, there is no evidence that the breed life span–body size relationship is caused primarily by recent strong selection for extremely large body size alone.

Body Size and Extrinsic Mortality

The standard explanation for small species evolving shorter life spans than large species is that smaller species have higher extrinsic mortality rates due to higher rates of predation or other hazards unrelated to senescence, which cause the strength of natural selection to decline more sharply with age, resulting in a higher rate of senescence (Williams 1957; Partridge and Barton 1993). This explanation is plausible if population size is regulated by changes in density-dependent juvenile recruitment (Abrams 1993; Williams et al. 2003, 2006). An explanation for the breed life span–body size relationship that has not previously been proposed to our knowledge is that large breeds had higher extrinsic mortalities than small breeds at their establishment because large dogs were bred for high-risk activities, such as hunting large and dangerous prey, guarding herd animals and property, or serving as weapons of war (Moody et al. 2006; De Vito et al. 2009). In contrast, small breeds were bred mainly to hunt small, less dangerous prey or as companion animals. This hypothesis, however, may be dismissed by comparison to the gray wolf. Dogs were domesticated from Eurasian gray wolves about 25,000 years ago (Freedman and Wayne 2017). Gray wolves weigh on average 39 kg (Nowak and Walker 1991) and have a median life span of 11 years in captivity (Che-Castaldo et al. 2019). For a body weight of 39 kg, a dog breed is expected to have a median life span of 9.5 years (fig. 2*A*) on average under present conditions. However, the largest dog breeds, weighing more than 50 kg, may have median life spans of only 7 years under present conditions (e.g., Irish wolfhound, mastiff, Great Dane, Saint Bernard). Since it would be difficult to argue that large dog breeds had higher extrinsic mortality rates than wild wolves, even at their establishment, the short life spans of the largest breeds should be due to their size rather than to high extrinsic mortality.

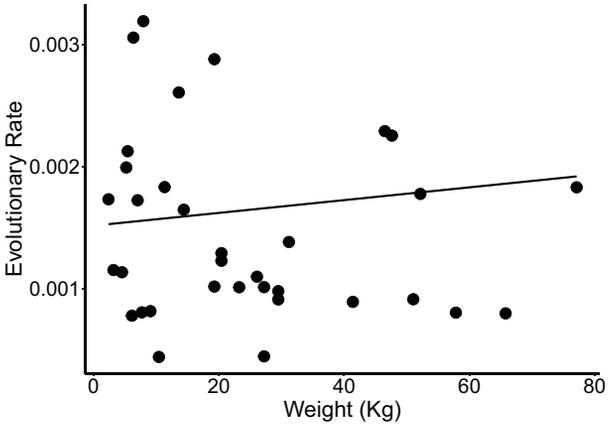

Figure 3: Phylogenetic generalized least squares regression of terminal branch evolutionary rate (substitutions/site/year) on breed adult weight: $y = 1.52 \times 10^{-3} + 5.22 \times 10^{-6}x$.

Body Size and Mortality Rate

The components of mortality rate responsible for the shorter life spans of larger breeds were investigated by estimating the parameters of the Gompertz-Makeham model of the instantaneous mortality rate as a function of age: $\mu_x = ae^{bx} + c$. The parameters were estimated from published life tables compiled for weight classes of insured dogs in Japan (Inoue et al. 2015): toy (<5 kg), small (5–10 kg), medium (10–20 kg), large (20–40 kg), and giant (40–80 kg). As shown in previous analyses (Kraus et al. 2013; Yordy et al. 2019), the probability of dying in an age interval is high at birth and declines to a minimum before increasing until the end of life. In the present data, the minimum was invariably at age 2 years, by which time all breeds have reached adult body size. Therefore, the model was fitted to the data from age 2 onward (fig. 4). Interestingly, large and giant breeds are estimated to have age-independent mortality $c \approx 0$, whereas smaller breeds have age-independent mortality $c > 0$, supporting the argument made above that large breeds do not have short life spans because of high extrinsic mortality. With this model, weight class differences in the rate of mortality due to senescence may be caused by the minimum age-dependent mortality rate (a), the rate of increase of mortality (b), or both (fig. 5). Regressing a on the upper weight limit of each weight class (the toy weight class does not have a defined lower limit, and therefore midpoint weights could not be used) shows a strong positive relationship (fig. 6*A*; $r^2 = 0.9878$, $F_{1,3} = 243.7$, $P = .0006$). However, regressing b on the upper weight limit gives a nonsignificant negative relationship (fig. 6*B*; $r^2 = 0.7422$, $F_{1,3} = 8.637$, $P = .06$). Therefore, the shorter life spans of larger dog breeds are caused by a higher minimum age-dependent mortality rate, starting at age 2, rather than a higher rate of increase of mortality. In other words, larger breeds have consistently higher mortality rates throughout adulthood but do not appear to age faster.

Body Size, Growth Rate, and Reproduction

To determine the tempo of the investment in growth, early postnatal growth rate was calculated as the amount of growth from birth to 50% of adult body weight, divided

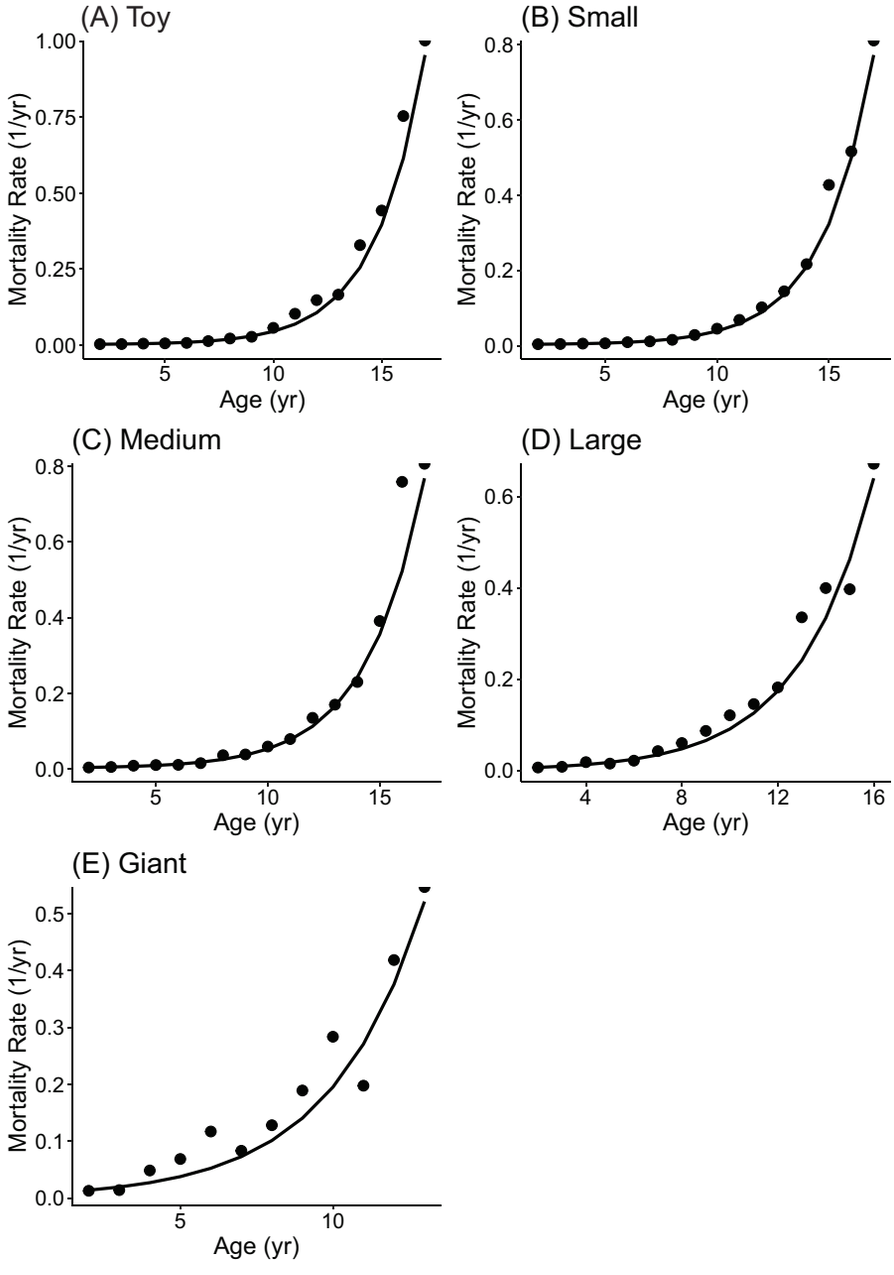

Figure 4: Gompertz-Makeham model fitted (line) to age-specific mortality rates (μ_x) for breed weight classes. *A*, Toy breeds: $\mu_x = 0.0008e^{0.4412x} + 0.0017$. *B*, Small breeds: $\mu_x = 0.0007e^{0.4381x} + 0.0031$. *C*, Medium breeds: $\mu_x = 0.0015e^{0.3868x} + 0.0027$. *D*, Large breeds: $\mu_x = 0.0049e^{0.3255x} + 0$. *E*, Giant breeds: $\mu_x = 0.0102e^{0.3275x} + 0$.

by the time to reach 50% of adult body weight. Regressing growth rate on adult body weight gives a very strong positive linear relationship (fig. 7*A*; $\lambda = 0.65$, $\delta = 3.00$, $\kappa = 3.00$; $r^2 = 0.9664$, $F_{1,10} = 287.3$, $P = 1.074 \times 10^{-8}$): adult body weight explains 97% of the variance in early growth rate, and increasing adult body weight by 10 kg increases early growth rate by 0.22 kg/week on average. Large breeds not only grow for longer (Jimenez 2016) but also grow at higher rates than small breeds.

Breed reproductive investment was defined as litter weight (litter size × birth weight). Regressing $\log_{10}$-transformed litter weight on $\log_{10}$-transformed adult body weight gives a very strong positive linear relationship ($\lambda = 0.59, \delta = 3.00, \kappa = 2.79$; $r^2 = 0.9151, F_{1,39} = 420.4, P <$

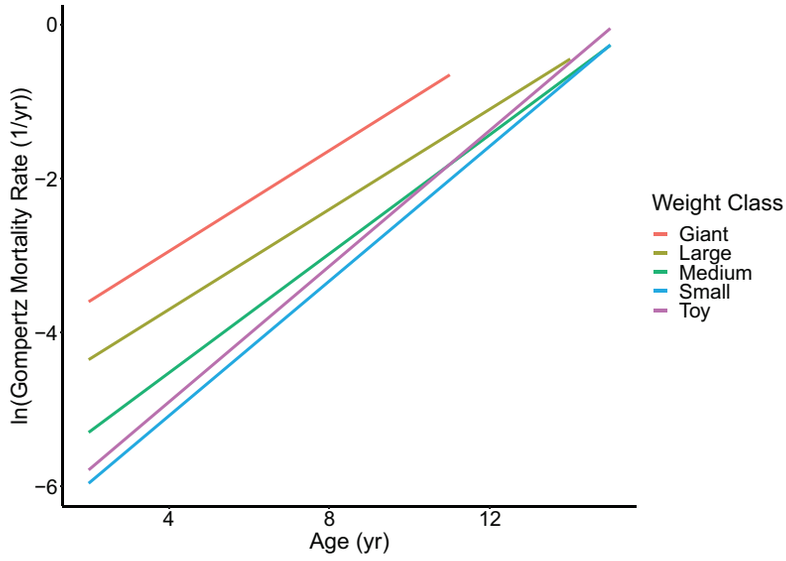

Figure 5: Natural logarithm of estimated Gompertz mortality rate, consisting of age-dependent components of mortality ($\ln a + bx$) calculated by subtracting age-independent parameter (c) from estimated Gompertz-Makeham mortality rate. For each line (weight class), the intercept is ln$a$ and the slope is b.

2.2×10^{-16}): adult body weight explains 92% of the variance in litter weight. The relationship is a power function with allometric exponent $b = 3/4$, showing that reproductive investment as a proportion of adult size decreases with adult size (fig. 7*B*).

Body Size and Causes of Mortality

Causes of the increase in mortality rate with breed body size were investigated. Fleming et al. (2011) grouped causes of death into 10 categories: congenital, degenerative, infectious, inflammatory, metabolic, neoplastic, toxic, traumatic, vascular, and unclassified. Several of these are extrinsic causes and either appear to affect all ages equally (toxic) or affect young individuals predominantly (traumatic and infectious). Regressing the arcsine square root–transformed probability of death from toxic causes on breed body weight shows a weak negative relationship (fig. 8*A*; $\lambda = 0$, $\delta = 1.41$, $\kappa = 3.00$; $r^2 = 0.07167$, $F_{1,66} = 5.095$, $P = .0273$). This may simply reflect that a smaller amount of toxin is necessary to kill a smaller dog. Frequencies of death from traumatic and infectious causes are not related to breed weight (fig. 8*B*, 8*C*). Therefore, none of the extrinsic causes of death have a higher risk for larger breeds and thus cannot explain the evolution of the shorter life spans of larger breeds. The only cause of death that affects older individuals predominantly is neoplastic (Fleming et al. 2011). Regressing the arcsine square root–transformed probability of death from neoplastic causes on $\log_{10}$-transformed breed body weight gives a significant positive relationship (fig. 8*D*; $\lambda = 0$, $\delta = 1$, $\kappa = 1$; $r^2 = 0.3552$, $F_{1,66} = 36.35$, $P = 8.248 \times 10^{-8}$). Thus, the risk of dying from cancer increases with breed body weight.

Discussion

Large breeds have shorter life spans than small breeds even after controlling for their shared evolutionary history. Several explanations for this pattern that do not involve senescence have been proposed. One explanation is that selection for extremely large size has been exceptionally strong and recent, resulting in growth abnormalities (Galis et al. 2007). However, there is no evidence for stronger selection on larger breeds. On the other hand, the frequency of death associated with the musculoskeletal system peaks before the attainment of adult size by age 2 and increases with breed body weight (Fleming et al. 2011). However, the only cause of death that increases in frequency with breed body size is cancer, indicating that it is not growth abnormalities affecting the musculoskeletal system that are responsible for the shorter life spans of larger breeds. In addition, although large breeds tend to be more inbred than small breeds, the level of inbreeding does not explain life span differences among breeds after controlling for body size (Yordy et al. 2019). Finally, larger breeds are not more likely to die from extrinsic causes, consistent with no estimated age-independent mortality for large and giant breeds.

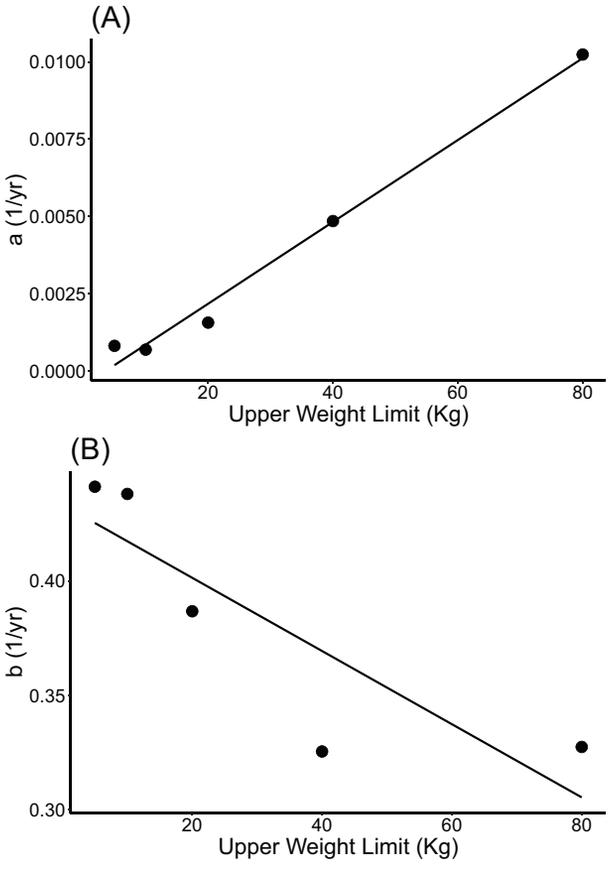

Figure 6: Simple linear regressions of mortality rate parameters on upper weight limits of breed weight classes. *A*, Minimum age-dependent mortality rate, *a*: $y = -4.669 \times 10^{-4} + 1.323 \times 10^{-4}x$. *B*, Exponential rate of increase of mortality rate, *b*: $y = 0.4334 - 0.0016x$.

The shorter life spans of larger breed size classes are due to higher minimum age-dependent mortality rates (*a*) rather than higher rates of increase of age-dependent mortality (*b*). Given the conclusion that extrinsic mortality is not higher for larger breeds, it appears that large breeds are less robust than small breeds and, as a result, experience higher mortality rates at all adult ages but do not age more quickly. This result is at odds with an earlier analysis that found that both the minimum age-dependent mortality rate and the rate of increase of mortality rate increase with breed body weight (Kraus et al. 2013). The cause of the discrepancy with the present study is not clear but may be an artifact of the previous study using life tables with age interval–censored data or not estimating age-independent mortality. Including the age-independent mortality parameter, *c*, with the Gompertz-Makeham model reduces bias in estimating the other model parameters and improves model fit (Golubev 2004; Pietrzak et al. 2015). A survey of mortality rate components estimated from life tables for wild-type and long-lived strains of laboratory mice also found that a decrease in the minimum age-dependent mortality rate rather than a change in the rate of increase of mortality explains the longevity of long-lived strains (Hughes and Hekimi 2016).

Both breed litter size and litter weight increase at a diminishing rate with breed size. Thus, larger breeds invest more in reproduction but at a diminishing rate relative to body size. In contrast, litter size increases with body size across small species of mammals but decreases with body size across large species of mammals (Tuomi 1980). Reproduction is generally expected to trade off against life span under the disposable soma theory, and sterilization increases life span in dogs (Michell 1999; Hoffman et al. 2013). However, the apparent reduced investment in reproduction relative to body size in larger breeds suggests

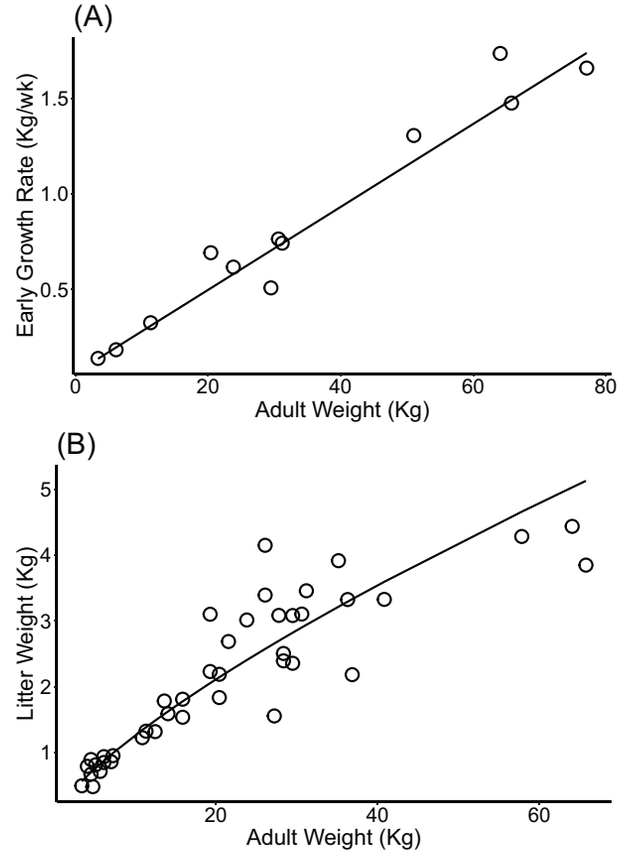

Figure 7: Phylogenetic generalized least squares regressions on adult weight. *A*, Early growth rate (to 50% of adult body weight; $y = 0.0641 + 0.0217x$). *B*, Litter weight ($y = 0.2267x^{0.7451}$).

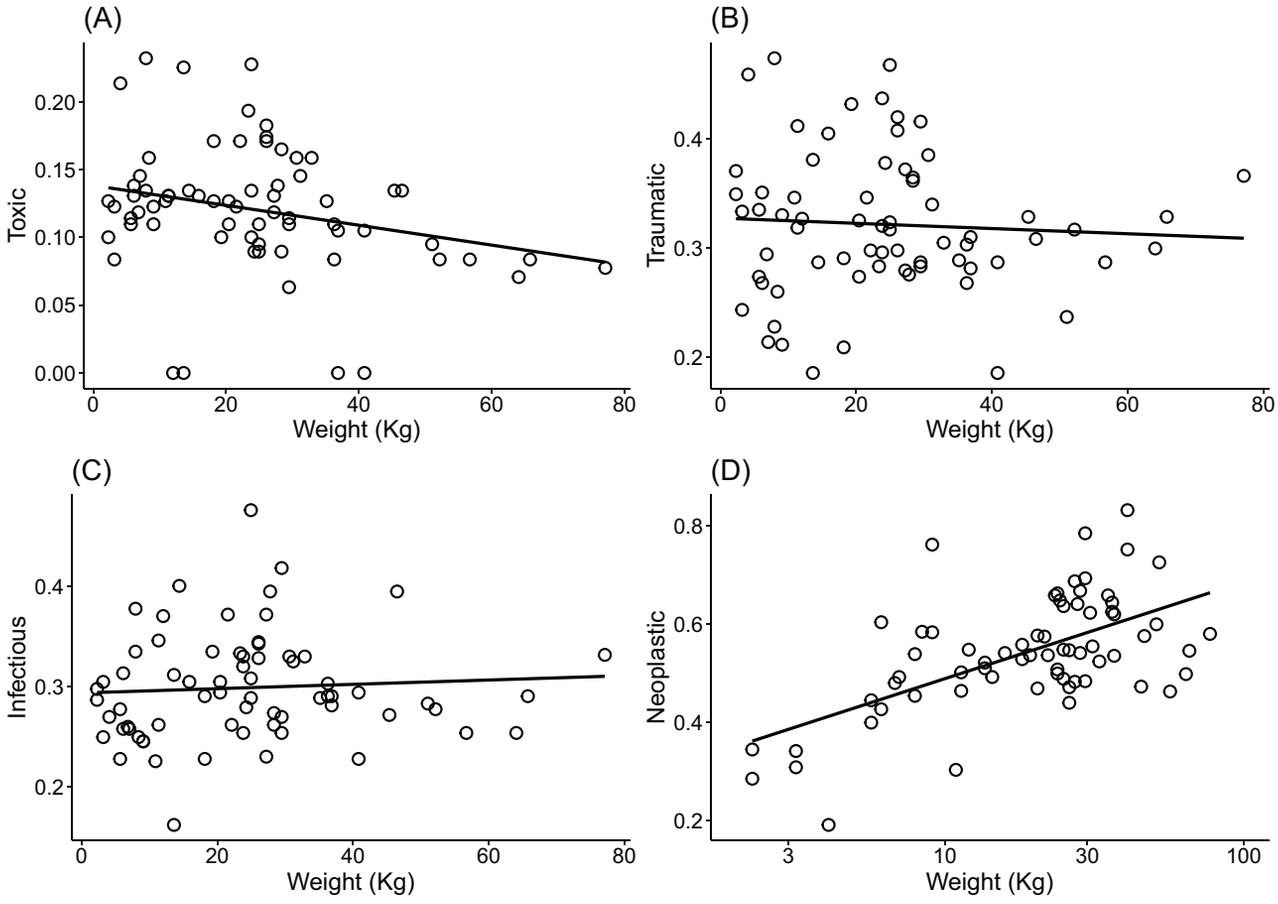

Figure 8: Phylogenetic generalized least squares regressions of breed arcsine square root–transformed probabilities of dying on breed adult weight. *A*, Toxic causes: $y = 0.1384 - 0.0007334x$. *B*, Traumatic causes: $y = 0.3272 - 0.0002388x$. *C*, Infectious causes: $y = 0.2936 + 0.0002157x$. *D*, Neoplastic causes: regressed on $\log_{10}$(weight): $y = 0.2914 + 0.1971x$.

that the allocation of resources to reproduction does not explain their lower life spans.

Larger breeds not only grow faster but also have more sustained postnatal growth (Jimenez 2016). Larger breeds exhibit higher signaling levels in the IIS pathway (Ostrander et al. 2017; Plassais et al. 2019, 2022), which appears to shunt resources from somatic maintenance to growth and reproduction in yeast, nematode worms, fruit flies, and mice (Kenyon 2010). This is one of the endocrine signaling pathways for which single-gene mutations that cause reduced signaling may result in large increases in life span in model organisms (Kenyon 2010). Interestingly, variants of genes in this pathway are associated with life span differences in dogs (Ostrander et al. 2017; Plassais et al. 2019). Postnatal growth rate is also negatively correlated with adult life span in mice selected for different rates of early growth (Miller et al. 2000). In mice, a causal connection has been made between lowered growth hormone levels and reduced signaling in the IIS pathway, which reduces growth rate and body size and increases life span (Bartke 2021). The apparent primary causes of the increase in life span are increased DNA repair and stress resistance and a reduced incidence of cancers, a leading cause of death in laboratory mice.

The probability of death due to cancer increases with age in dogs, and cancer is the only cause of death that increases with breed size. Cancers are typically late-onset diseases resulting from the accumulation of somatic mutations caused by cell division rather than the result of late-acting germ line mutations (Weinberg 2014). Therefore, neoplastic causes of death are expected to be more frequent when there is greater investment in growth (cell division) and less in somatic repair (e.g., DNA repair and immune surveillance of dysregulated cells). Consistent with this, the

largest breeds have greater cellular senescence, indicating a decreased capacity for somatic repair (Li et al. 1996). In addition, tumor formation is associated with the activation of the IIS pathway in humans and dogs (Khanna and Paoloni 2006), thus linking increased death from cancer to increased growth rate and body size in dogs.

The mutation accumulation theory would explain the shorter life spans of larger breeds as the result of greater senescence caused by the strength of selection declining more steeply because of higher rates of extrinsic mortality (Medawar 1952). The weaker selection at late ages would permit deleterious germ line mutations to reach higher equilibrium frequencies under mutation-selection balance or to have larger effects (Charlesworth 1994). Increased age-independent extrinsic mortality is expected to decrease the strength of selection and thus select for a higher rate of senescence if population size is regulated by changes in density-dependent juvenile recruitment (Abrams 1993; Williams et al. 2003, 2006). This likely occurs for dog breeds, where the availability of a breed is affected by production rather than culling adults. The lack of evidence of greater extrinsic mortality for larger breeds argues against this theory.

The optimization theories explain the shorter life spans of larger breeds as ultimately the result of higher mortality caused by selection for higher growth rates. This may be viewed as the result of antagonistically pleiotropic effects of mutations for greater growth. The disposable soma theory in particular would explain the shorter life spans of larger breeds as the result of greater mortality caused by selection for greater investment in growth and thus reduced investment in somatic maintenance. This explanation is consistent with mutations that increase growth through increased signaling in the IIS pathway, which in turn reduce resource allocation to somatic maintenance and increase the rate of tumor formation, explaining the higher probability of dying from cancer. The disposable soma theory may also explain why larger breeds have a higher minimum age-dependent mortality rate but not a higher rate of increase of mortality: the allocation of resources toward growth and away from somatic maintenance early in life may reduce physiological robustness throughout life. In contrast, the mutation accumulation theory would explain reduced life spans as the result of higher frequencies (or greater effects) of deleterious germ line mutations that affect late ages and thus would seemingly predict an increase in the rate of senescence.

Viewing the life span–body size relationship of dogs through the lens of the disposable soma theory helps us resolve the paradox of why it does not follow the life span–body size relationship across species. Peto's paradox is the observation that larger species—which are the result of more cell divisions and thus should be more susceptible to cancer—do not have higher cancer rates than smaller species (Nunney 2013; Vincze et al. 2022). The explanation for this pattern is that large species have adapted to the greater risk of cancer with greater investment in somatic maintenance, including defenses against cancer (Caulin and Maley 2011; Nunney and Thai 2020). For example, while humans have a single copy of the *TP53* tumor suppressor gene, elephants have 20 copies (Abegglen et al. 2015; Sulak et al. 2016). This is consistent with a fairly constant somatic mutation burden across mammal species, which exhibit a 40,000-fold range in body mass but only a 30-fold range in life span (Cagan et al. 2022). The apparent greater cancer defense in larger-bodied species could evolve if larger species have lower rates of extrinsic mortality and thus experience a lower rate of decline in the strength of selection with age, which in turn selects for a lower rate of senescence (Williams 1957; Partridge and Barton 1993). Larger dog breeds are the result of more cell divisions than smaller breeds, explaining their higher rates of mortality due to cancer. The same pattern holds for humans, with taller individuals more susceptible to cancer and living less long (He et al. 2014; Nunney 2018). Thus, the decline in life span with increasing breed size may represent an adaptive lag, with the evolution of greater defense against cancer lagging behind the rapid increase in body size during recent breed establishment. The higher rates of age-independent extrinsic mortality of smaller breed weight classes and the higher probability of death from toxicity of smaller breeds seem to support this view.

In conclusion, the causes of the shorter life spans of larger dog breeds allow us to test the two classes of evolutionary theories of senescence. The reduction in life span appears to be the result of recent indirect selection for higher growth rates reducing somatic maintenance and thus increasing susceptibility to cancer. This is consistent with the life history optimization theories, especially in the form of the disposable soma theory, but not with the mutation accumulation theory. Furthermore, the disposable soma theory can explain the shortening of life spans as the result of an increase in the minimum age-dependent mortality rate rather than an increase in the rate of senescence. That larger species generally live longer than smaller species and do not experience higher rates of cancer suggests that the dog life span–body size relationship is the result of an adaptive lag.

Acknowledgments

We acknowledge the support of the School of Biological Sciences, University of Adelaide, including a Summer Vacation Scholarship awarded to B.J.C. We also acknowledge the useful suggestions made by two anonymous referees.

Statement of Authorship

J.d.S. conceived the project, developed the methods, and wrote the manuscript. J.d.S. and B.J.C. collected, analyzed, and visualized the data.

Data and Code Availability

Data and code have been deposited in the Dryad Digital Repository (https://doi.org/10.5061/dryad.wwpzgmsn6; da Silva and Cross 2023).

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Associate Editor: Jeff Leips
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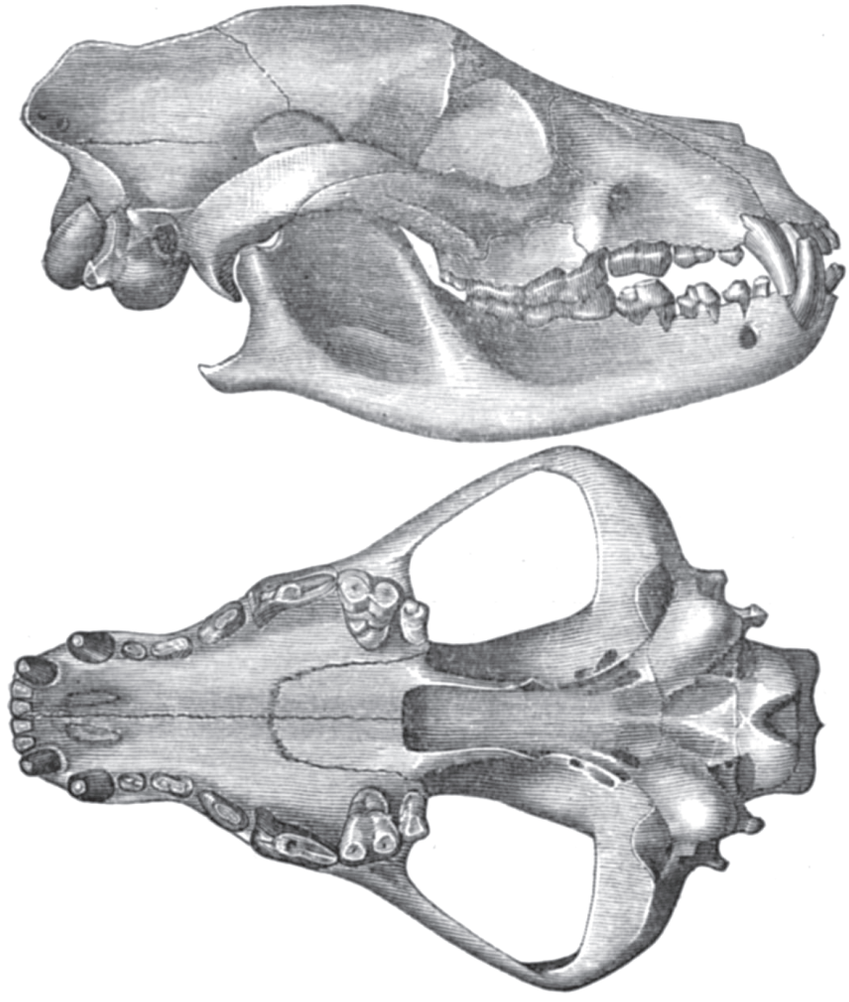

"The genus Ælurodon must be referred to the Canidæ, and distinguished from Canis proper, only by the presence of an anterior cutting lobe of the superior sectorial tooth, the character on which Dr. Leidy originally proposed it." Figured: "*Ælurodon sævus* Leidy. . . . From the Loup Fork beds of Nebraska." From "On the Extinct Dogs of North America" by E. D. Cope (*The American Naturalist*, 1883, 17:235–249).