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Ageing: It's a Dog's Life

The relationship between size and lifespan is complex. Larger species normally outlive smaller species, but within species smaller individuals generally outlive larger individuals. Research comparing size and mortality in dogs suggests that big dogs die young because they age faster.

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Explaining the staggering diversity in organismal lifespan and ageing patterns across species, populations and individuals is a challenge of ever-increasing importance in modern biology and biomedicine. By understanding the genetic, cellular and environmental forces responsible for this diversity, we may revolutionise our ability to understand and control the ageing process in our own species, as well as in livestock and companion animals. Evolutionary theory and mounting empirical data suggest that developmental trajectories and growth rates can shape the onset and rate of ageing in later life [1–3]. Large animal species tend to live longer than small species [3,4], although as with all apparently general rules in biology, there are important exceptions: for instance, birds live exceptionally long lives for their body size [2]. Paradoxically, within species the relationship between body size and lifespan shows the opposite trend to cross-species comparisons: larger individuals seem to live short lives. Lower than average body mass and relatively slow growth rate early in life are positively correlated with longevity within several vertebrate species ([5,6] but see also [7]). So how can we explain these complex and at times conflicting patterns?

The magnitude of the within-species variation in size and lifespan seen across dog breeds is particularly striking. Consequently, man's best friend is rapidly emerging as an important study species through which to understand the causes of

variation in the ageing process. Through concentrated selection pressure by humans for a range of phenotypic traits over the last few hundred years, over 400 breeds are now described. Dogs show huge variation in body size, with big breeds such as St Bernard being over two-orders of magnitude larger than breeds such as Pekinese [8,9]. Canine life expectancy is inversely correlated with body mass (Figure 1), with differences in lifespan across dog breeds also being dramatic; small breeds typically live much longer than large breeds [8,9]. While it is well established that big dogs die young, the reasons for this are unclear. Are big dogs simply more susceptible to injury or infection, are they inherently weaker in some way, do they start growing old earlier or simply grow old faster? There is evidence that small

and large dog breeds are differentially susceptible to certain diseases [8], with large dogs being more prone to musculoskeletal, gastrointestinal and neoplastic disorders, and small dogs to endocrine-related disease. Hormonal and genetic factors that have been found to modulate lifespan in model organisms [10] also vary significantly across big and small breeds [9,11].

A recent study by Kraus *et al.* [12] aimed to find out whether the rate of ageing is faster in larger dog breeds or whether they have higher mortality rates irrespective of age. This was done using mortality information, body mass and gender data from 74 dog breeds collected between 1984 and 2004 from North American veterinary teaching hospitals. The explicit, non-mutually exclusive hypotheses they tested were that larger dog breeds die earlier because a) there is an earlier onset of senescence, b) there is a higher minimum mortality hazard or c) there is a greater rate of aging (Figure 2). Body mass explained 44% of the variance in mortality risk amongst breeds at the onset of senescence, equating to a reduction in lifespan of one month for

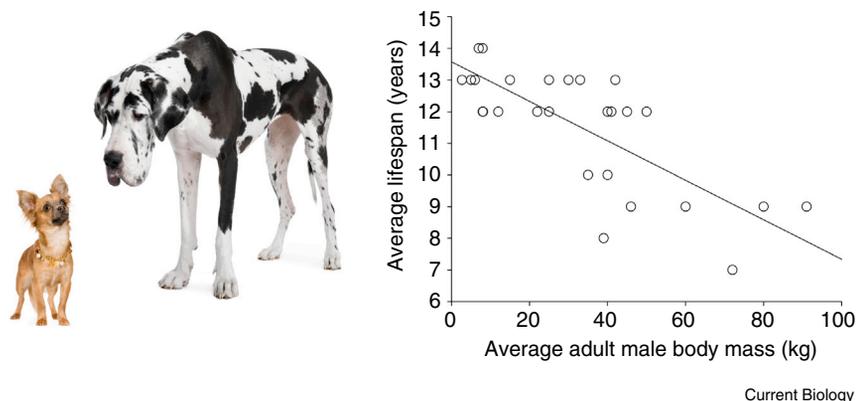
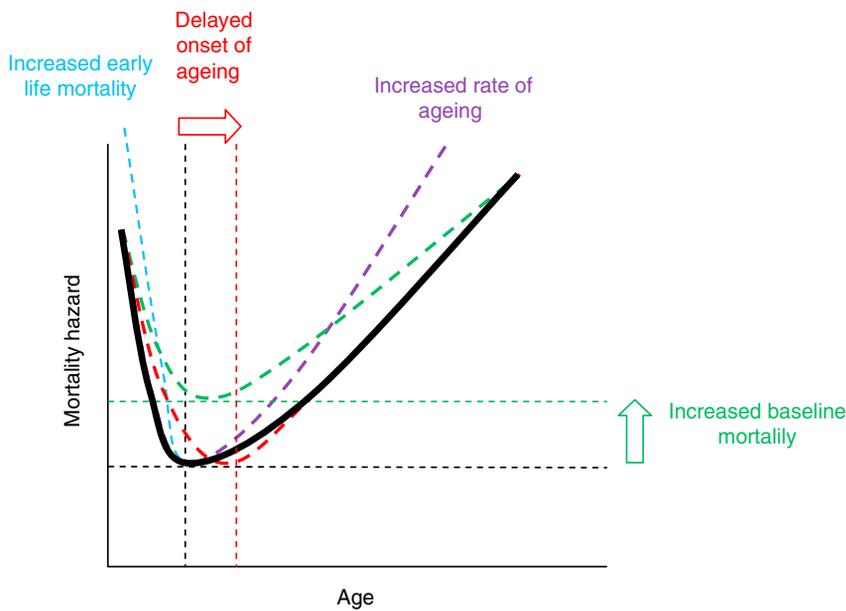


Figure 1. Body size and lifespan in dogs.

The relationship between body mass and lifespan across 32 different dog breeds. The diversity of size and lifespan among dog breeds is remarkable, but it is also well known that larger breeds tend to be short-lived relative to small breeds. (Photo credit: iStockphoto; the authors acknowledge Rob Docherty for collating the data used in this plot.)



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Figure 2. Mortality and lifespan.

Illustration of the different aspects of the mortality curve that might vary to drive differences in the longevity of different dog breeds. The heavy black curve represents the hazard trajectory for comparison, with coloured dashed lines reflecting the four different ways in which trajectories could vary.

every 2 kg increase in mass. Perhaps surprisingly, the age at which mortality started increasing (i.e., senescence mortality) did not differ significantly across small and large breeds. However, this onset in senescence did occur somewhat earlier in giant breeds (>50 kg), suggesting that these 'giants' might be physiologically frailer at an earlier age. A clear positive relationship between the absolute rate of aging and body mass was detected, with the mortality hazard increasing more rapidly in larger breeds following the onset of senescence. In a nutshell, the data show that big dog breeds die young because, once senescence begins, they age more rapidly than small breeds. It is important because it tells us that the selection for increased size has been accompanied by faster aging.

As the authors acknowledge, the data set they use is prone to a number of unavoidable biases. For example, information on age at death was restricted to rather uneven categories, resulting in the resolution of information worsening with age: the last two categories were simply 10–15 and greater than 15 years old. Mortality following accidents is also included, which may not be very

informative for a study of senescence, unless for some reason older dogs are more prone to accidents. Bigger breeds do show a slightly higher baseline mortality, perhaps suggestive of a greater risk of accidental death, although previous research reports that death from trauma does not appear to differ between large and small breeds [8]. The inherent nature of such data sets also leads to non-random selection of diseases, ages, breeds and owner behaviour. While the actual size of each breed population was unknown, it was assumed that both this and the age distribution remained constant throughout the 20 year study period. Consequently, the number of healthy dogs in each class was unknown, and the popularity of different breeds is known to wax and wane over time [13]. These assumptions do have the potential to influence the study's main conclusions, but the association between body size and the rate of aging observed here does seem to be strong. Replicate demographic studies using data drawn from different kinds of veterinary databases or other countries could help establish the generality and robustness of the findings.

Kraus *et al.* [12] fitted different mortality hazard models to the dog mortality data and consequently can only provide insights into demographic patterns in mortality across different breeds. The challenge now is to understand what biological mechanisms underlie the apparent differences among breeds in ageing rate. This, of course, will not be a trivial exercise but luckily potential clues may help focus research efforts. Work in model organisms has shown that aging is plastic and that alterations in components of various pathways, particularly those related to metabolism and growth, e.g. insulin/IGF-1 signalling, can modulate both lifespan and healthspan in a highly conservative manner [10]. It is interesting to note that small dogs actually possess a distinct polymorphism in the *Igf1* gene compared to large dogs [9], although whether this is a modulator of ageing or simply a by-product of selection for body size has yet to be established. Large dogs grow faster and for longer than small dogs and also have higher levels of IGF-1 [11], a powerful stimulator of bone and muscle growth. As with all things in life, too much of anything can be bad and elevated IGF-1 is associated with an increased risk of certain diseases, including cancer [14]. Interestingly, small dog breeds have longer telomeres on average, so this may also be part of the jigsaw [15].

Life-history theory suggests that resources are limited and consequently animals can maximise fitness only by trading metabolically costly activities (growth, reproduction, somatic maintenance) off against one another. While in certain ecological contexts a large body mass may be advantageous (increased fecundity, decreased predation risk), rapid growth particularly early in life can have negative fitness consequences later in life [1,16]. As Kraus *et al.* demonstrate in their analysis, being large if you are a dog carries a lifespan penalty. Consequently, it is worth speculating on what the possible mechanisms might be that mediate the lifespan cost. It is well established that rapid growth is correlated with increased oxidative damage, greater cellular senescence and telomere shortening [17–19], and rapid growth can also increase the risk of disease, including certain cancers

[20], later in life. Interestingly, the onset of senescence in giant dog breeds appeared to occur at a time at which these animals were still growing.

The paper by Kraus *et al.* [12] tells us why big dogs die young: a St Bernard ages more rapidly following the onset of senescence than a Pekinese does. We now need to focus in on potential mechanisms driving these differences. On a more cautionary note, dogs are rather peculiar given that they have been artificially selected for phenotypic diversity, in stark contrast to more routine model organisms primarily selected for similarity. However, there is no doubting that experimental approaches leading on from the work by Kraus *et al.* will complement those studying ageing using classical and non-classical model organisms in the laboratory, and under both semi-natural and natural conditions. We suggest that comparative approaches both across and within species are likely to give key insights into what mechanisms underlie the ageing process.

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Insect Biotechnology: Controllable Replacement of Disease Vectors

To fight human vector-borne diseases, first releases of sterile transgenic mosquitoes have been performed. Someday, disease-refractory mosquitoes will replace wild types to stop transmission. For such population replacements, gene drive mechanisms must be established that allow local confinement and reversibility.

Ernst A. Wimmer

The fight against Malaria and Dengue — the two major insect-borne diseases in tropical and subtropical areas — is threatened by the increasingly fast evolution of insecticide resistance in its insect vectors. Therefore, alternative control tools need to be included into pest management strategies [1]. Insect transgenesis promises to provide such

novel tools through the establishment of conditional reproductive sterility or the refractoriness to disease transmission [2,3]. In the transmission of vector-borne diseases, the insect is only a nuisance, but does not actually cause the illness itself. This has led to the long-standing hope that wild mosquito populations could actually be replaced by biotechnologically engineered strains that would be refractory to the disease causing

pathogens, such as protists or viruses [4,5], and therefore interrupt disease transmission [3]. As the simple replacement of a complete insect population by a desired strain is not feasible, strategies need to be developed that cause population replacement by changing the genetic make-up of the population through spreading the required refractoriness-causing transgenes. However, the transgenes providing refractoriness to human disease transmission are not likely to spread through the population by themselves. This requires effective gene drive mechanisms that allow for non-Mendelian inheritance and 'selfish genes' are thought to be some of the best vehicles for such a gene drive [6]. Conversely, there are concerns on how to contain such selfish genes and the accompanied