

Do Large Dogs Die Young?

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Interim Report

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DO LARGE DOGS DIE YOUNG?

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Abstract. -

In most animal taxa longevity increases with body size across species, as predicted by the oxidative stress theory of aging. Contrastingly, in within-species comparisons of mammals and especially domestic dogs (e.g. Patronek, '97; Michell, '99; Ekenvall et al., 2000; Speakman et al, 2003) longevity decreases with body size.

We explore two datasets for dogs and find support for a negative relationship between size and longevity if we consider variation across breeds. Within breeds, however, the relationship is not negative. The negative across-breed relationship is probably the consequence of short lifespans in large breeds. Artificial selection for extremely high growth rates in large breeds appears to have led to developmental diseases that seriously diminish longevity.

The commonly found positive interspecific relationship between size and longevity can be explained relatively well with the oxidative stress theory of aging (Harman, '56; Beckman and Ames, '98). This theory postulates that aging is linked with energy expenditure because of cellular damage induced by free radicals that are a by-product of oxidative metabolism. Speakman et al. (2002) have indeed found a negative interspecific relationship between energy use and longevity in mammals. Since small mammalian species in general have a higher mass-specific metabolic rate than large species, a positive interspecific relationship between size and longevity would be expected. Within species small adult individuals also have higher metabolic rates than large individuals (Burger and Johnson, '91; Speakman et al., 2003). This fact taken by itself leads to an expectation of a positive intraspecific relationship between size and longevity (Speakman et al., 2003).

Several other hypotheses have been proposed to explain why some species live longer than others, given their size and metabolic rate. The 'mutation accumulation' theory of Medawar ('52) proposes that populations that experience high mortality rates accumulate deleterious mutations that reduce fitness late in life, because purifying selection has little effect on late-acting mutations from the gene pool. The 'antagonistic pleiotropy' hypothesis of Williams ('57) proposes that high mortality rates will select for earlier maturity and a higher rate of investment in reproduction early in life, even if this incurs a cost later in life. The 'disposable soma' hypothesis of Kirkwood ('77) assumes that anti-aging mechanisms are costly and that, therefore, selection for anti-aging mechanisms will vary depending on the strength of extrinsic mortality. When extrinsic

mortality is high and animals invariably die young, anti-aging mechanisms such as lower free radical production and better avoidance and repair mechanisms will have little impact on life span and thus will not be favored. However, when extrinsic mortality is low, anti-aging mechanisms may have a substantial impact on lifespan and, therefore, a strong selective advantage. Although practical limitations often constrain the choice of species for comparative gerontological analyses (Rose, 1991; Speakman, 2002) considerable support for the latter hypothesis has now accumulated (Austad, '93; Ku et al., '93; Barja et al. '94; Cortopassi and Wang, '96; Ogburn et al., '98; Kapahi et al., '99; Ricklefs and Scheurlein, 2001, Blanco and Sherman, 2005). Recently it has been shown for guppies that the relationship between extrinsic mortality and longevity may be more complex, with strong predation leading to a high rate of aging late in life, but to a low rate of aging earlier on (Reznick et al., 2004). Yet another hypothesis does not concern extrinsic mortality rates but proposes that a high growth rate will shorten lifespans by increasing free-radical production (reviewed in Rollo, 2002). Growth rate indeed appears to be negatively associated with longevity (Ricklefs, '93; Olsson and Shine, 2002; Reznick et al., 2002; Rollo, 2002; Metcalfe and Monaghan, 2003, but see Anisimov 2004).

Several authors (Austad, 1997; Rollo, 2002; Speakman et al., 2003) have concluded that size and longevity may be negatively correlated within species of mammals. Support comes from rodents in which small size was induced by a calorie-restricted diet or by mutations resulting in a low growth rate (Rollo, 2002). In nature, however, a large size might also be the result of a protracted growth period rather than of a fast growth rate. Most other support comes from studies on dogs. In dogs, small

individuals have a much higher mass-specific metabolic rate than large ones (Burger and Johnson, '91; Speakman et al., 2003).). There is no indication that small dogs have been selected for anti-aging mechanisms that could explain their longer life spans. A negative intraspecific relationship, therefore, provides a challenge for the oxidative stress theory of aging (Speakman et al., 2003), unless high growth rates in large dogs would explain the shorter life spans (Rollo, 2002). It is not known however, to what extent the differences in lifespan between small and large dogs may be confounded by genetic differences between small and large breeds. Strong selection and inbreeding have led to genetic differences between breeds (e.g. Ubbink et al., '98). To evaluate the influence of the differences between breeds we have investigated the relationship between adult size and longevity across breeds and within breeds in two datasets. One dataset (Veterinary Medical DataBase, VMDB) recorded weight (in classes) as a size measure and the other (Natural History Museum Bern, NMBE) a precise length measure in the skull that is highly correlated with other skeletal length measurements (Lüps '74).

MATERIAL AND METHODS

Datasets

Data on size and longevity were obtained from the Veterinary Medical Database (VMDB) and the Natural History Museum Bern (NMBE). We used longevity and weight measurements from 44363 dogs from 134 breeds at the VMDB (longevity and weight (at death) measures in categories, longevity: 1-2yrs, 2-4, 4-7, 7-10, 10-15, 15+; weight: 0-0.5(kg), 0.5-2.3, 2.3-6.8, 6.8-13.6, 13.6-22.7, 22.7-34.0, 34.0-45.4, 45.4+). We analysed those by using midpoint values of each category, except for the uppermost categories,

where we used the lower bound of that category, because no upper limit was given. We only included breeds with individuals in at least three weight classes. The NMBE dataset consists of precise data on 859 dogs from 42 breeds. The length of the base of the brain stem (in mm.) was taken as a measure of size for the dogs in the NMBE collection. This measure correlates highly with the length of the vertebral column, femur, pelvis and skull in most breeds (Lüps '74). Breeds with a low correlation between the length of the base of the brain stem and other length measures were excluded from the dataset (Chihuahua, Greyhound, Bulldog, Boxer, Chow Chow, Bullterrier, Borzoi, French Bulldog, Akita, Pug, Dachshund, see Lüps, '74).

Age at death is recorded in months. Dogs that were known to have died in an accident, euthanized for behavioural problems or that were younger than one year old were not included in the dataset.

Statistical Analysis

The data were analysed using bivariate linear random effect models (Meyer, '85). For both datasets, the same procedure was followed. Per trait y and per sex, we estimated parameters of a model of the form $y_{ij} = \mu + z_i + e_j$ with μ the mean of that data subset, z a random effect specific to the i -th breed, and e the residual error within breeds (indexed by individuals j). Between sexes and for the same trait, the random breed effects were assumed to be the same. When we investigated whether that assumption was warranted using single-trait analysis, we found that sex-specific random effects were not significantly different between sexes.

In the bivariate analysis, we estimated a variance-covariance matrix of the breed effects for lifespan and size (weight or length), and a variance covariance matrix of the residual within-breed error terms. Estimation was performed using ASReml software for mixed linear models (Gilmour et al. 2002). Standard errors were calculated from the estimated Fisher information matrix. We tested for significant differences from zero for the variance components using *t*-tests (Table 1, Coltman et al., 2001). Two-sided *p*-values are reported. We also did likelihood ratio tests for significance of the covariances in the bivariate model, and conservative likelihood ratio tests for the breed variances in univariate models (Pinheiro and Bates, 2000), which are in agreement with the *t*-tests.

The VMDB dataset has a relatively low number of lifespan and weight classes as variables. Therefore the measurement error is large. In addition, both emaciated and obese dogs will influence the relationship. However, we believe that the very large size of the dataset makes the conclusions we draw reliable. We treated breed effects as independent and did not correct for phylogenetic correlations, because of the highly reticulate nature of the evolution of most dog breeds (see Discussion).

RELATIONSHIP BETWEEN SIZE AND LONGEVITY

We find negative correlations between lifespan and size for variation between breeds (see Fig. 1 and Table 1), but overall positive correlations within breeds (see Table 1, see also Fig. 2). In other words, females and males of larger and heavier breeds die younger, but within breeds larger and heavier individuals die older on average, with the proviso that the correlations are only significant for the large VMDB dataset and that the correlations

within breeds are much lower than between breeds. Figure 1 suggests that, in the NMBE dataset, size might have a non-linear relationship with lifespan, since very small dogs seem to have reduced lifespan too. However, the same breeds are represented in the VMDB dataset and no reduced lifespan is visible for very small dogs in this dataset.

DISCUSSION

No negative relationship within breeds. We found a slightly positive relationship within breeds between size and longevity in our datasets (see Table 1), but the relationship is only significant in the larger dataset (VMDB). Similarly, the negative association across breeds is only significant in the larger dataset (negative trend for the NMBE). The discrepancy between the two datasets is most probably due to the difference in sample size (Fig. 2). The estimated correlation coefficients have similar values. Within breeds large dogs do not die younger than small ones, contrary to the assumption in the literature. Other data on within-breed and within-strain comparisons show no significant relationship (Patronek '97; Speakman 2002). However, Miller et al. (2002) found a negative relationship between size and longevity in a population of lab mice. This population, though, was composed of four different inbred mouse strains and the results may, therefore, have been confounded by genetic differences between strains (see also Anisimov et al. 2004 and Khazaeli et al. 2005 on the importance of differences between strains).

Phylogenetic angle. We did not correct our results for phylogenetic correlations, because the most complete and recent phylogenetic analysis does not reveal significant genetic differences between 78 of 85 breeds (Parker et al. 2004). This is presumably

because the bifurcating tree model of the analysis is not a good approximation for the intensely reticulate nature of the evolution of most dog breeds (Parker et al. 2004, Bannasch 2005, see also Vilà et al. 2005). A particularly striking example is provided by the Irish Wolfhound which is supposedly a mix of Glengarry Deerhounds, Borzois, Great Danes, Tibetan Mastiffs and perhaps also of original Irish Wolfhounds and some other breeds. Freckleton et al. (2002) conclude that the contribution of the phylogenetic signal tends to be small in such circumstances and may even be misleading. Finally, a check on separate Pearson correlation coefficients within individual breeds confirms our conclusion that within breeds larger dogs do not die younger than smaller dogs, because there was not a single significantly negative relationship between size and longevity in either of the two datasets. For most breeds there was no significant relationship and in both datasets there were significantly more positive correlation coefficients than negative ones, reflecting the slightly positive trend of our analysis (Fig. 2).

Why do dogs from large breeds die young? Dogs from large breeds usually die around the age of six years, which is young for dogs in general (and for wolves, Mech '70, MacDonald '84). This early mortality cannot be explained by oxidative damage due to size-related energy expenditure because dogs from large breeds have a lower mass-specific metabolic rate than dogs from small breeds (Burger and Johnson, '91; Speakman et al., 2003). In addition, there is no indication that breeds were selected for anti-aging mechanisms that could explain differences in mortality between breeds. Rollo (2002) has suggested that the elevated mortality of large individuals might be caused by high growth rates, which would induce high rates of oxidative damage during early life. Indeed, growth rates in large breeds during the first year are very high. Great Danes increase in

weight 100-fold from birth in the first year, compared to 60-fold in wolves in captivity, 20-fold in poodles and 3-fold in humans (Mech '70; Hawthorne et al. 2004). The proposal that a high free radical production is involved in the early mortality is in agreement with extremely high rates of bone cancer in large breeds, 60 to 100-fold that of smaller breeds (Tjalma, '66; Withrow et al., '91). In addition, the high plasma levels of the growth promoting insulin-like growth factor I (Igf-1) that are found in large breeds (Eigenmann et al. '88; Tryfonidou et al. 2003), combined with the inverse relation between Insulin/Igf1 signaling and longevity in invertebrates and probably vertebrates (Partridge and Gems, 2002; Barbieri et al., 2003; Holzenberger et al., 2003, but see Carter et al. 2002) supports the idea that high growth rates cause the early mortality in large dog breeds.

However, when deaths from free-radical associated diseases such as cancer and cardiovascular diseases are excluded, the average age at death of giant breeds is not increased, at least for Irish Wolfhounds and St. Bernard Dogs (Bernardi, '88, SBCA Survey, '92). The oxidative stress theory of aging can, thus, only in part explain the early mortality. Additional important factors in the early death of dogs from such large breeds are developmental skeletal diseases, such as hip dysplasia and osteochondrosis (Dämmrich, '91; Slater et al., '92; Kealy et al., '92). These diseases are also linked to high growth rates and appear to be due to a mismatch between the rate of weight increase and skeletal development and growth. The situation in large breeds is so unnatural, that drinking ad libitum from the mother leads to a considerably increased incidence of joint diseases, when compared to a reduced intake of milk from bottles (Slater et al., '92). The high growth rates are presumably the result of artificial selection, as a side-effect of

selection for large mature size (Dämmrich, '91). In this respect it is of interest to note that in *Drosophila* extreme artificial selection for rapid development has also led to pathological conditions and early mortality (Chippindale et al. '97). The size of giant dog breeds (Great Dane, Newfoundland, St. Bernard dog, Irish Wolfhound) has remarkably increased since 1800-1900 (see Fig. 3). For instance, the breed standard for St. Bernard dogs now specifies a shoulder height of between 70-90 cm and these dogs weigh 65-85 kg, whereas a typical 19th century dog was approx. 60 cm high and weighed less than 50 kg (Nussbaumer, 2000). The negative traits associated with the high growth rates would, presumably, be strongly selected against in nature. Only the relaxed selection due to human care allows these traits to persist. The early mortality in large dog breeds, thus, does not appear to pose a threat to the oxidative stress theory of aging. Artificial selection on size has apparently led to pathological conditions in large breeds that misleadingly suggest that large body sizes negatively affect lifespan in dogs.

Our study shows that research on aging and other fitness-related parameters may easily be flawed if no attention is given to the confounding effects of differences in the genetic backgrounds of breeds and strains (see also Anisimov 2004, Khazaeli et al. 2005). This is particularly relevant because artificial selection has played such an important role in the species that are most often used for experimentation. Hence, for a better understanding of the intraspecific relationship between size and longevity in mammals studies on natural populations are eagerly awaited.

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Table 1. Variances of lifespan and size (weight or length) between and within breeds.

VMDB	Lifespan	Weight
<i>Between breeds</i>		
Covariance Matrix Breed Effects		
Lifespan	1.22 (s.e. 0.18, $p < 0.001$)	-6.47 (s.e. 1.26, $p < 0.001$)
Weight	$r = -0.54$	116.20 (s.e. 14.41, $p < 0.001$)
<i>Within breeds</i>		
Covariance Matrix Residual Effects		
Lifespan	14.15 (s.e. 0.01, $p < 0.001$)	1.73 (s.e. 0.13, $p < 0.001$)
Weight	$r = 0.06$	50.32 (s.e. 0.34, $p < 0.001$)
NMBE	Lifespan	Length
<i>Between breeds</i>		
Covariance Matrix Breed Effects		
Lifespan	3.08 (s.e. 0.95, $p = 0.002$)	-6.85 (s.e. 3.74, $p = 0.07$)
Length	$r = -0.36$	116.20 (s.e. 25.93, $p < 0.001$)
<i>Within breeds</i>		
Covariance Matrix Residual Effects		
Lifespan	12.79 (s.e. 0.72, $p < 0.001$)	0.57 (s.e. 0.45, $p = 0.21$)
Length	$r = 0.05$	10.05 (s.e. 0.57, $p < 0.001$)

FIGURE LEGENDS

Fig. 1. Dogs from large breeds usually die younger than dogs from small breeds. Lifespan and size effects are shown per breed, i.e. the predicted lifespan of a breed relative to the overall mean, corrected for sex (as predicted by a random effects model, see Methods). Size is represented by bodyweight (kg) in the VMDB dataset (left) and by the length of the base of the brain stem (mm) in the NMBE dataset (right), lifespan is in years. The area of each point is proportional to the sample size per breed. Maximum sample size per breed is 97 in the NMBE dataset, 3378 in the VMDB dataset. Minimum sample sizes are 4 (NMBE) and 5 (VMDB).

Fig. 2. Pearson correlation coefficients between lifespan and size are shown within breeds (solid circles: males, open circles: females). Size is represented by bodyweight in kg in the VMDB dataset (left) and by the length of the base of the brain stem in mm in the NMBE dataset (right), lifespan is in years. Correlations are plotted as a function of sample size per breed. In the VMDB dataset, there is a clear tendency towards positive correlations, corresponding to the significant test in Table 1. This trend is most clearly visible at large sample sizes. Correlation estimates are 41 times positive and 21 negative in the NMBE dataset and 184 times positive and 69 negative in the VMDB dataset.

Fig. 3. Selection for large size during the last century has been successful in Saint Bernard Dogs, similarly to that in other large breeds. Top left: male, 1968; top right: female, 2001. Bottom left: male, 1893, Bottom right: female, ca. 1880-1890.

Fig. 1

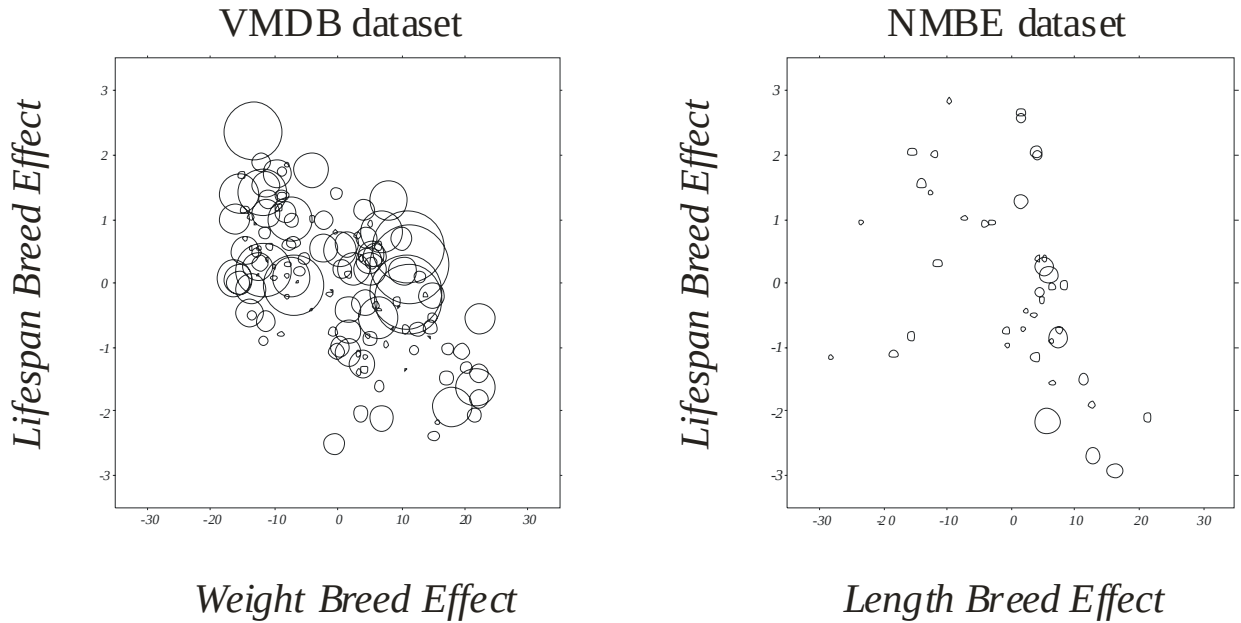


Fig. 1. Dogs from large breeds usually die younger than dogs from small breeds. Lifespan and size effects are shown per breed, i.e. the predicted lifespan of a breed relative to the overall mean, corrected for sex (as predicted by a random effects model, see Methods). Size is represented by bodyweight (kg) in the VMDB dataset (left) and by the length of the base of the brain stem (mm) in the NMBE dataset (right), lifespan is in years. The area of each point is proportional to the sample size per breed. Maximum sample size per breed is 97 in the NMBE dataset, 3378 in de VMDB dataset. Minimum sample sizes are 4 (NMBE) and 5 (VMDB).

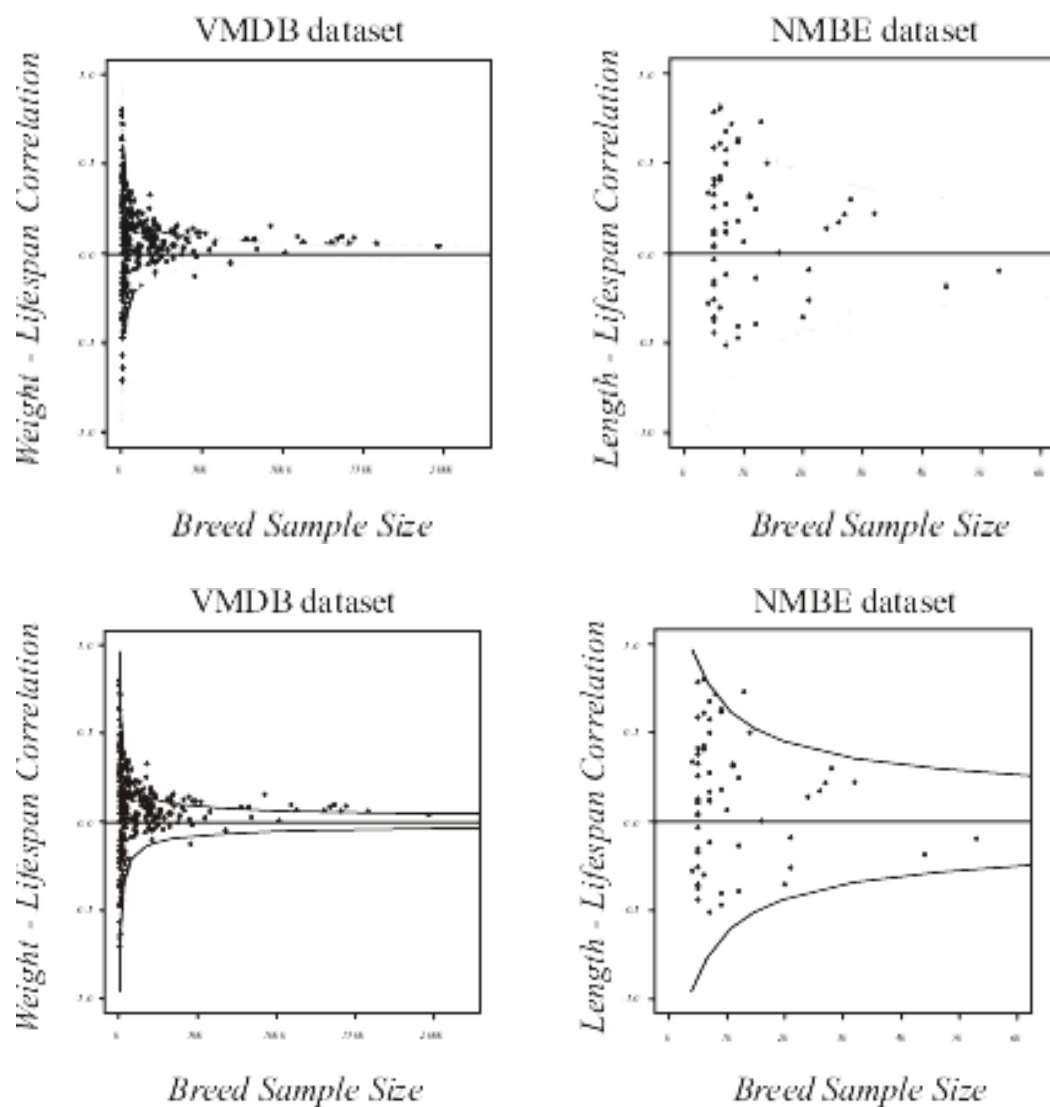


Fig. 2

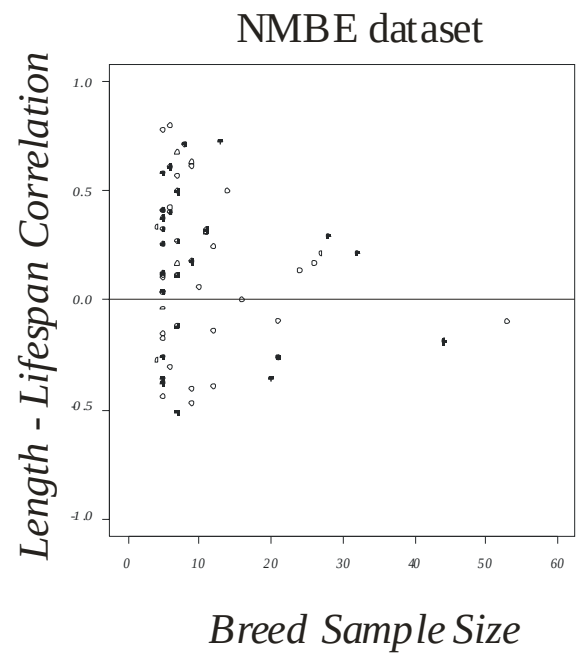
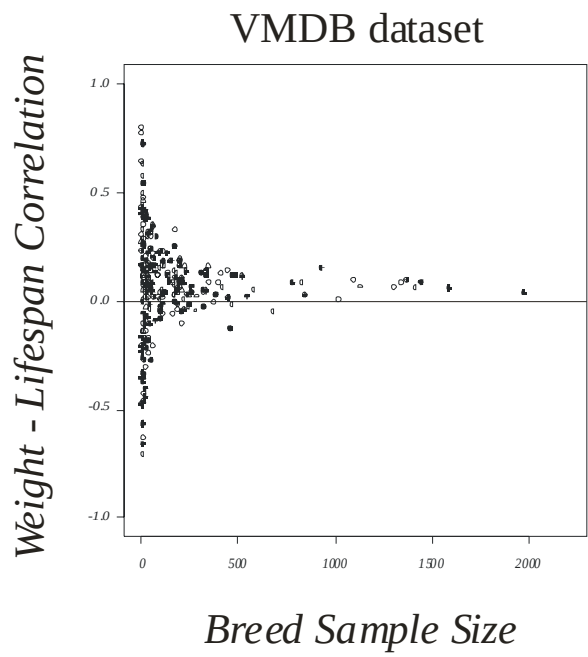


Fig. 3

