Life expectancy in a birth cohort of Boxers followed up from weaning to 10 years of age

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Objective—To determine mortality rate over time, risk factors for death, and heritability of life expectancy in Boxers.

Animals—1,733 purebred Boxers born in The Netherlands between January 1994 and March 1995.

Procedure—Dogs were followed up from weaning (ie, 49 days of age) to 10 years of age through use of a written questionnaire sent to owners every 6 months. Mortality rate over time, risk factors potentially associated with death, and heritability of life expectancy were examined by use of a proportional hazards model based on the Weibull distribution.

Results—Estimated mortality rate during the 10-year study period for this birth cohort of Boxers was 45%. The probability of surviving to 5 years of age was 88%; the probability of surviving to 10 years of age was 55%. Estimated effective heritability of life expectancy was 0.076, meaning that in this population, an estimated 7.6% of the observed variation in life expectancy could be attributed to genetic differences among dogs that were passed from parents to their offspring.

Conclusions and Clinical Relevance—Results suggest that cumulative incidence of death from weaning to 10 years of age among this birth cohort of Boxers was 45%. The estimated heritability of life expectancy suggested that life expectancy can be improved by use of selective breeding. (*Am J Vet Res* 2005;66:1646–1650)

Differences in life expectancy between purebred and mixed-breed dogs and among dogs of various breeds have been described.[1] On average, mixed-breed dogs live longer than purebred dogs, but dogs of several breeds (eg, Jack Russell Terriers, Miniature Poodles, and Whippets) live longer than typical mixed-breed dogs. In contrast, little is known about differences in life expectancy for dogs within a breed. Age- and breed-specific estimates of morbidity and mortality rates have been derived from analyses of data obtained from the Veterinary Medical Database, which records information on animals examined at a number of the veterinary teaching hospitals in North America,[2,3] and from insurance data.[4-6] This kind of information, however, is biased, and population-based studies are preferred.

In all breeds, the risk of death increases with age, but the pattern varies by breed.[6] Dogs of sporting and hound breeds live to a significantly older mean age than do dogs of herding or working breeds.[7] Similarly, the mean age for various breeds differs, ranging from 6.8 years for Bernese Mountain Dogs to 13 years for Poodles.[8] Boxers are considered as a breed to have a high risk for shorter life spans,[5] with low probabilities for survival to 5 and 10 years of age.[4,6] Breeding strategies for purebred dogs are expected to influence life expectancy, even if the trait has not been selected for directly. Therefore, population studies are necessary.

The purposes of the study reported here were to determine mortality rate over time, risk factors for death, and heritability of life expectancy in Boxers. A cohort of Boxers was followed from birth to 10 years of age to estimate postweaning mortality rate over time, and information on various environmental factors was collected to study potential risk factors for death and the role of genetic variation.

Materials and Methods

Dogs—Purebred Boxers born in The Netherlands between January 1994 and March 1995 were followed up from weaning (ie, 49 days of age) to 10 years of age. Dogs that died or were euthanatized prior to weaning (ie, prior to 49 days of age) were excluded from the study, as were dogs that were sold to owners outside The Netherlands or to owners in The Netherlands who refused to participate in the study. Details of the study have been published.[9] In addition, information on preweaning mortality rate, litter effects on preweaning mortality rate, and risk factors has been published.[10,11]

Data collection—A written questionnaire was sent to owners of dogs included in the study every 6 months. The questionnaire solicited information on survival, diseases, behavioral abnormalities, and environmental risk factors. Individual factors that were assessed included sex, age, and neuter status (ie, sexually intact vs castrated). Litter factors that were assessed included age and parity of the dam, inbreeding coefficient of the litter, season of birth, litter size at birth, and preweaning mortality rate for the litter. Body type and weight were not included in our analyses because data were lacking.

Data analyses—The number of categories for each risk factor was reduced as necessary to obtain sufficient numbers of observations in each category for analysis. We used 3 categories for age of the dam (< 3 years, 3 to 4 years, and > 4 years old) and parity of the dam (parity 1, parity 2, and parity > 2). Seven categories were used for season of birth (January and February 1994, March and April 1994, May and

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June 1994, July and August 1994, September and October 1994, November and December 1994, and January and February 1995). Two categories were used for litter size (3 to 8 puppies vs ≥ 9 puppies) and for preweaning mortality rate (≤ 40% vs ≥ 41%). Analyses incorporated all dogs reported to have died, even if the cause of death was not specified. Dogs that were lost to follow-up were regarded as censored at the time of final follow-up.

Genetic parameters for life expectancy of dogs included in the study were estimated by use of a proportional hazards model based on the Weibull distribution.[12] For this analysis, the term hazard was used to refer to the instantaneous mortality risk at a particular time (t), given that the individuals had survived to time t. The hazard function for death was described by the following function:

$$\lambda(t, w) = \lambda_0(t)\exp(w, \theta),$$

where $\lambda_0(t)$ was the baseline hazard function at time t, w was a vector of risk factors (eg, sex and age) affecting the probability of survival at time t, and θ was the design matrix allocating observations to the risk factors.

In these analyses, the baseline hazard function was approximated with a Weibull hazard function that had a parametric form as follows:

$$\lambda_0(t) = \lambda\rho(\lambda t)^{\rho-1}.$$

We carefully weighted the choice of distribution for the baseline hazard function. First, we checked the best possible distribution by the use of Akaike index criteria. We analyzed the data with a parametric model that included only random litter effects, testing for Weibull, normal, logistic, log-normal, and log-logistic distribution, and the Weibull distribution was found to be the best choice. In addition, the Weibull distribution is one of the most frequently used parametric forms, as it is proportional and accounts for accelerated failure time.[13] It is highly flexible, and in special cases, it can easily be adjusted to an exponential distribution.

We carefully examined the validity of the Weibull distribution by plotting the logarithm of the survival rate against the logarithm of time. This plot approximated a straight line, suggesting the Weibull distribution was valid. Preliminary analysis showed that the parameter ρ approximated 1. Therefore, we fixed this parameter at 1, so that the baseline distribution was assumed to follow an exponential distribution. The risk factors that were included in the exponent of the full model included sex, neuter status, litter size at birth, preweaning litter mortality rate, age of the dam, parity of the dam, inbreeding coefficient for the litter, and season of birth. Neuter status was included in the model as a time-dependent effect, accounting for the various ages at which castration had been performed.

The Kaplan-Meier estimate of the survival function[14] was plotted. This survival function represented the proportion of dogs that survived on each day of the observation period. The frailty variable of the model consisted of $\exp(\theta_q + a_{si})$, where θ_q was the random effect of the qth litter in which animal i was born (time independent) and a_s was the random effect of the sire that produced this litter (time independent), which equaled the **estimated breeding value (EBV)** of the sire.

The common method in animal breeding to describe the additive genetic value of animals is to assume the sire variance follows a multivariate normal distribution where the covariance structure between individuals is modeled by the matrix of genetic relationships. Therefore, sire variance was assumed to follow a normal distribution ($\sim N[0, A\sigma_s^2]$), where A was the numerator relationship (ie, between-sires) matrix and σ_s^2 represented the sire variance.

The litter effect can be estimated jointly when this effect is assumed to follow a log gamma distribution.[15] Therefore, litter effects were assumed to be independent and to follow a log gamma distribution.

Additive genetic variation was estimated as the variance of the log-frailty associated with the random breeding values of the sires (a_s). Heritability on the original scale (ie, the so-called effective heritability) can be calculated by use of the following formula:

$$h_{eff}^2 = 4\sigma_s^2/(\sigma_s^2 + \psi(\gamma) + 1/p),$$

where $\psi(\gamma)$ is the variance of the log-frailty associated with random litter effects.[16] This variance is a trigamma function, and p is the proportion of progeny that survived until time t.[12]

Pedigree analyses—Data on sire and dam of each litter were provided by the breeder and linked to the official pedigree information of the Dutch Kennel Club. Pedigree information for 10,000 Boxers registered by the Dutch Kennel Club was linked to health data from the birth cohort included in the study.[17] We used 3 generations of male ancestors for the birth cohort to estimate genetic variation (n = 161). Of these 161 male dogs, 96 sired dogs included in the birth cohort. Number of litters per sire ranged from 1 to 19, except that 1 dog sired 32 litters. Fifty-one of the 96 sires produced > 1 litter, and mean number of litters per sire was 3.15.

Results

Dogs—During the period from January 1994 to March 1995, 2,629 purebred Boxer puppies were born in 414 litters in The Netherlands. Of these, 571 (21.7%) died or were euthanatized before 49 days of age and were excluded from the study. In addition, 195 (7.4%) puppies were sold outside The Netherlands or to individuals in The Netherlands who refused to participate in the study and were also excluded from the study. Finally, because it is difficult to analyze risk factors for binary traits with data from dogs born in small litters, 130 (4.9%) puppies born in litters that consisted of < 3 puppies were also excluded from the study. The remaining 1,733 Boxers were included in the study. Of these, 674 were still alive at the time of final follow-up, 506 were dead at the time of final follow-up, and 553 had been lost to follow-up after weaning at 49 days of age.

Disease rate and risk factors—The 1,733 dogs included in the study consisted of 823 females and 910 males. The proportion that survived was calculated for each day of the observation period (**Figure 1**).

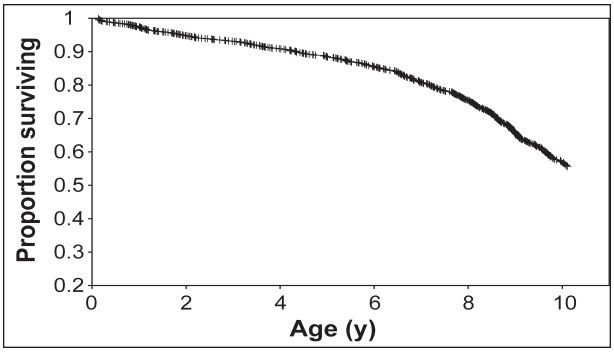

Figure 1—Kaplan-Meier survival curve for a birth cohort of 1,733 Boxers in The Netherlands that were followed up from weaning (ie, 49 days of age) to 10 years of age. All dogs still alive at 10 years of age were censored at 10 years.

Table 1—Results of survival analysis of factors associated with mortality risk for a birth cohort of 1,733 Boxers in The Netherlands that were followed up from weaning to 10 years of age.

Risk factor	Category	Estimate	SE	*P* value	Risk ratio	95% CI
Inbreeding coefficient (%)	Continuous	–0.22	0.096	0.02	NA	NA
Litter size at birth	3–8	Reference	NA	NA	NA	NA
	≥ 9	–0.28	0.14	0.04	0.75	0.57–0.99
Season of birth	Jan–Feb 1994	–0.13	0.15	0.36	0.87	0.65–1.18
	Mar–Apr 1994	0.00	0.15	1.00	1.00	0.75–1.34
	May–Jun 1994	Reference	NA	NA	NA	NA
	Jul–Aug 1994	–0.27	0.17	0.10	0.76	0.55–1.06
	Sep–Oct 1994	–0.17	0.17	0.32	0.85	0.61–1.18
	Nov–Dec 1994	–0.29	0.16	0.08	0.75	0.55–1.02
	Jan–Feb 1995	–0.49	0.19	0.01	0.61	0.42–0.89
Preweaning litter mortality rate	0%–40%	Reference	NA	NA	NA	NA
	> 40%	0.23	0.16	0.17	1.26	0.92–1.72
Sex	Male	Reference	NA	NA	NA	NA
	Female	–0.16	0.09	0.08	0.86	0.71–1.02
Neuter status	Sexually intact	Reference	NA	NA	NA	NA
	Castrated	0.54	0.11	< 0.001	1.71	1.38–2.14

CI = Confidence interval. NA = Not applicable.
Neuter status was included as a time-dependent variable (ie, equal to 0 until the dog was castrated and equal to 1 thereafter).

Estimated mortality rate during the 10-year study period for this birth cohort of Boxers was 45%. In the early years, the risk of death was low, except that there was a small peak in mortality rate during the first year of life. Mortality rate increased after 5 years of age and peaked at 9 years of age. The probability of surviving to 5 years of age was 88%; the probability of surviving to 10 years of age was 55%.

There did not appear to be any association between risk of death and age of the dam or between risk of death and parity of the dam. Therefore, these factors were excluded from the final model.

Litter size was associated with mortality risk, with mortality risk for dogs born in litters with ≥ 9 puppies significantly lower than risk for dogs in litters with 3 to 8 puppies (**Table 1**). Dogs born in litters whelped during January or February 1995 had a lower mortality risk, compared with dogs born in litters whelped during May or June 1994. Inbreeding was associated with a reduced mortality risk. When neuter status was included in the model as a time-dependent variable (ie, equal to 0 until the dog was castrated and equal to 1 thereafter), mortality risk increased when the dog changed from sexually intact to castrated. Mortality risk was not associated with age of the dam ($P = 0.51$) or parity of the dam ($P = 0.61$). Age and parity of the dam and litter size were not included in the final model that was used to estimate genetic parameters.

Heritability—Estimated effective heritability of mortality risk was 0.076. To evaluate the importance of genetic variance among sires on life expectancy, we calculated the mean EBV for the 10 sires with the lowest and the 10 sires with the highest EBVs. The mean EBV was –0.25 for the 10 sires with the lowest EBVs and 0.29 for the 10 sires with the highest EBVs. For progeny of the 10 sires with the highest mean EBV, probability of surviving to 10 years of age was only 40%, whereas for progeny of the 10 sires with the lowest mean EBV, probability of surviving to 10 years of age was 65% (**Figure 2**). The predicted risk ratio that progeny would survive with age was 0.78 for progeny of the 10 sires with the lowest mean EBV and 1.34 for progeny of the 10 sires with the highest mean EBV.

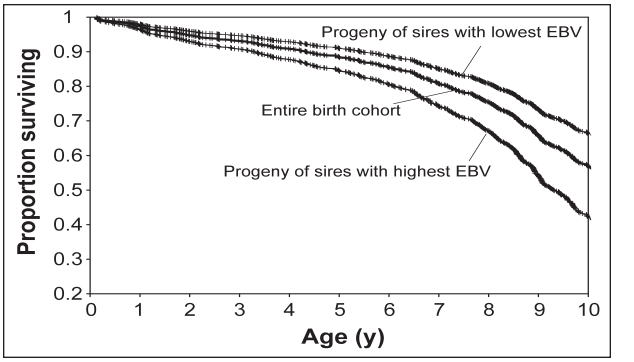

Figure 2—Predicted life expectancy of 1,733 Boxers in The Netherlands that were followed up from weaning (ie, 49 days of age) to 10 years of age and of the subset of dogs sired by the 10 sires with the lowest mean estimated breeding value (EBV) and the subset of dogs sired by the 10 sires with the highest mean EBV.

Discussion

Results of survival analysis of data for the birth cohort of Boxers included in the present study suggested that cumulative incidence of death from weaning to 10 years of age was 45%. As expected, more dogs died as age increased, with the graph of surviving proportion as a function of time being similar to findings in a previous study[6] of death for insured Boxers in Sweden. In the present study, the probability of dogs surviving to 5 years of age was 88% and the probability of dogs surviving to 10 years of age was 55%. These values were similar to values reported in the previous study[6] (92% and 49%, respectively).

Mean age at the time of death could not yet be determined in the present study. In a Danish study[18] of life expectancy of purebred and mixed-breed dogs, the 50% and 75% quartiles for Boxers were 9 and 11 years, respectively, and in a Swedish study,[6] median age at death for Boxers was 10 years. On the basis of available data, we expect that the mean age at the time of death

for the birth cohort included in the present study would also be approximately 10 years.

Surprisingly, inbreeding seemed to be associated with a significantly reduced mortality risk later in life in the present study. In general, inbreeding tends to reduce fitness and, therefore, characteristics closely connected with fitness (eg, life expectancy).[19] However, we calculated the inbreeding coefficient of the litter on the basis of both paternal and maternal effects, rather than on the basis of maternal effects alone. Also, we only included dogs that survived the first 49 days after birth. Preweaning mortality rate and inbreeding are related.[11] Therefore, excluding puppies that died prior to weaning probably affected our results. For dogs from litters with a high preweaning mortality rate (> 40%), mortality risk was increased, compared with mortality risk for dogs from litters with a low preweaning mortality rate, which was consistent with the possible influence of inbreeding on preweaning mortality rate. Litter size is another important component of fitness.[19] For instance, a previous study[20] found that small and large litters had the highest preweaning mortality rates. In the present study, larger litter size was associated with a lower mortality risk, possibly because we excluded litters with < 3 puppies.

Including neuter status as a time-dependent variable in the present study surprisingly showed that mortality risk increased when neuter status changed from sexually intact to castrated. In a study[7] of death in military working dogs, castrated male dogs typically lived longer than did spayed females or sexually intact males, although sexually intact male dogs were more numerous in the study population. This positive influence was thought to be attributable to prophylactic or therapeutic influences of neutering on the urogenital system.[7] However, the authors also suggested that because the number of reasons for neutering often increases with age, their results may reflect census distributions rather than sex-related mortality rates. We included neuter status as a time-dependent effect in the model to account for various ages at which castration had been conducted and the fact that castration only affects the risk of death after it is performed. Because neuter status was included as a time-dependent variable, dogs were more likely to change from sexually intact to castrated at an older age. To determine whether the surprising result of increased mortality risk in association with neuter status was indeed a result of this time-dependent effect, we performed an additional analysis in which neuter status was included as a time-independent variable. With neuter status treated simply as an indicator (yes vs no) variable, the effect reversed, in that castration was associated with a decreased risk of death (risk ratio, 0.56), whereas risk ratios for other risk factors did not change. This substantiated the suggestion that neutering often increases with age and that including neuter status as a time-independent variable reflects census distributions rather than sex-related mortality risk and suggested that age of castration should be taken into account in future studies involving the effects of neuter status.

Although we have no reason to believe that selection bias was a problem in the present study, it cannot be excluded that censoring attributed to loss to follow-up may have contributed to our findings. Of the 1,733 dogs enrolled in the study, 533 were censored because of loss to follow-up. Considering that the study extended over 10 years, we believe this can be considered a relatively low rate (a mean of 55 dogs lost to follow-up/y). To determine whether this selection bias had a large influence in the present study, we determined the mean loss to follow-up in litters. It appeared that loss to follow-up was equally distributed over all litters. However, if censored animals have different life expectancies because of the reasons for censoring and the reasons for censoring differ among risk factor categories, then our findings may have been biased.

Because the study was terminated after 10 years, before most of the dogs had died, a rather high percentage of dogs (39%) were censored (right censoring). Unfortunately, financial and time limitations did not allow us to continue monitoring this birth cohort. However, we believe the number of dogs for which follow-up was complete (506) was large enough to justify the claim that this was a study of life expectancy.

The estimated effective heritability of 0.076 found in the present study means that among Boxers in The Netherlands, 7.6% of the variation in life expectancy arises from genetic differences among animals that are passed from parents to their offspring. Heritability of life expectancy in other dog breeds is not known. However, the estimate is well within the range reported for farm animals.[21-24]

Results of our study show that there is scope for genetic improvement in life expectancy of Boxers. Further research to study the various causes of death may provide more detailed information on genetic background and further improve the implementation of genetic evaluation.

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