

Incidence, risk factors, and heritability estimates of hind limb lameness caused by hip dysplasia in a birth cohort of Boxers

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Objective—To determine incidence, risk factors, and heritability estimates of hind limb lameness caused by hip dysplasia in a birth cohort of Boxers.

Animals—1,733 Boxers from 325 litters.

Procedure—Status of Boxers with respect to clinical signs of canine hip dysplasia (cCHD) was registered during an 8-year period. Survival analysis accounted for dogs lost to follow-up. Effective heritability for developing cCHD was estimated by use of a proportional hazard model on the basis of the Weibull distribution. Parametric survival models were developed to identify the influence of potential risk factors.

Results—Cumulative hazard rate for cCHD from 7 weeks to 8 years of age was 8.5%. Dogs that were kept on a floor covered with a slippery material were 1.6 times as likely to develop cCHD, compared with dogs kept on a nonslippery floor. Risk of cCHD doubled in dogs from litters with a high preweaning mortality rate. Dogs that were neutered at 6 months prior to a diagnosis of CHD were 1.5 times as likely to develop cCHD, compared with sexually intact dogs. Dogs > 5 years of age were 1.8 times as likely to develop cCHD, compared with younger dogs. Estimated effective heritability of cCHD was 0.11. In terms of the risk of cCHD in progeny, mean estimated breeding value (EBV) of the 10 best and 10 worst sires was -0.32 and 0.42 , respectively.

Conclusions and Clinical Relevance—Registration of Boxers that develop cCHD may provide a strategy for disease prevention. In addition to diagnostic evaluation of radiographs, sire EBVs provide useful information for breeding selection decisions. (*Am J Vet Res* 2005;66:307–312)

Canine hip dysplasia (CHD) is characterized by an abnormal joint conformation and secondary degenerative joint disease. Hip instability in young

dogs alters the concentration of forces on the growing femoral head and acetabulum.¹ This affects bone growth and remodeling, resulting in (abnormal) friction between both joint surfaces and, subsequently, joint deformity with a mechanically induced osteoarthritis.^{2,3} Currently, CHD is identified in most dog breeds, but it has a propensity to occur most often in fast-growing dogs of large breeds. Radiographic findings confirm the clinical diagnosis of CHD.

Estimated risks of CHD in the literature are based on the diagnostic evaluation of radiographs, regardless of whether clinical signs are present. Information on dogs that develop **clinical signs of canine hip dysplasia (cCHD)**, mostly later in life, is scarce. Phenotypic expression of CHD in dogs genetically predisposed to cCHD may be modified by important environmental factors such as nutrition and exercise. Also, other factors (ie, joint laxity, body type, growth rate, and hormones) can influence the course of the disease in individual dogs.^{2,4,5} The quantitative characteristic of CHD manifests as a continuous variation between a sound joint and the worst alteration, permanent luxation. Like other chronic degenerative arthropathies, no direct relation can be found between the degree of pain with the resulting movement difficulties and the degree of morphologic changes in the articulation.⁶

Diagnostic evaluation of radiographs has been essential for any successful combat against CHD.⁶ Results of several studies indicate that the frequency of CHD can be decreased by selection on the basis of the individual's own degree of radiographic hip dysplasia,⁷ and until now, this had been applied in practical breeding schemes.⁶ Despite many attempts to control the disease through these selective breeding programs, CHD is still a common orthopaedic disease.^{2,3,8,9} The success of this individual selection depends on the frequency of CHD in the population,¹⁰ making it harder to achieve genetic improvement at lower degrees of incidence. The genetic improvement can be increased considerably if the potential sires are ranked according to their estimated sire effects on the basis of their own progeny.⁷ The most rapid genetic progress is achieved by use of best linear unbiased prediction procedures to estimate breeding values.^{11–13} These procedures require an estimate of the heritability of the trait, along with the variance components used to calculate the estimate.¹⁴

In our study, a birth cohort of Boxers was followed from birth to 7 to 8 years of age. Dogs with and without cCHD were registered to estimate adequately the

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disease rate over time. Dogs that had hind limb lameness with CHD and an appropriate diagnosis made by the local veterinarian are described here as dogs with cCHD. Data of various environmental influences such as sex, birth weight, and litter size were also collected as well as the role of genetic variation. Parametric survival models were developed to identify the influence of these potential risk factors for cCHD. The purpose of the study reported here was to determine the incidence, risk factors, and heritability estimates of hind limb lameness caused by hip dysplasia in a birth cohort of Boxers.

Materials and Methods

Population—Purebred Boxers from litters born in the Netherlands between January 1994 and March 1995 were followed from birth to 7 to 8 years of age. Dogs were monitored every 6 months by use of written questionnaires as previously described by Nielen et al.¹⁵

Data—Our data set comprised 1,863 Boxers, 46.7% males, and 53.3% females, including dogs with and without cCHD. Data from birth until the first 49 days of life were collected from the dog breeders. Data on puppies included birth weight and information on housing. After the puppies were sold, data were obtained from the new owners. Data on survival, diseases, and environmental risk factors were collected. Data concerning cCHD were available from January 1994 to June 2002.

The local veterinarian made a diagnosis of CHD after clinical signs manifested in the dog. All observations of owners (clinical history) included that the dogs had difficulty in standing up after lying down and lameness in 1 or both hind limbs. Orthopaedic examination excluded other possible causes of hind limb lameness. Radiographic findings consistent with cCHD resulted in a final diagnosis of the disease. Severity of the clinical signs was not classified.

In the analysis, only those dogs for which data collection was continued after the puppy was sold (ie, excluding puppies that did not survive the first 49 days) were considered. Dogs that were lost to follow-up were regarded as censored. For a binary trait, it is difficult to analyze differences in risk factors within small litters. Therefore, litters with < 3 puppies were excluded from the analysis. Finally, our data set comprised 1,733 Boxers, including 97 dogs with cCHD. Birth weight was recorded for only a limited number of dogs (n = 1220). A subset consisting of the 1,220 Boxers with known birth weight, including 66 dogs with cCHD, was analyzed separately to investigate the effect of birth weight on the risk of developing cCHD.

Risk factors—Risk factors included individual data such as sex and whether a dog was sexually intact or

neutered. Neutering was considered a risk factor when it was performed at least 6 months prior to the diagnosis of CHD. Litter data consisted of age of the dam, number of prior litters of the dam, inbreeding coefficient, season of birth, slippery or nonslippery floor cover (ie, the housing of the dam and her puppies), litter size, and preweaning mortality rate in the litter before 7 weeks of age. With the exception of birth weight, these risk factors were known for all 1,733 Boxers. Other possible risk factors such as body type and growth rate were not included in our analyses because these data were lacking. In the study design from the outset, owners were not asked to weigh the dog or measure the dog's height. Although the body weight of most dogs with cCHD was registered, body weights of dogs without cCHD were not known. Therefore, body weight could not be included in the analysis. Only birth weight was included in the analysis of a subset of data. The ratio of Boxers to owners was 1:1, and with some exceptions, the same was true for the ratio of Boxers to veterinarians. Therefore, the effect of owner or veterinarian was not included in the analysis.

Three levels of age in years were used to study the influence of the age of the dam (Table 1). The number of prior litters of the dam varied from 0 to 5 litters and were classified into 3 levels. To study the influence of the floor cover, 2 levels were used: slippery and nonslippery. The floor cover was defined slippery when it was covered with tarpaulin or newspapers and nonslippery when covered with carpet, rubber, blankets, sawdust, or straw. To study the influence of the season of birth, 7 levels of 2 months each were used that spanned 14 months. For litter size, 2 levels were used. Mean (\pm SD) litter size was 6.4 (\pm 2.5) puppies. To study the influence of preweaning mortality rate in the litter, 2 classes were used: high mortality rate (> 40%) and low mortality rate (< 40%).

Estimate of genetic parameters and risk factors—Genetic parameters and risk factors for developing cCHD in 7- or 8-year-old Boxers were estimated by use of a proportional hazard model on the basis of the Weibull distribution, as implemented in a survival kit software program.¹⁶ The term hazard refers to the (instantaneous) risk of an event at a given time t , given that dogs were free of cCHD up to time t . In this instance, the event was the diagnosis of CHD. For example, if 2 groups of dogs have hazards of 0.5 and 1.5, the latter group is 3 times as likely to have a diagnosis of CHD than the former. The hazard ratio in this example is 3.

The hazard function of an event is used to describe the hazard of this event at any time t as follows (formula 1):

$$\lambda(t; w) = \lambda_0(t) \exp\{w' \theta\},$$

where $\lambda_0(t)$ is the baseline hazard function (or mean risk that a diagnosis of CHD is made) at time t , w is a vector of risk

Table 1—Levels of risk factors that were included in the full model fitted to the age at which a diagnosis of canine hip dysplasia (CHD) was made in the birth cohort of Boxers (n = 1,733).

Level	Dam		Months	Litter		Housing
	Age (y)	No. of prior litters		Size (No. of puppies)	Preweaning mortality (%)	Floor cover
1	≤ 3	0	Jan and Feb (1994)	3–8*	0–40	Slippery
2	3–4	1	Mar and Apr (1994)	≥ 9	41–100	Nonslippery
3	≥ 4	> 1	May and Jun (1994)	NA	NA	NA
4	NA	NA	Jul and Aug (1994)	NA	NA	NA
5	NA	NA	Sep and Oct (1994)	NA	NA	NA
6	NA	NA	Nov and Dec (1994)	NA	NA	NA
7	NA	NA	Jan and Feb (1995)	NA	NA	NA

*Litters of < 3 puppies were excluded from analysis.
NA = Not applicable.

factors (eg, sex and age) affecting the hazard of this event at time t , and θ is the design matrix allocating observations to the risk factors.

Model—In our analysis, the baseline hazard function is approximated by a Weibull hazard function having a parametric form as follows:

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

Preliminary analysis revealed that the parameter p approximated 1. Therefore, this parameter was fixed at 1 so that the baseline is assumed to follow an exponential distribution. The number of levels of the risk factors was decreased to get a sufficient number of observations in each level (Table 1).

The risk factors included in the final model were obtained by use of stepwise backward elimination of the least significant risk factors from the full model. A χ^2 test was used to determine the significance of an individual risk factor. The test criterion was the difference in the $-2 \ln(\text{likelihood})$ of the model with and without this effect with associated degrees of freedom. At each step of elimination, the difference between $-2 \ln(\text{likelihood})$ of the model and $-2 \ln(\text{likelihood})$ of the model without the risk factor was calculated as a test criterion. Elimination of risk factors continued until the final model had the highest degree of significance according to a χ^2 test on the test criterion. Risk factors that were included in the exponent of the final model (formula 1) were the following: sex, neutered at least 6 months prior to a diagnosis of CHD, litter size, mortality rate in the litter, age of the dam, number of prior litters of the dam, floor cover, inbreeding coefficient (continuous), season of birth, and aging (cCHD before or after the age of 5 years). Neutering was included in the model as a time-dependent effect, accounting for varying ages at which neutering had been conducted.

The Kaplan-Meier estimate of the survival function¹⁷ was plotted for cCHD (Figure 1). The survival function represents the proportion of Boxers without cCHD up to day (t) of the observation period. From the literature,¹⁸ it was expected that an acceleration of the aging process would start between 4 and 6 years of age. From the plot of the Kaplan-Meier estimate, it appeared that the slope changed after 5 years of age. Whether a significant difference in risk was found before and after 5 years of age was analyzed by validation of the baseline hazard. Aging was included as a time-dependent constant in the exponent of the model and tested the suitability of the assumed exponential distribution graphically (ie, plot of $\ln[-\ln(S_0 [t])]$ against $\ln(t)$ produces a straight line). An appropriate fit of our baseline hazard was achieved when the effect of aging was included in the model.

The frailty variable of the model consists of $\exp\{\theta_q + a_{si}\}$, where θ_q is the random effect of the q th litter in which puppy i is born (time independent) and a_s is the random effect of the sire that produced this litter (time independent); a_s equals the estimated breeding value (EBV) of the sire. Sire variance was assumed to follow a normal distribution ($-N[0, A\sigma_s^2]$), where A is the numerator relationship matrix and ρ_s^2 represents the sire variance. Litter

effects were assumed to be independent and to follow a log- γ distribution ($-\log-\gamma [\gamma, \gamma]$), where γ is the parameter of the log- γ distribution, as described by Ducrocq and Casella.¹⁹

Additive genetic variation—Additive genetic variation was estimated as the variance of the log-frailty associated with the random breeding values of the sires (a_s). According to Yazdi et al,²⁰ the heritability on the original scale (the so-called effective heritability) can be calculated by the following equation:

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

where $\psi[\gamma]$ is the variance of the log-frailty associated with the random litter effects. This variance is a trigamma function, and p is the proportion of progeny that did not have hind limb lameness caused by CHD until time t .²⁰

Pedigree—Data on sire and dam of litter provided by the breeder were linked to the official pedigree informa-

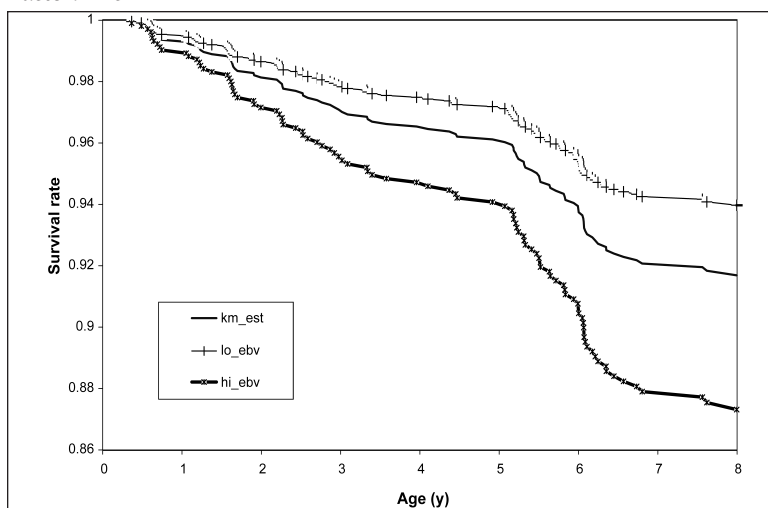


Figure 1—Kaplan-Meier estimate (km_est) of the survival function for clinical signs of canine hip dysplasia (cCHD), which represents the proportion of Boxers without cCHD up to day of the observation period (ie, from 49 days to 8 years of age) in a birth cohort of Boxers ($n = 1,733$). To predict the risk of developing cCHD in the progeny of different sires, the mean estimated breeding value (EBV) was calculated for the 10 best sires with the lowest EBVs (lo_ebv) and the 10 worst sires with the highest EBVs (hi_ebv).

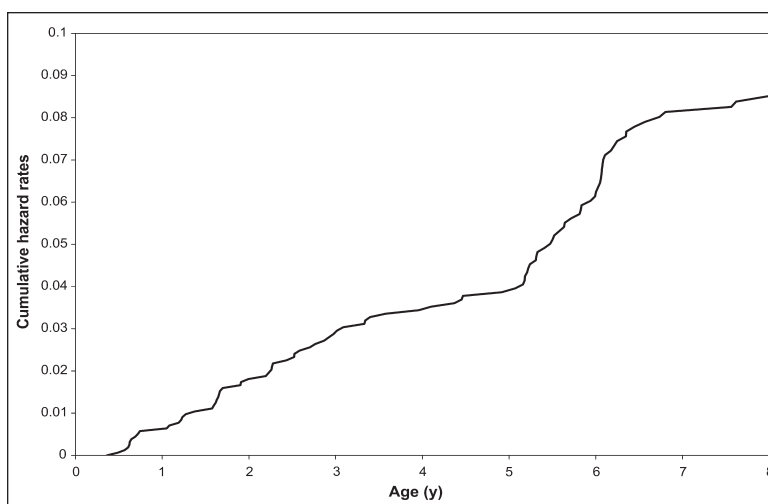


Figure 2—Cumulative hazard rates of Boxers with cCHD on each day of the observation period (ie, from 49 days to 8 years of age) in a birth cohort of Boxers ($n = 1,733$).

Table 2— χ^2 Values and associated degrees of freedom (df) for risk factors that were included in the final model fitted to age when a diagnosis of CHD was made with random litter effects in the birth cohort of Boxers.

Variables	Final models						
	Final model (n = 1,733)			Without birth weight (1,220)		With birth weight (1,220)	
	df	χ^2	Probability > χ^2	χ^2	Probability > χ^2	χ^2	Probability > χ^2
Litter							
Litter size	1	2.4404	0.1182	1.0363	0.3087	0.1227	0.7262
Floor cover*	1	3.0429	0.0811	0.4075	0.5300	0.2228	0.6369
Prewaning mortality	1	3.2364	0.0720	2.0408	0.1531	1.4736	0.2248
Individual							
Birth weight	1	NA	NA	NA	NA	3.5158	0.0608
Neutering†	1	2.6022	0.1067	1.3826	0.2397	1.6861	0.1941
Aging‡	1	7.9897	0.0047	7.4231	0.0064	7.4590	0.0063

*Floor cover during preweaning housing. †Neutering at a minimum of 6 months prior to a diagnosis of CHD. ‡Diagnosis of CHD prior to or after 5 years as a piecewise constant (aging process).
NA = Not applicable.

Table 3—Estimates of the final parametric survival model for the 97 Boxers with clinical signs of CHD at different age (dependent variable) with random litter effects in a birth cohort of Boxers (n = 1,733).

Variables	Levels	Final parametric survival model			
		Estimates	SE	P value	Hazard ratio
Litter size	< 9 puppies	0.000	NA	NA	1.00
	≥ 9 puppies	-0.445	0.288	0.123	0.64
Floor cover*	Nonslippery	0.00	NA	NA	1.00
	Slippery	0.490	0.277	0.077	1.63
Prewaning mortality (%)	≤ 40%	0.000	NA	NA	1.00
	> 40%	0.737	0.391	0.059	2.09
Neutering†	No	0.000	NA	NA	1.00
	Yes	0.392	0.238	0.099	1.48
Aging‡	< 5 years	0.000	NA	NA	1.00
	≥ 5 years	0.614	0.214	0.004	1.85

See Table 2 for key.

tion of the Dutch Kennel Club (for further details, see Nielen et al²¹). Pedigree information of 10,000 Boxers registered by the Dutch Kennel Club was linked to health data from the birth cohort of 1994. Three generations of male ancestors of the birth cohort of Boxers were used to estimate genetic variation (n = 161). Of the 161 sires, 95 fathered our birth cohort of Boxers. The mean (\pm SD) litter size was 6.4 (\pm 2.5) puppies.

Results

Incidence and risk factors—At the beginning of this study, 1,733 dogs were at risk (823 females and 910 males). The number of registered dogs with cCHD at the end of the observation period was 98, corresponding to a cumulative hazard rate of 8.5% of Boxers with cCHD in this population. The (cumulative) hazard rates of Boxers with cCHD on each day of the observation period were determined (Figure 2). As expected, with increasing age, more Boxers had a diagnosis of cCHD made by the local veterinarian.

After elimination of possible risk factors, the final model with the highest degree of significance (the model with the smallest P value; P = 0.003) was

obtained. This final model excluded the individual risks of developing cCHD on the basis of sex, age, number of prior litters of the dam, and season of birth. The χ^2 values and associated degrees of freedom for the risk factors included in this final model (P = 0.003) with random litter effects were determined (Table 2). The influence of the individual risk factors included in the final model was evaluated by size of the estimate and relative risk, thereby accounting for the size of the data set and relatively low incidence of cCHD (Table 3). This evaluation showed that dogs that were > 5 years of age were 1.8 times as likely to develop cCHD, compared with younger dogs. Neutering at least 6 months prior to making a diagnosis of cCHD influenced the risk of developing cCHD over time; neutered dogs were 1.5 times as likely to develop cCHD, compared with sexually intact dogs. The mean age at the time of neutering was 3 years. An influence was found for litter size and preweaning mortality rates. With an increasing number of puppies in the litter, the risk of developing cCHD over time decreased and the risk doubled in litters with high preweaning

mortality. When the floor cover was slippery, the risk of developing cCHD increased as well.

Analyses of the subset consisting of 1,220 Boxers with known birth weight revealed similar results via the same model as described for the complete data set (Table 2), although χ^2 values were decreased as a result of the smaller data set. Therefore, the subset was considered to be a suitable random test of the influence of birth weight. Adding the risk factor to our final model revealed a considerable influence of birth weight. As expected, adding birth weight decreased the influence of litter size because birth weight and litter size are related.

Heritability—A heritability estimate of 0.11 for cCHD was found in this birth cohort of Boxers. The mean (\pm SD) inbreeding coefficient was 5.76% (\pm 5.04) and ranged from 0% to 22%. The inbreeding coefficient was not included in the final model that was used to estimate genetic parameters. The additive genetic variation and therefore the heritability did not change when inbreeding was taken into account as a risk factor.

To illustrate the use of EBVs to predict the risk of developing cCHD in the progeny of different sires, the mean EBV was calculated for the 10 sires with the lowest and the 10 sires with the highest EBVs. The mean EBV of the best 10 sires was -0.32 , and the mean EBV of the 10 worst sires was 0.42 (Figure 1). At the age of 8 years, the predicted proportion of Boxers that were free of cCHD from sires with the lowest mean EBV was decreased by 6%, in contrast to the Boxers fathered by the sires with the highest mean EBV, of which 13% were predicted not to be free of cCHD. The predicted risk ratio of the progeny of the 10 best and 10 worst sires to develop cCHD with age was 0.725 and 1.526, respectively.

Discussion

We have studied a birth cohort of Boxers in which dogs with and without cCHD were registered. By use of survival analysis, we found a cumulative incidence of 5.6% of cCHD during 8 years. Because the radiographs in our study were obtained on the basis of clinical indication, our incidence figure cannot be compared directly with estimates in literature that are based on diagnostic evaluation of radiographs that were obtained, regardless of whether clinical signs of hind limb lameness were present. Furthermore, radiographic observations are often performed at a fixed age. We assume that if radiographs of Boxers without clinical signs of lameness had been available, a large number of those dogs would have had radiographic signs of CHD. In our follow-up study, we not only knew whether a diagnosis of cCHD was made but also at what time the diagnosis of cCHD was made.

We found that dogs that were > 5 years of age were 1.8 times as likely to develop cCHD, compared with younger dogs. We expected an increased risk with age because often locomotor dysfunction increases as the dog becomes older as a result of a gradual deterioration in the joint structures.¹⁸ The increasing probability of having degenerative joint diseases with age has also been

described in 4 other common dog breeds (ie, German Shepherd Dogs, Golden Retrievers, Labrador Retrievers, and Rottweilers).²² With an increase in age, more Boxers in our study were brought to the local veterinarian because of hind limb lameness. Besides an increase in general wear and tear on the joint, this finding may be related to an increase in body weight that often occurs by 4 to 6 years of age, which is associated with the onset of lethargy.¹⁸ Neutered dogs were 1.5 times as likely to develop cCHD, compared with dogs that were sexually intact. This increase in risk may also be explained by the influence of body weight because neutering generally leads to an increase in body weight within 6 months of the procedure.²³ In addition, a higher odds ratio for being neutered (odds ratio, 2.8) in overweight dogs has been described by Robertson.²⁴ Body weight was a significant risk factor for degenerative joint disease for the 4 breeds described by Smith et al.²² The speed with which secondary osteoarthritis worsens depends on the degree of the original CHD and the amount of stress on the joint, which is related to the size and weight of the dog.¹⁸ Findings in a clinical trial of 9 overweight client-owned dogs with hind limb lameness secondary to hip osteoarthritis revealed that weight reduction alone may result in a substantial improvement in lameness.²⁵ In our study, the calculated increase in risk of CHD in neutered Boxers with clinical signs of lameness is in accordance with these findings.

In our study, the positive influence of a high birth weight on cCHD supports the theory that increasing body weight increases the risk of developing cCHD because high birth weight, rapid growth, and high mature body weight are correlated. Heritabilities and genetic correlations were estimated for birth weight, mature weight, and mature height in German Shepherd Dogs and Labrador Retrievers by Helmink et al.²⁶ In our study, the decreased risk of developing cCHD with an increasing number of puppies in the litter may be related to lower birth weights in large litters or other less obvious factors. A decrease in the effect of litter size was found when birth weight was included in the analyses of the subset (Table 2). This illustrates the importance of considering the effects included in a model when comparing results across studies. Birth weight could not be evaluated in our full data set, but the analysis of a subset revealed that it must be considered as a risk factor in future analyses.

In our study, the estimated heritability of 0.11 indicates that in the Boxer population, 11% of the phenotypic variation observed in cCHD arises from genetic differences among dogs that are passed from parents to their offspring. Because heritability is based on the incidence of dogs with clinical signs of lameness, the question is whether this variation is the result of the heritability of CHD or is related to an increased risk of developing osteoarthritis. Although the inheritance of osteoarthritis in dogs per se is questioned,² it is reported in human literature that differences in the prevalence of osteoarthritis may be attributable to genetic and lifestyle factors.²⁷ Furthermore, the laxity of the hip joint, which has been recognized as a constant feature of CHD,^{28,29} appears to have a hereditary basis in that the progeny of dogs without CHD had less laxity than did those from dysplastic parents.²⁹

On the basis of a variety of studies,^{6,13,14,30} CHD is assumed to be a complex polygenic trait with heritability ranging from 0.11 to 0.5, depending on the breed and cohort of the study. We expected the heritability to be relatively low because breeds with rare hip dysplasia occurrence will also have a smaller additive genetic variation and lower heritability.⁶ Breed-specific information on disease susceptibility should be incorporated when making breeding decisions concerning cCHD.²² The registration of disease in the offspring can help to select the best breeding dogs by creating a breeding index by means of evaluating the offspring of the male dogs.³¹ In our study, the comparison of the mean EBV of the 10 sires with the highest EBV with the mean of the sires with the lowest EBV illustrates that the registration of cCHD in the offspring can help to select the best breeding dogs.

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