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Risk factors for hip-related clinical signs in a prospective cohort study of four large dog breeds in Norway

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ABSTRACT

We conducted a prospective cohort study including privately owned dogs from the breeds Newfondland (NF), Labrador Retriever (LR), Leonberger (LEO), and Irish Wolfhound (IW) followed from birth until age 9 yrs. We wanted to investigate whether radiological hip dysplasia status given at approximately age 12–18 mos and other factors during growth influenced development of clinical signs due to hip-joint disease necessitating veterinary consultation. Whether or not such signs occurred due to hip dysplasia or due to secondary or primary DJD could not be distinguished, and we therefore used the term "owner-reported veterinary-diagnosed hip-related clinical signs" ("the event"). The included dogs were followed from birth to the event or until a maximum of 9 yrs of age. Our objectives were to describe breed differences in time to incidence and to evaluate potential risk factors for the time to event. We used Kaplan–Meier curves to describe time to incidence, and potential risk factors were assessed by use of a Cox proportional-hazards model. We enrolled 494 dogs from 103 litters, and 46 dogs were reported as having had the event during the observation period. We observed a significant time-varying effect (TVE): LR and LEO developed clinical signs later in life than NF. If the radiological hip status was either mild, moderate, or severe the hazard of experiencing the event was significantly increased. Access to off-leash exercise at age 12 mos decreased the hazard of the event, and the hazard varied by litter. The findings supported the hypothesis that radiological hip status at screening and exercise conditions during growth influenced the time to incidence of the event and that there were breed differences in time to the event.

1. Introduction

Hip dysplasia and degenerative joint disease (DJD) in the hips are common causes of lameness and exercise intolerance in large-breed dogs (Vaughan, 1990; Roush, 2001). Canine hip dysplasia is a uni- or bilateral developmental disorder with a genetic predisposition, and the occurrence and severity of radiologically diagnosed hip dysplasia are influenced by environmental factors (Lust et al., 1973; Riser, 1974; Fry and Clark, 1992; Kealy et al., 1992; Zhu et al., 2009; Ginja et al., 2010; Krontveit et al., 2010, in press). DJD of the hips often occurs secondary to canine hip dysplasia, and both hip-joint laxity and increased bodyweight/body-condition score are risk factors for development of DJD in dogs with hip dysplasia (Smith et al., 1995, 2001; Runge et al., 2010). Hip instability allows the femoral head to subluxate during weight bearing which in turn alters the concentration of forces on the femoral head and acetabulum and results in DJD (characterized by loss of articular cartilage, fibrosis, bone remodeling, and loss of normal function) (Alexander, 1992; Fries and Remedios, 1995; Todhunter and Lust, 2003).

Clinical signs related to hip dysplasia can range from mild or intermittent lameness and stiffness with difficulty rising after rest, to nonambulation in severely affected

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dogs (Fry and Clark, 1992). Commonly, a bimodal age distribution is observed with affected younger dogs developing signs between age 3 and 12 mos and mature dogs displaying gradually increasing severity of signs due to progression of DJD (Riser, 1975; Vaughan, 1990; Dassler, 2003). The onset of signs in mature dogs varies from 2 to 12 yrs (Fry and Clark, 1992; Dassler, 2003; Ginja et al., 2010).

When relating clinical signs to the diagnosis of canine hip dysplasia, other causes of lameness or gait abnormalities must be ruled out (Fry and Clark, 1992). High frequencies of cranial cruciate-ligament ruptures have been found in dogs referred for lameness attributed to hip dysplasia (Roush, 2001; Powers et al., 2005). Additionally, both immature and mature dogs with hip dysplasia sometimes also have DJD in both shoulder and stifle joints which could contribute to lameness (Olsewski et al., 1983). Clinical tests can give information about hip joint-laxity and detect signs of DJD (Ginja et al., 2010). Standard radiographic examination of the coxofemoral joints might confirm the diagnosis of hip dysplasia through evaluation of hip-joint congruence and DJD, while stress radiography provides information about hip-joint laxity (Smith, 1997; Fluckiger et al., 1999; Ginja et al., 2010). Standard radiographic examination is used for official screening for canine hip dysplasia in many countries, including Norway, and the results of the radiographic screening are commonly registered in databases of national kennel clubs (e.g. the Norwegian Kennel Club (NKK)).

Aging, high birth weight, slippery pre-weaning floor cover, and neutering are risk factors for development of clinical signs related to canine hip dysplasia (van Hagen et al., 2005). The effect of neutering might be mediated by an increase in bodyweight (van Hagen et al., 2005). An association exists between radiological hip-dysplasia status at screening and incidence of veterinary insurance claims related to canine hip dysplasia (Malm et al., 2010). Not all dogs with a radiographic hip-dysplasia diagnosis develop clinical signs, and the severity of clinical signs will not always correspond with the radiographic findings (Brass, 1989; Fry and Clark, 1992; Dassler, 2003; Ginja et al., 2010).

In our analysis, a cohort of privately owned dogs from four large breeds was followed from birth until age 9 yrs. We wanted to investigate whether radiological hip-dysplasia status given at approximately age 12–18 mos and other factors during growth influenced development of clinical signs due to hip-joint disease necessitating veterinary consultation later in life. Whether or not such signs occurred due to hip dysplasia or due to secondary or primary DJD could not be distinguished, and we therefore used the term “owner-reported veterinary-diagnosed hip-related clinical signs” (also referred to as “the event”). The incidences over time under various exposures were studied. Specifically, our aims of the study were to describe breed differences in time to event and to evaluate potential risk factors by applying a Cox proportional-hazards model. The hypotheses were that radiological hip status at screening, bodyweight, and housing and exercise conditions during growth would influence time to the event.

2. Materials and methods

Our study was carried out in agreement with the provisions enforced by the National Animal Research Authority in Norway.

2.1. Study design

The present study is part of a larger study (the so-called *main study*) including privately owned dogs from four large breeds: Newfoundland (NF), Labrador Retriever (LR), Leonberger (LEO) and Irish Wolfhound (IW) (Trangerud, 2008). We conducted a prospective single-cohort study to investigate factors affecting time to the event in dogs from the *main study*.

2.2. Study population, inclusion criteria

The initial sampling procedure and inclusion of dogs was previously described for dogs in this cohort (Krontveit et al., 2010). Puppies born in Norway between November 1998 and June 2001 were eligible for inclusion in the *main study*. All geographic areas of Norway were represented. Inclusion of a litter began when the bitch was mated. All puppies were registered in the NKK.

Each breeder, dog owner, and veterinarian who participated in the project signed a written agreement of cooperation to comply with the project plan. Not all enrolled dogs continued to completion. Reasons for dropouts included (but were not limited to) death of the dog, relocation of the owners during the study, and export of dogs abroad (Trangerud et al., 2007a). In total, 647 dogs from 106 litters from the *main study* were potentially eligible for inclusion in the present study, which is a convenience sample consisting of 23.2% of the total number of litters born of the included breeds in Norway during 1998–2001.

The inclusion criteria for the present study were that: the dogs were radiologically screened for hip dysplasia at the official NKK ages (12 mos for LR and IW, 18 mos for NF and LEO); they were still present in the cohort at age 3 mos; and that they had bodyweight, housing, and exercise conditions registered at least once during the first year of life. Dogs that were radiologically examined before ages 12 or 18 mos (due to clinical signs of hip disease) were included if their hip radiographs were judged by the panelist in the NKK. A few dogs had hip radiographs taken and registered in the Swedish ($n = 7$) and Danish ($n = 2$) Kennel Clubs.

2.3. Questionnaires and clinical registrations

History, husbandry, and clinical information for each included dog were obtained from three sources: (1) the breeder of the litter; (2) the owner of the puppy/dog; and (3) the veterinarian examining the puppy/dog. All three sources completed questionnaires and recorded information in a booklet prepared for each of them. The breeder recorded data during the period from birth until age 8 wks, and the owner and veterinarians at specific ages, called “the observational ages”: 3, 4, 6, 12, 18, and 24 mos. After age 24 mos, annual questionnaires were mailed to the dog owners until death of the dog or the end of the observation period. Owners not responding for various reasons were contacted by telephone to regain contact.

2.3.1. Outcome variable

During the veterinary visits scheduled especially as a part of this project, at "the observational ages", the dogs were examined by a veterinarian and any clinical signs and treatments were recorded. The dog owners could also contact their veterinarian for an examination if their dogs had any signs of disease between the scheduled visits. After age 24 mos, health status was recorded by the owner on the annual questionnaires including information about any diagnoses and treatments given by a veterinarian. The owners were encouraged to include copies of any veterinary records from the preceding year. Definition of the event was based on both of the following two criteria applied blindly (with no knowledge of exposure status like breed and radiological hip dysplasia status): (1) owner-reported clinical signs (e.g. difficulties in standing up after rest, stiffness, exercise intolerance, and lameness) and (2) clinical signs and findings on veterinary examination (e.g. hip-joint laxity, pain, and reduced movements of the hip joints) reported either on one of the scheduled veterinary visits on one of "the observational ages" or as stated by the owner in the annual questionnaires. The impact of any concurrent causes of hind-limb lameness (as diagnosed by the veterinarian), were also taken into consideration: if other musculoskeletal conditions were reported (by the veterinarian or stated by the owner) as the dog's main problem, this dog was not included as having the event at that time. A few dogs were reported (by the owner) to have been euthanized due to hip dysplasia/hip-related problems without veterinary reports of clinical signs prior to euthanasia. These dogs were also included as events, and the time of incidence of clinical signs for such a dog was considered the midpoint between the last observation point and the time of euthanasia (Dohoo et al., 2009). Dogs that died or were euthanized due to other causes, or were lost to follow-up, or were still alive at the end of the study were included up until the last time at which they were known to be alive without the event (and were thereafter censored in the analysis). Based on these data and assumptions, the outcome variable "time from birth to owner-reported veterinary-diagnosed hip-related clinical signs" (the event) was obtained.

2.3.2. Risk factors

We evaluated four types of data from the questionnaires and clinical registrations as potential risk factors for the event: individual-dog characteristics (*dog data*), bodyweight measurements (*bodyweight data*), housing conditions during growth (*housing data*), and exercise conditions during growth (*exercise data*). All variables are defined in Table 1.

Of the *dog data*, breed, sex, and season of birth were explored as potential explanatory, confounding, or intervening variables; radiological hip and elbow status (graded by and registered in the NKK) were explored as potential explanatory variables. The radiological screening procedure for hip dysplasia was described previously (Krontveit et al., 2010). The Fédération Cynologique Internationale (FCI) five-class grading scale was used for the hip status of the dogs: A (excellent), B (normal), C (mild dysplasia), D (moderate dysplasia), and E (severe dysplasia) (Fluckiger, 2007). For our analysis, the official hip status was reclassified into free (A and B), mild (C), moderate (D), and severe (E) and this variable was termed "radiological hip status". The International Elbow Working Group (IEWG) elbow protocol was used for grading elbow radiographs (International Elbow Working Group, 2001). Elbow status was dichotomized into a yes/no variable. The calendar year was divided into four seasons according to the temperature and climate conditions in Norway.

Previous studies regarding growth in dogs from this cohort and in dogs from the *main study* guided the selection of *bodyweight data* for our study (Trangerud et al., 2007a, 2007b; Krontveit et al., 2010).

The *housing data* consisted of variables thought to affect general exercise conditions for the dogs during growth: type of house at the breeder's, environment in outside run at the breeder's, general living conditions at the owner's, and the presence of children and other dogs in the owner household. Environment in the outside run was categorized according to softness into two separate dichotomous variables, with the presence of snow and ice as a third separate outdoor environment variable; these variables were not mutually exclusive (Table 1).

Exercise data were recorded by the owners in detail, with duration of the different kinds of exercise on an average day. Preliminary analyses revealed bias in the owners' recordings; to minimize this bias, the different kinds of exercise were studied as separate dichotomous variables. The *exercise data* studied were the use of stairs and different types of outdoor exercise (such as walks on-leash and running off-leash in different types of terrain) at the ages 3 and 12 mos (Table 1).

2.4. Statistical analyses

We used the software package Stata 11 (Stata Corporation, 4905 Lakeway Drive, College Station, TX 77845, USA) for all analyses.

2.4.1. Descriptive statistics

The distribution of dogs by breed, sex, radiological hip and elbow status, and season of birth was calculated. The number and percentage of events, mean time to event or censoring, and total number of dogs in each category of these variables were calculated. The numbers of events by official hip status in each of the breeds were described. Incidence rate of the event per 1000 dog-years at risk was estimated for each breed by relating the number of events to the total time at risk for the breed. We used Kaplan–Meier survival curves by breed and by breed and simultaneously with radiological hip status to describe breed differences in time to event.

2.4.2. Survival analyses

We used a Cox proportional-hazards model to evaluate potential risk factors for time to the event. Time at risk was defined as months from birth to the event or

Table 1
Definition of potential risk factors for owner reported veterinary-diagnosed hip-related clinical signs in a prospective cohort study of four large dog breeds in Norway (1998–2010).

Variable	Definition	Abbreviated name
Dog data		
Breed	Breed of the dog (categorical): Newfoundland, Labrador Retriever, Leonberger, and Irish Wolfhound	Breed
Sex	Sex of the dog (dichotomous): female and male	Sex
Season of birth	Season of birth (categorical): winter (December–March), spring (April–May), summer (June–August), and fall (September–November)	Season
Hip dysplasia grade	Grade of hip dysplasia at official radiological screening (categorical): free, mild, moderate, and severe	Radiological hip status
Elbow dysplasia	Presence of concomitant elbow dysplasia at official radiological screening (dichotomous)	Radiological elbow status
Bodyweight data		
Bodyweight at birth	Bodyweight in g at birth Birth BW	
Bodyweight at 3 mos	Bodyweight in kg at age 3 mos	3 mos BW
Mature bodyweight	Bodyweight in kg at age 24–36 mos	Mature BW
Aging/old bodyweight	Bodyweight in kg at the highest recorded age up to age 9 yrs (end of study period)	Aging BW
Housing data		
Type of house at the breeders	Type of building in which the litter lived at the breeders (categorical): single family house or farm/small farm (holding)	Breeder house
Outside run at the breeders	Outdoor environment if the puppies were allowed to be in an outside run (3 dichotomous variables): soft (grass, ground, gravel) and hard (wooden, asphalt, concrete), snow/ice	Outside run
Living conditions at owners	Area of living (categorical): countryside, suburban, and city	Owner region
Children	Presence of children in the owner household (dichotomous)	Children
Other dogs	Presence of other dogs in the owner household (dichotomous)	Other dogs
Exercise data		
Use of stairs	Daily use of indoor stairs at age 3 and 12 mos (dichotomous)	Stairs 3 mos and 12 mos
Leash on asphalt paving	Daily walks on leash on asphalt paving at age 3 and 12 mos (dichotomous)	Leash asphalt 3 mos and 12 mos
Leash on graveled road	Daily walks on leash on graveled road at age 3 and 12 mos (dichotomous)	Leash gravel 3 mos and 12 mos
Leash in rough terrain	Daily walks on leash in forest, mountain, or other rough terrain at age 3 and 12 mos (dichotomous)	Leash rough 3 mos and 12 mos
Off-leash in garden	Daily off-leash exercise in garden or yard at age 3 and 12 mos (dichotomous)	Off-leash garden 3 mos and 12 mos
Off-leash in park	Daily off-leash exercise in park terrain at age 3 and 12 mos (dichotomous)	Off-leash park 3 mos and 12 mos
Off-leash in rough terrain	Daily off-leash exercise in forest, mountain, or other rough terrain at age 3 and 12 mos (dichotomous)	Off-leash rough 3 mos and 12 mos

censoring. The end of the observation period was set to 9 yrs (108 mos). The dogs in the study were clustered into litters. The assumption of independence between observations was therefore violated and a shared frailty term for litter was included in the model (Dohoo et al., 2009).

All of the potential risk factors were tested alone applying univariable Cox proportional-hazards models while controlling for litter (the frailty term for litter included). The variables were tested for collinearity (by Goodman and Kruskal's gamma for ordinal and dichotomous variables, the *phi* coefficient for nominal variables, and pair-wise correlations for continuous variables). Associations >0.7 or <−0.7 were considered evidence of collinearity. The variables with a univariable P-value ≤ 0.20, provided that there was no collinearity between them, were then considered for further multivariable analysis. When collinearity was detected between two predictors, the predictor with fewest missing data was selected for further analyses. To assess the functional form of continuous predictors, martingale residuals were plotted against the continuous predictor of interest.

A multivariable Cox proportional-hazards model with shared frailty for litter was constructed using manual forward selection by offering variables selected from the univariable analyses one-at-a-time to the model by ascending P-value. We retained variables in the model when the P-value of the likelihood-ratio test (LRT) was <0.05. We constructed a causal diagram to evaluate potential confounding and intervening variables. Changes of >20% in the coefficients in the model with the potential confounder present were also used as an indication of confounding. A variable was considered to be "intervening" if adding it removed the entire effect of another variable and if the intervening variable lay on the causal path between the factor and the outcome. Intervening variables were excluded from the final model. All possible two-way interactions between the predictors in the final model were tested by adding interaction terms to the model, and an interaction term was retained if $P < 0.01$. The significance of the shared frailty term was evaluated through a LRT. The multiple Wald test and LRT were used to evaluate differences between categories of categorical predictors.

Table 2
Descriptive statistics for individual-dog characteristic (*dog data*) variables in a study investigating risk factors for owner reported veterinary-diagnosed hip-related clinical signs in a prospective cohort of 494 dogs from four large breeds in Norway (1998–2010).

Variable and level	Number of events	% events	Mean time to event (yr)	Mean time to censoring (yr)	Total number of dogs	% dogs of total
Breed						
Newfoundland	13	10.7	1.9	6.8	122	24.7
Labrador Retriever	10	7.6	6.5	7.6	131	26.5
Leonberger	19	10.7	3.9	6.3	178	36.0
Irish Wolfhound	4	6.3	3.1	6.2	63	12.8
Sex						
Female	30	11.5	4.0	6.8	260	52.6
Male	16	6.8	3.5	6.7	234	47.4
Radiological hip status						
Free	10	2.7	6.1	6.8	375	75.9
Mild	9	21.4	3.5	6.5	42	8.5
Moderate	15	26.8	3.4	6.5	56	11.3
Severe	12	57.1	2.8	6.6	21	4.3
Radiological elbow status[a]						
Non-affected	33	8.3	4.4	6.9	398	83.3
Affected	8	10.0	3.2	6.6	80	16.7
Season						
Winter	16	8.5	4.1	7.0	189	38.3
Spring	7	6.6	3.3	6.6	106	21.5
Summer	9	8.9	4.3	6.6	101	20.4
Fall	14	14.3	3.6	6.4	98	19.8

[a] Radiological elbow status was missing for 16 dogs.

2.4.3. Model evaluation

The assumption of proportional hazards was evaluated for the model using the test for proportional hazards based on the Schoenfeld residuals for each variable in the model. If the assumption of proportional hazards was violated and the graphical assessment indicated a time-varying effect (TVE) of a variable, an interaction term between the variable and time was included in the final model. The assumption of independent censoring, overall fit, concordance, and identification of any outliers were tested as described in the literature (Dohoo et al., 2009).

3. Results

3.1. Descriptive statistics

The number of events, mean time to event or censoring, and total number of subjects in each category of *dog data* are provided in Table 2. Of the 494 dogs enrolled, 65 were lost to follow-up some time during the 9-yr observation period and 237 died or were euthanized. At the end of the study 46 NF, 85 LR, 53 LEO, and 8 IW were still alive.

Of the 46 dogs considered to have had the event (Table 3), 10 dogs were reported to have been euthanized due to hip dysplasia/hip-related problems without veterinary reports of clinical signs prior to euthanasia. We made the assumption that the time of occurrence of the event was placed at the midpoint between the last observation point and the time of euthanasia. In 5 of these dogs this time interval was <3 mos. Total amount of time at risk was 3197 dog-years. Estimated incidence rate of the event per 1000 dog-years at risk was 17 for NF, 10 for LR, 18 for LEO, and 11 for IW. Figs. 1–4 show Kaplan–Meier curves for NF, LEO, LR, and IW by official hip status. Kaplan–Meier curves for all four breeds combined are presented in Fig. 5.

Table 3
Number of dogs with owner reported veterinary-diagnosed hip-related clinical signs/total number within radiological hip status by breed in a prospective cohort study of four large breeds in Norway (1998–2010).

Breed	Radiological hip status			
	Free	Mild	Moderate	Severe
Newfoundland	0/79	2/14	4/18	7/11
Labrador Retriever	4/106	2/10	2/11	2/4
Leonberger	5/133	4/15	7/24	3/6
Irish Wolfhound	1/57	1/3	2/3	–
Total	10/375	9/42	15/56	12/21

3.2. Risk factors

Collinearity was detected between the weight variables. The following variables were thus selected for multivariable modeling after unconditional screening ($P < 0.20$): breed, sex, radiological hip status, 3-mo bodyweight,

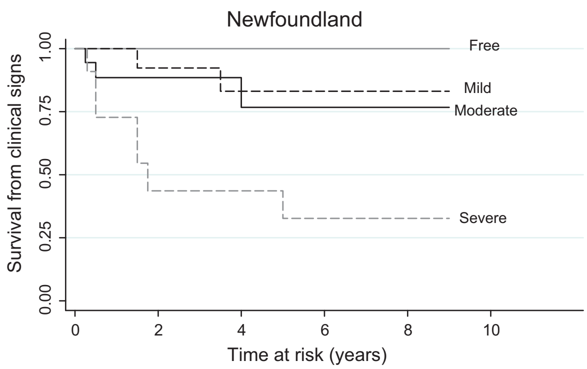

Fig. 1. Kaplan–Meier curves for Newfoundland ($n = 122$) in a prospective cohort of four large dog breeds describing time to occurrence of owner reported veterinary-diagnosed hip-related clinical signs. Time at risk is from birth to 9 yrs of age (Norway, 1998–2010).

Table 4
Results from a multivariable Cox proportional-hazards model estimating the effects of breed, radiological hip dysplasia status, and exercise conditions on time from birth to owner reported veterinary-diagnosed hip-related clinical signs ($n = 46$) in a prospective cohort study of four large dog breeds ($n = 494$) in Norway (1998–2010).

Variable and level	Estimate	SE	Hazard ratio	*P* value	95% confidence interval
Main effects					
Breed					
Newfoundland	–		1.00	–	–
Labrador Retriever	−3.24	1.47	0.04[a]	0.03	0.00, 0.70
Leonberger	−1.19	0.81	0.30[a]	0.14	0.06, 1.49
Irish Wolfhound	0.50	1.29	1.66	0.70	0.13, 20.60
Radiological hip status					
Free	–		1.00	–	–
Mild	2.48	0.54	12.00	<0.001	4.18, 34.40
Moderate	2.90	0.50	18.24	<0.001	6.84, 48.61
Severe	4.52	0.59	91.96	<0.001	28.77, 293.88
Off-leash garden 12 mos					
No	–		1.00	–	
Yes	−0.75	0.35	0.47	0.03	0.24, 0.95
Off-leash rough 12 mos					
No	–		1.00	–	
Yes	−1.04	0.37	0.35	0.005	0.17, 0.73
Leash asphalt 12 mos					
No	–		1.00	–	
Yes	−1.12	0.38	0.33	0.003	0.16, 0.68
Time-varying effect (TVE)					
Breed					
Newfoundland					
Labrador Retriever	0.07	0.03	–	0.01	0.02, 0.12
Leonberger	0.04	0.02	–	0.03	0.01, 0.08
Irish Wolfhound	0.02	0.02	–	0.46	−0.04, 0.08
Frailty (litter)					
Frailty variance	0.74	0.54	–	0.03[b]	–

[a] Estimates of effect of factor varied over time – see text for interpretation.
[b] Likelihood ratio test of frailty variance.

breeder house, outside run snow/ice, leash rough 3 mos, off-leash park 3 mos, leash asphalt 12 mos, off-leash rough 12 mos, and off-leash garden 12 mos. In the final model, radiological hip status and the exercise variables off-leash garden 12 mos, off-leash rough 12 mos, and leash asphalt 12 mos were significant ($P < 0.05$) (Table 4). Breed was retained in the final model (Table 4) as a potential confounder to control for breed differences. The multiple Wald test and LRT for comparing models with and without the categorical variable radiological hip status were both significant at $P < 0.001$. No confounding or intervening effect was detected for the variable sex; hence this variable was not retained in the model. None of the tested interactions was significant (all $P \geq 0.10$). The shared frailty variance for litter was significant as judged by the LRT (Table 4).

3.3. Model evaluation

Because the assumption of proportional hazards was violated for LR and LEO, a TVE for breed was included, and it was significant for LR and LEO (Table 4). Relating the main effects coefficient for LR to the TVE coefficient indicated

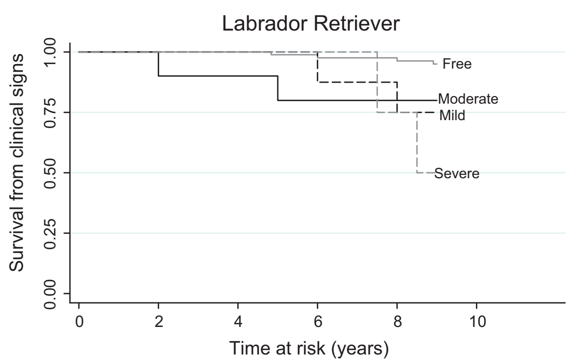

Fig. 2. Kaplan–Meier curves for Labrador Retriever ($n = 131$) in a prospective cohort of four large dog breeds describing time to occurrence of owner reported veterinary-diagnosed hip-related clinical signs. Time at risk is from birth to 9 yrs of age (Norway, 1998–2010).

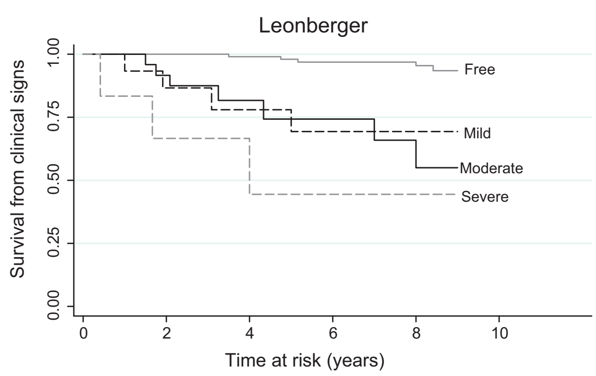

Fig. 3. Kaplan–Meier curves for Leonberger ($n = 178$) in a prospective cohort of four large dog breeds describing time to occurrence of owner reported veterinary-diagnosed hip-related clinical signs. Time at risk is from birth to 9 yrs of age (Norway, 1998–2010).

Fig. 4. Kaplan–Meier curves for Irish Wolfhound ($n = 63$) in a prospective cohort of four large dog breeds describing time to occurrence of owner reported veterinary-diagnosed hip-related clinical signs. Time at risk is from birth to 9 yrs of age (Norway, 1998–2010).

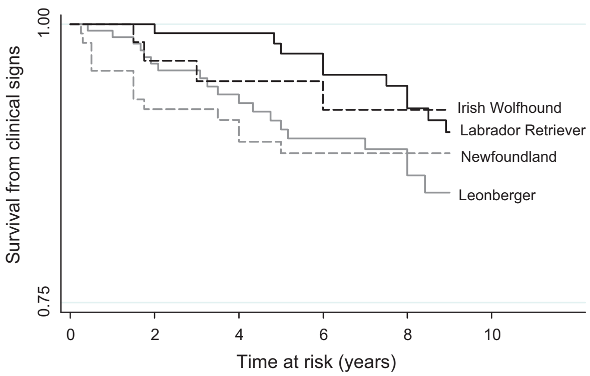

Fig. 5. Kaplan–Meier curves for 494 dogs in the breeds Newfoundland ($n = 122$), Labrador Retriever ($n = 131$), Leonberger ($n = 178$), and Irish Wolfhound ($n = 63$) in a prospective cohort study describing time to occurrence of owner reported veterinary-diagnosed hip-related clinical signs. Time at risk is from birth to 9 yrs of age (Norway, 1998–2010).

that the protective effect of being LR compared to NF was lost by ~4 yrs (age 47 mos). For LEO the protective effect was lost by ~2.5 yrs (age 28 mos). For IW the TVE was not significant (Table 4).

No major shortcomings of the model were detected through the model diagnostics.

4. Discussion

Our main findings were that there were breed differences in time to event, that dogs with radiographic hip status mild, moderate or severe had significantly shorter time to event (increased hazard) compared with dogs with radiographic hip status free, and that dogs exercised off-leash at 12 mos of age in garden and rough terrain had longer time to event (decreased hazard) compared to dogs not exercised this way.

The protective effect of being LR rather than NF disappeared by 4 yrs and by 2.5 yrs for LEO as indicated by the TVE for breed. Primary DJD develops as a consequence of wear-and-tear and appears with advancing age; secondary DJD might be a result of conditions interfering with the normal mechanics of the joint (Vaughan, 1990; Roush, 2001). Canine hip dysplasia is a developmental condition that can produce secondary DJD of the hips (Vaughan, 1990). DJD in the hips progresses throughout life (Kealy et al., 1997; Smith et al., 2006). Differentiating between primary and secondary DJD might be difficult when examining joints of old dogs (Vaughan, 1990; Roush, 2001). We followed dogs until age 9 yrs. It seems plausible that in the dogs experiencing the event late in life, these signs might be attributed to primary DJD and not necessarily secondary to hip dysplasia.

Factors significantly influencing time to event were radiological hip status and both on-leash and off-leash exercise at age 12 mos. Increasing severity of radiological hip status shortened the time to event. Association between radiological hip status at screening and subsequent veterinary insurance claims related to hip dysplasia was recently reported (Malm et al., 2010). Some of the dogs in our study were reported as having the event although they had an official radiological hip status “free”. These dogs might have had increased hip joint laxity not identified on conventional radiographs and developed DJD secondary to hip dysplasia with clinical signs increasing over time but the signs might also be due to primary DJD.

We had detailed information about exercise conditions at different ages. Specific exercise conditions at age 3 mos were selected for investigation as they might have influenced early occurring events. Exercise conditions at age 12 mos were selected because they could influence later occurring events but were not biased by the radiological hip dysplasia diagnosis assigned after screening at ages 12–18 mos. Furthermore, the exercise conditions at age 12 mos might be representative for how the dogs were exercised later in life. Among the exercise-related variables we studied, off-leash exercise in garden or yard and in rough terrain at age 12 mos combined with on-leash exercise on asphalt at age 12 mos delayed time to event (after controlling for breed and radiological hip status). Off-leash exercise in moderately rough terrain early in life was protective against radiographically diagnosed hip dysplasia at screening in a previous study in this cohort (Krontveit et al., in press). These kinds of exercise might be beneficial by strengthening muscle mass and improving range of motion in the hip joints (Holler et al., 2010; Millard et al., 2010), thus possibly delaying time to event. Both off-leash and on-leash exercise is recommended for dogs with DJD, but excessive stress (such as that induced by playing with other dogs and chasing balls or sticks) should be avoided because these activities might result in flare-ups of clinical signs (Vaughan, 1990).

Neither of the bodyweight measurements was associated with time to event. Other studies have reported that restricted feeding prevented overweight and reduced both frequency and severity of the development of DJD of the hips in dogs (Kealy et al., 1997; Smith et al., 2006). Overweight can exacerbate clinical signs of DJD (Vaughan, 1990; Impellizeri et al., 2000). Bodyweight does not take into account breed differences in size; body-condition score might be a better measure than bodyweight for assessment of “being overweight or obese” (Laflamme, 1997). In the present study, body-condition scores were not available.

Due to the clustering of the dogs in litters, a shared frailty term had to be included in all analyses. The shared frailty term was significant, indicating that dogs from certain litters had higher hazard than others. The dogs lived most of their lives separated from their littermates under differing environmental conditions. The common genetic background of dogs in a litter and other unmeasured litter factors might be important parts of the frailty variance.

The outcome variable was defined as time to owner-reported veterinary-diagnosed hip-related clinical signs. Based on the breeds included and the reported clinical presentation, most of these clinical signs are assumed to be related to canine hip dysplasia although primary DJD or secondary DJD of other causes cannot be excluded. Radiographs are necessary to diagnose DJD and stress radiography or specific clinical tests are necessary to diagnose hip laxity (McLaughlin, 2001; Roush, 2001). These evaluations were not performed in all of the dogs. Also, concurrent musculoskeletal conditions in other body areas might have contributed to the signs observed and wrongly interpreted by the veterinarian as hip joint disease. In all cases, however, the reported signs were the main musculoskeletal problem considered by both the owner and the veterinarian. Some dogs ($n = 10$) were included as having the event because they had been euthanized by a veterinarian due to hip dysplasia/hip-related problems without preceding record of clinical signs, as also reported in another study (Malm et al., 2010). These dogs were considered likely to have had the event (Malm et al., 2010). The assumption that these dogs showed clinical signs prior to euthanasia might be associated with an uncertainty because reasons for euthanizing a dog are influenced by several factors. Additionally, the decision to set time of event at the midpoint between the last observation point and time of euthanasia for these dogs might cause a bias towards shorter time to event since the distribution of events might not be uniformly distributed. However, due to the relatively small number of dogs in this category and the long follow-up time, the amount of bias due to the inclusion of these dogs as events is expected to be low.

The event in our study is a reflection of an owner-perceived clinical problem necessitating veterinary consultation for these patients. Norwegian dog owners have great animal-directed empathy, and empathy was the best predictor of how the owners rated pain in dogs (Ellingsen et al., 2010). Such attitudes towards dogs could probably increase the number of reported events in the current study, because Norwegian dog owners could have a low threshold for consulting a veterinarian. Also, the dog owners' knowledge of the radiological hip dysplasia status of their dogs could increase the reporting because owners could be more aware of signs (such as exercise intolerance, lameness, and stiffness) thus having even lower thresholds for contacting veterinarian (especially in dogs with the more-severe grades of hip dysplasia). Among insured Swedish dogs, German Shepherds had very high risk of being euthanized shortly after hip dysplasia screening if graded with the more-severe dysplasia-grades (possibly because this is a breed commonly used as working dogs) (Malm et al., 2010). Norwegian dog owners have higher empathy and pain perception towards their dog when the dogs are kept for companionship than when kept primarily for working purposes (hunting) (Ellingsen et al., 2010). However, most of the dogs in the current study were kept as companions and not as working dogs.

Misclassification of the outcome is a possible bias in this study. Non-differential misclassification of the outcome during follow-up in a cohort study will bias the measure of association towards the null and this potential bias will have a conservative effect on the results of the study and could possibly lead to associations between exposure and outcome being underestimated (Dohoo et al., 2009). We tried to reduce the amount of non-differential misclassification bias by including dogs from birth (free of clinical disease), by having criteria for being considered as an event, and by evaluating all information about the individual dogs "blindly" without information about breed and radiological hip dysplasia status. Differential misclassification (i.e. dog owners or veterinarians knowing the radiological hip dysplasia status affect the reporting of clinical signs and diagnosis) could bias the measure of association in any direction (Dohoo et al., 2009). Some of the dogs ($n = 10$) having the event were graded as free of hip dysplasia at the radiological screening. This could indicate that the bias caused by owner (and veterinarian) knowing of the official radiological hip dysplasia status might be relatively low.

Differential loss to follow-up related to exposure and outcome can bias the measure of association (Dohoo et al., 2009), and such bias can be an important problem in cohort studies of long duration as in our study (Pfeiffer, 2010). The number of events could be underestimated, especially after age 24 mos. Strategies aimed to reduce this bias were signed owner contracts for participation in the project, regular follow-up during the first 2 yrs of the study, and then by sending annual questionnaires accompanied by a cover letter encouraging owners to answer. Non-response bias might be important if there are dog-related differences between responders and non-responders (Dohoo et al., 2009), but the socio-economic status of the owners could also be a source of bias if this is associated with both exposure and outcome (Dohoo et al., 2009).

On the other hand, a strength of our data set is that all dogs were free of the clinical disease at inclusion because the observation period started at birth. The dogs were further followed until event or censoring; thus, selective survival bias was less likely to occur. Non-differential misclassification of health-status at inclusion can lead to either under- or overestimation of associations, and is a more serious bias (Dohoo et al., 2009). Other potential shortcomings of this cohort are described in detail previously (Krontveit et al., 2010).

5. Conclusion

Our findings supported our hypothesis that less severe radiological hip status at screening and provision of exercise during growth delayed the time to event. The LR and LEO breeds developed the event later than the NF. However, no effect of bodyweight was detected.

Conflict of interest statement

None of the authors of this paper has financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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