



A prospective study on Canine Hip Dysplasia and growth in a cohort of four large breeds in Norway (1998–2001)

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ABSTRACT

The study-objective was to measure the effect of weight and growth related parameters on the risk of development of Canine Hip Dysplasia (CHD). The hypothesis was that heavy and fast growing dogs of large sized breeds were at increased risk of development of CHD compared to lighter and slower growing dogs. A prospective cohort study was conducted among dogs of four large breeds: Newfoundland (NF), Leonberger (LEO), Labrador retriever (LR), and Irish wolfhound (IW). The dogs were privately owned with individualized nutrition and environment, and they were followed from birth and throughout the growth period until the official screening for CHD was performed. The study sample consisted of 501 dogs from 103 litters, with the breed distribution 125 NF, 180 LEO, 133 LR, and 63 IW. Because the dogs were clustered in litters a multivariable random effects logistic regression model was used to assess statistically significant growth-related risk factors for CHD. The estimated incidence risk of CHD was 36% in NF, 25% in LEO, 20% in LR, and 10% in IW. Based upon the final multilevel model it appears that the odds of CHD among both LR and IW (odds ratio (OR) 0.22) are about one-fifth of the odds for NF. The odds for LEO (OR 0.60) are not significantly different from NF. There appeared to be an inverse relationship between body weight at 3 months of age and odds of CHD, with an OR of 0.89 ($P=0.044$). The degree of clustering at the litter-level was high (22.6%) and highly significant ($P<0.001$). Findings failed to support the hypothesis that heavy and fast growing dogs from four large sized breeds were at increased risk for development of CHD. There might be other unmeasured environmental risk factors for CHD in this cohort of dogs, although the contribution of the genetic variance to the litter-level clustering also needs further investigation.

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1. Introduction

Canine Hip Dysplasia (CHD) is a common developmental orthopedic disease (Todhunter and Lust, 2003). Although not completely understood, two broad etiological categories have been proposed; hip joint laxity causing hip instability and abnormal progression of the endochondral

ossification in multiple joints (Todhunter and Lust, 2003). In puppies, lesions in the coxofemoral joint can be observed as early as 14–30 days of age (Riser, 1975; Alexander, 1992).

The true occurrence of CHD is not known, although there are several reports on the prevalence of CHD from official registries in different countries. However, it has been suggested that the prevalence of CHD in many registries may not be truly representative of the general or breed specific populations because a relatively small proportion of the dogs are examined for CHD and also because dogs affected by severe forms of CHD often are not officially screened

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(Smith, 1997; Leppanen and Saloniemi, 1999; Paster et al., 2005; Genevois et al., 2008; Kaneene et al., 2009). Reported breed prevalences vary from 2% to 67%, and in general large and giant breeds have the highest prevalences although exceptions exist. Medium and small sized breeds appear to have lower prevalences (Priester and Mulvihill, 1972; Corley and Hogan, 1985; Lingaas and Heim, 1987; Fluckiger et al., 1995; LaFond et al., 2002).

Conventional radiography of the hip joints or distraction index radiography (PennHip) is used to diagnose CHD (Adams, 2000; Adams et al., 2000; Dassler, 2003). Efforts to reduce the occurrence of CHD have been made by radiographic screening of dogs at a certain age and subsequently imposing breeding restrictions for dogs with radiographic diagnosis of CHD (Corley and Hogan, 1985; Lingaas and Klemetsdal, 1990; Willis, 1997; Swenson et al., 1997; Leppanen and Saloniemi, 1999; Heim, 1999; Janutta et al., 2008). The screening procedure has been standardized worldwide, and there are three somewhat different radiographic scoring modes in use; the Fédération Cynologique Internationale (FCI), the Orthopedic Foundation for Animals OFA (OFA), and the British Veterinary Association/The Kennel Club (BVA/KC) (Fluckiger, 2007).

Several studies on heritability of CHD have been based on the radiographic diagnosis from official registries without considering clinical signs and support a genetic basis for CHD with moderate to high heritability estimates (Swenson et al., 1997; Maki et al., 2000; Janutta and Distl, 2006; Malm et al., 2008; Engler et al., 2008; Madsen, 2008). Thus CHD is considered to be a genetic disease, but there also appears to be environmental factors which affect the development of dysplasia in the hip joints of genetically predisposed puppies (Fries and Remedios, 1995; Janutta et al., 2006).

The most extensively studied factors regarding development of CHD are rapid growth rate and high food consumption, and most investigators conclude that overfed dogs grow faster than dogs fed a restricted diet and hence are more prone to the development of CHD (Lust et al., 1973; Kasstrom, 1975; Kealy et al., 1992). Dietary components, such as the amount of protein and calcium in the diet, have also been studied (Richardson, 1992). Furthermore, body type and body condition have been studied as risk factors for development of CHD (Comhaire and Snaps, 2008; Roberts and McGreevy, 2010). Other environmental risk factors for the development of CHD are not extensively studied, but hormonal influences and amount of exercise have been investigated as possible predictors (Lust et al., 1973; Kasstrom et al., 1975; Goldsmith et al., 1994; Steinetz et al., 2008).

Most studies regarding development of CHD are done in populations of dogs preselected for certain purposes (e.g. guide dogs) or as controlled studies. These dogs are often offspring of hip dysplastic parents, and they are living in kennels with feeding, exercise, and housing regimen controlled and standardized and therefore not necessarily representative of privately owned dogs with a more diverse husbandry. We hypothesized that heavy and fast growing dogs in a prospectively followed cohort of four large sized breeds were at increased risk for development of CHD when compared to lighter and slower growing

dogs. The aim of the current study was to measure the effect of weight and growth related parameters on the odds of development of CHD in privately owned dogs followed from birth and throughout the growth period until the diagnosis of CHD was made.

2. Materials and methods

The study was carried out in agreement with the provisions enforced by the National Animal Research Authority (NARA)

2.1. Study design

The present study is part of a larger study (the so-called *main study*) aimed at investigating the effects of risk factors on the occurrence of skeletal diseases: CHD, elbow dysplasia, panosteitis, and osteosarcoma. The *main study* included dogs from four large breeds: Newfoundland (NF), Labrador retriever (LR), Leonberger (LEO), and Irish wolfhound (IW). A prospective single cohort study was conducted to investigate factors affecting the development of CHD in growing dogs from the *main study*.

2.2. Inclusion of dogs

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. The breeding stock consisted of dogs born in Norway as well as dogs that had been imported. Inclusion of a litter began when the bitch was mated. All puppies were registered in the Norwegian Kennel Club (NKC).

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 dogs enrolled in the study continued to completion. Reasons for dropouts included but were not limited to death of the dog, relocation of the owners during the study, and exportation of dogs abroad (Trangerud et al., 2007a).

Inclusion criteria for the present study were that the dogs were officially screened for CHD and that they had at least one recorded weight measurement during the growth period. The dogs were privately owned, and each dog had a housing and feeding regimen decided by its owner.

2.3. Screening for CHD

The signed written agreement of cooperation encouraged dog owners to have their dogs officially CHD screened. LR and IW were radiographed at 12 months of age, and LEO and NF at 18 months of age, which are the screening ages for these breeds in the NKC. More than 90% of the radiographs were scrutinized by the same radiologist at the NKC. All dogs were sedated or anaesthetized before the radiographic examination to achieve complete muscle relaxation. The identity of the dogs (NKC registration number, tattoo or microchip) was photographed onto the film before developing the radiographs. The radiographs were made at 100-cm film to focus distance.

The dogs were placed in dorsal recumbency with the hind limbs extended and abducted so that the patellae

were superimposed over the femora. The entire pelvis and femora including the patellae were included on the radiographs. The FCI five class grading scale was used to classify the hip status of the dogs: A (excellent), B (normal), C (mild dysplasia), D (moderate dysplasia) and E (severe dysplasia). The CHD grades are defined descriptively based on the size of the Norberg angle (NA), degree of subluxation, shape and depth of the acetabulum, and signs of secondary joint disease (Fluckiger, 2007). Each hip joint was graded separately, and the final grading was based on the worst hip joint. Dogs graded C (mild dysplasia), D (moderate dysplasia), and E (severe dysplasia) were considered affected by CHD.

2.4. 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, and (3) the veterinarian examining the dog. All three sources completed questionnaires and recorded information in a booklet prepared for each included dog. All questionnaire sheets appeared in duplicates in the booklet, so that one sheet could be mailed to the researchers and a copy retained in the booklet.

The breeder was asked to record the bodyweight in grams for each puppy at birth and on days 3 and 7, and then weekly until 56 days of age. The breeder decided the feeding and housing regimen of the litter, and this information along with information about any medications given including routine antiparasite treatments were recorded in the booklet. The puppies stayed with the bitch until approximately 8 weeks of age when they were sold.

The owners reported information regarding feeding, housing, exercise, and any signs indicative of disease in their dogs. The owner completed the questionnaires and reported information regarding the dog at the scheduled ages 3, 4, 6, and 12 months (so-called observational ages).

The owners agreed to have their dogs examined at the scheduled veterinary visits. Clinical examination, blood sampling, measurement of bodyweight in kg, and measurement of the circumference of the distal radius and ulna (CDRU) in cm were done at each of the veterinary visits. Vaccinations and antiparasitic treatments were administered at the veterinary visits. Average daily gain (ADG) was generated from the weight measurements for specific intervals of the growth period until 12 months of age. Changes in CDRU between ages (CDRU change) were generated from the measurements of CDRU.

2.5. Laboratory analyses

Complete blood counts (CBCs) were carried out at ages 3, 4, 6, and 12 months, and the blood serum was analyzed for the following 20 biochemical variables; alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine kinase (CK), amylase, lipase, total protein, albumin, globulin, urea, creatinine, bile acids, total bilirubin, cholesterol, glucose, inorganic phosphate, potassium, calcium, sodium, and chloride. The

analyses were conducted at the Central Laboratory, Norwegian School of Veterinary Science, Oslo, Norway.

2.6. Statistical analyses

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

2.6.1. Power calculation

The power of the present study to detect a difference of 15% and 20% in occurrence of CHD was calculated for the whole cohort with significance level 0.05 and a two-sided test.

2.6.2. Descriptive statistics

The incidence risks of CHD were calculated by relating the number of CHD-affected dogs to the total number of dogs in each breed in the cohort. Mean litter size in the four breeds was estimated, as well as sex distribution and mean litter size in dogs with CHD and without CHD. Bodyweight data separated by breed, sex, and the groups with and without CHD were fitted to a Gompertz function. A Gompertz function is a nonlinear, sigmoid function, with its point of inflection at 36.8% of mature bodyweight. Growth was modeled with the following equation (Helmink et al., 2000), using the NLIN procedure (SAS Inst.Inc., Cary, NC):

$$W_t = W_{\max} \exp\{-e^{-(t-c)/b}\},$$

where W_t is the bodyweight at time t , W_{\max} the mature bodyweight, b the proportional to duration of growth, c the age at point of inflection, 36.8% of mature bodyweight is reached, t is the age in days.

Analyses were carried out separately for each breed and sex and groups with and without CHD. Duration of growth was estimated by $(4b+c)$, which describes 98% of the growth duration (Helmink et al., 2000). The derivative of the Gompertz function describes the growth rate.

2.6.3. Multivariable analyses

For the purpose of these analyses the hip status was reclassified into 2 categories: free (grades A and B) and affected (grades C, D, and E). Thus the dependent variable CHD is a dichotomous variable (CHD free or CHD affected), and a logistic regression model of the relationship between predictors and CHD was considered. The dogs in the study were clustered into litters which violate the assumption of independence between observations, and a random effect for litter was therefore included in a generalized linear mixed model. A random effect for breeder was considered, but since the breeder: litter ratio was close to one, the breeder level was omitted.

Due to the large number of variables, they were arranged in three groups of risk factors: signalment data, weight/growth/size measurements, and blood sample variables. Overview of the type of variables in these groups is presented in Table 1.

Associations between the dependent variable and the predictor variables were first screened with univariable random effects logistic regression. Variables with a P -value

Table 1

Overview of the variables used to investigate potential risk factors regarding weight/growth and Canine Hip Dysplasia (CHD) in four large breeds in Norway (1998–2001).

Variable	Definition	Abbreviated name
Signalment data (3 variables)		
Breed	Breed of the dog (categorical): Newfoundland Labrador retriever Leonberger Irish wolfhound	NF LR LEO IW
Sex	Sex of the dog (dichotomous): female, male	Sex
Litter size	Number of puppies in each litter (continuous)	Litter size
Weight, growth, and size measurements (34 variables)		
Bodyweight	Bodyweight in grams at birth, and at 3, 7, 14, 21, 28, 35, 42, 49, and 56 days of age (continuous)	BW
Average daily gain	Bodyweight in kg at 3, 4, 6, and 12 months of age (continuous) Average daily gain in kg/day in the following periods (continuous): Birth to 7 days Birth to 14 days Birth to 21 days Birth to 56 days Birth to 3 months Birth to 6 months Birth to 12 months 35 days to 3 months 56 days to 3 months 3–4 months 4–6 months 6–12 months	ADG
Circumference of distal radius and ulna	Measurement of this circumference in cm at 3, 4, 6, and 12 months of age (continuous) Changes in these measurements between the following ages (continuous): 3–4 months 3–12 months 4–6 months 6–12 months	CDRU
Blood sample variables (135 variables)		
Complete blood count	Counts of leucocytes, erythrocytes, thrombocytes, neutrophils, eosinophils, lymphocytes, monocytes, and basophils at 3, 4, 6, and 12 months of age (continuous)	CBC
Clinical chemistry parameters	Measurement of mean cell volume, hematocrit, hemoglobin, and mean cell hemoglobin concentration at 3, 4, 6, and 12 months of age (continuous) Measurement of alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine kinase (CK), amylase, lipase, total protein, albumin, globulin, urea, creatinine, bile acids, total bilirubin, cholesterol, glucose, inorganic phosphate, potassium, calcium, sodium, chloride, and sodium/potassium ratio at 3, 4, 6, and 12 months of age (continuous) Changes in ALP between the following ages (continuous): 3–4 months 4–6 months 6–12 months	CCP

≤ 0.20 , provided that there was no collinearity ($r < 0.70$) between variables, were then considered for further analysis in a multivariable random effects logistic regression model to assess the relationship with CHD. For screening of the blood parameters a more restrictive P -value of 0.10 was applied due to the large number of variables. When collinearity was detected between two predictors, the predictor with least missing data was selected. Lowess curves were used to assess the linear relationship between the continuous variables and the logit of the outcome. Variables with many missing values (>20% missing observations) were not used in the multivariable analysis.

The Stata command `xtmelogit` using adaptive quadrature was used for the multilevel modeling. A multivariable random effects logistic model for signalment and

weight/growth/size measurements was constructed using manual backward elimination. Predictor variables were retained in the models when the P -value was < 0.05 . Potential confounding and intervening variables were considered after constructing a causal diagram. Changes of more than 20% in the coefficients in the model with the potential confounder present were used as additional indication of confounding. Interactions between significant predictors were tested by adding an interaction term to the final model, and the interaction term retained when $P < 0.01$. Following manual backward elimination, the model was build again by forward selection by offering the excluded variables one at a time to the final model. A variable was considered intervening if adding it removed the entire effect of another variable. Intervening

variables were excluded from the final model. The likelihood ratio test (LRT) was used to evaluate the significance of the random litter effect in the models with and without random litter effect, but containing the same fixed effects. The LRT was considered significant at $P=0.05$ and one-sided test. Due to the large number of variables the blood sample variables were analyzed in a separate sub model, and the same model building procedure was applied to these variables. Significant and biologically explainable variables from this sub-model were entered to the weight model and retained if they were significant at the $P<0.05$ level. The multiple Wald test and LRT were used to evaluate differences between categories of categorical predictors. The Stata command `lincom` was used to conduct contrasts among each category of categorical predictors.

From the final multivariable random effects logistic regression model the between litter variance (σ_{litter}^2) was estimated. The intraclass correlation coefficient (ICC) calculated by the latent variable approach, assuming that dog level variance (σ^2) is the constant $\pi^2/3$, was calculated using

$$\text{ICC} = \frac{\sigma_{\text{litter}}^2}{\sigma^2 + \sigma_{\text{litter}}^2}$$

To evaluate and assess the fit of the final multi-level model the residuals at the dog level were estimated and the residuals at the litter level were estimated and evaluated by plotting of residuals against both predicted values and against fitted values to evaluate homoscedasticity and normality.

3. Results

3.1. Study sample

In total, 647 dogs from 106 litters from the *main study* were eligible for inclusion in the present study, which is a convenience sample consisting of 23.2% of the total number of litters born in the included breeds in Norway. Of these dogs, 501 dogs from 103 litters were officially screened for CHD and thus included in the study sample. Among dogs eligible for inclusion, 146 were not officially screened and thus not included. Reasons for not screening were commonly due to death of the dog or unwillingness of the owner to take the cost of radiographing the dog. The 103 litters were the offspring of 94 dams from 86 different breeders.

The breed distribution was 180 LEO, 125 NF, 133 LR and 63 IW. The vast majority of the CHD radiographs were scrutinized by the radiologist in NKC ($N=491$), and 10 dogs had their radiographs scrutinized by the radiologists in the Swedish and Danish Kennel Club. The power of the present study was 0.85 for the cohort of 501 dogs.

Not all breeders, owners, and veterinarians that completed the questionnaires answered all questions at all observational ages, hence there was a varying number of missing values.

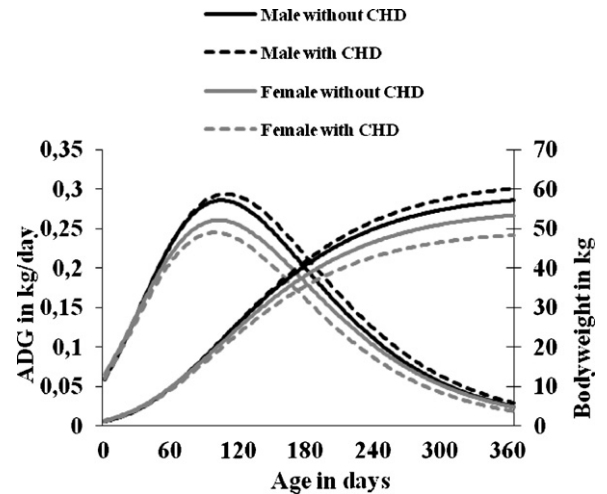


Fig. 1. Gompertz derivative (left axis) and average growth (ADG) curves (right axis) estimated with Gompertz function for male and female Newfoundland in Norway with and without Canine Hip Dysplasia (CHD) (1998–2001).

3.2. Descriptive statistics

Among the 501 dogs that were officially screened for CHD there were 260 females (51.9%) and 241 males (48.1%). There were 123 dogs (24.6%) affected by CHD. NF was the breed with the highest occurrence of CHD with an 18 months incidence risk of 36%. In LEO, the 18 months incidence risk was 25%, and in LR and IW the 12 months incidence risks were 20%, and 10%, respectively. The mean litter size was smallest in NF with a mean of 7.5 puppies followed in increasing order by IW (8.0 puppies), LR (8.6 puppies), and LEO (9.0 puppies). Distribution of CHD among sexes and mean litter size in dogs with and without CHD in the four breeds are outlined in Table 2.

ADG and bodyweight are shown in Figs. 1–4, and least squares means for the variables of the Gompertz func-

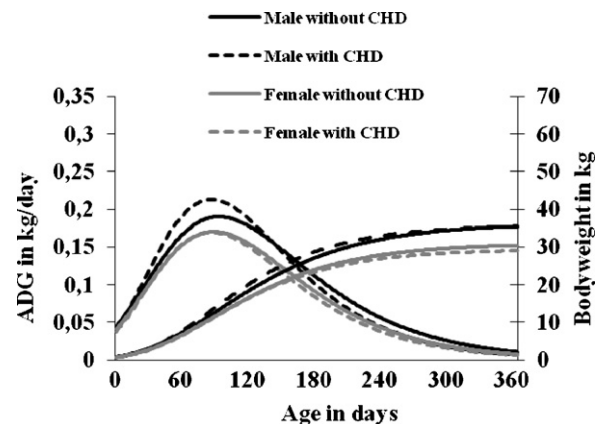


Fig. 2. Gompertz derivative (left axis) and average growth (ADG) curves (right axis) estimated with Gompertz function for male and female Labrador retriever in Norway with and without Canine Hip Dysplasia (CHD) (1998–2001).

Table 2

Descriptive statistics of the variables sex and litter size in dogs with and without Canine Hip Dysplasia (CHD) in four large breeds in Norway (1998–2001).

	CHD ^b	Breed ^a			
		NF N (%)	LR N (%)	LEO N (%)	IW N (%)
Female	0	38 (60.3)	50 (75.8)	70 (72.2)	31 (86.1)
	1	25 (39.7)	16 (24.2)	27 (27.8)	5 (13.9)
Male	0	42 (67.7)	56 (83.6)	63 (78.3)	26 (96.3)
	1	20 (32.3)	11 (16.4)	18 (21.7)	1 (3.7)
Litter size ^c	0	7.8 (1, 12)	8.7 (6, 12)	9.0 (2, 13)	8.2 (4, 12)
	1	6.8 (1, 12)	8.1 (6, 12)	8.7 (3, 13)	6.8 (4, 11)

^a Newfoundland (NF), Labrador retriever (LR), Leonberger (LEO), and Irish wolfhound (IW).^b 0 = without CHD, 1 = with CHD.^c Mean litter size (minimum, maximum).

tion by CHD status and mean birth weight are outlined in Table 3. Estimated bodyweight increased rapidly during the first 100 days and then plateaued reaching maturity between 422 days (male NF with CHD) and 335 days (male LR with CHD) (Figs. 1–4, Table 3). ADG expressed by the derivative of the Gompertz function, reached its maximum value between 87 days (female LR with CHD) and 109 days (male NF with CHD), after which is gradually declined as mature bodyweight was reached (Figs. 1–4, Table 3). The growth curves for the groups with and without CHD, diverged slightly after approximately 60 days, and females with CHD being less heavy than females without CHD, most pronounced in NF (Figs. 1–4). For the males the divergence of the curves was most obvious for male NF and LEO where the males with CHD appeared to be heavier (Figs. 1–4). In male LR with CHD there seemed to be a peak in ADG between approximately 50 and 120 days (Fig. 2).

3.3. Multivariable analyses

Weight variables which did not meet the criteria for further model building were weight at birth, 3, 7, 21–56 days, 4 months, 6 months, 12 months, ADG variables in the period from birth to 4 months, from 6 to 12 months, and birth to 12 months. All of the CDRU measurements had *P*-values greater than 0.20 in univariable screening, and they were not considered in further analysis. Colinearity ($r > 0.7$) was detected between the following variables: body weight at 3 days, 42 days, 49 days, and 3 months, and ADG from birth to 3 months, from 2 to 3 months, from birth to 14 days, and from birth to 56 days. The variables with least missing data were selected for further analyses.

From unconditional screening ($P < 0.10$) of the blood parameters, the following variables were selected for building of a sub-model: ALP change from 6 to 12 months (OR 1.74), chloride 3 months (OR 0.90), sodium/potassium

Table 3Least squares means for the variables^a of the Gompertz function and mean birth weight by status on Canine Hip Dysplasia (CHD) and sex in four large breeds in Norway (1998–2001).

Breed	CHD ^b	W_{\max} (kg) Estimate (SE)	c (days) Estimate (SE)	b (days) Estimate (SE)	$4b + c$ (days) Estimate (SE)	Birth weight (g) Mean (SE)
Newfoundland						
Male	0	59.04 (0.35)	105.20 (1.07)	76.05 (1.32)	409.40 (6.24)	611 (14.3)
	1	62.44 (0.89)	109.10 (2.29)	78.17 (2.78)	421.78 (18.27)	637 (28.9)
Female	0	55.22 (0.42)	102.80 (1.47)	77.99 (1.94)	414.76 (9.90)	584 (17.3)
	1	49.77 (0.53)	99.23 (1.74)	74.79 (2.15)	398.39 (12.20)	579 (20.3)
Labrador retriever						
Male	0	36.21 (0.20)	94.11 (0.90)	70.07 (1.18)	374.40 (5.27)	406 (12.6)
	1	35.80 (0.55)	87.26 (2.30)	61.97 (2.93)	335.14 (16.67)	417 (38.2)
Female	0	30.95 (0.21)	89.61 (1.06)	66.90 (1.41)	357.19 (6.45)	390 (11.6)
	1	29.44 (0.26)	87.12 (1.29)	63.87 (1.63)	342.60 (8.01)	374 (15.4)
Leonberger						
Male	0	55.76 (0.28)	95.68 (0.91)	70.55 (1.16)	377.95 (5.22)	510 (12.5)
	1	55.00 (0.53)	98.96 (1.71)	71.77 (2.27)	386.05 (12.01)	513 (23.9)
Female	0	44.84 (0.23)	89.80 (0.84)	65.75 (1.09)	352.83 (4.84)	464 (10.9)
	1	45.70 (0.46)	95.09 (1.71)	69.20 (2.27)	371.90 (11.79)	469 (31.1)
Irish wolfhound						
Male ^c	0	66.64 (0.43)	106 (1.18)	76.26 (1.50)	411.10 (7.23)	603 (26.3)
	1	63.31 (1.15)	103.00 (2.91)	69.62 (3.62)	381.49 (27.14)	580 (-)
Female	0	55.82 (0.52)	93.80 (1.50)	67.93 (1.89)	365.51 (9.81)	614 (21.3)
	1	54.66 (1.16)	95.30 (3.14)	69.07 (4.18)	371.56 (30.89)	680 (10.0)

^a W_{\max} = mature weight, c = age at point of inflection (36.8% of mature bodyweight), b = proportional to duration of growth, $4b + c$ = duration of growth (98% of the growth duration).^b 0 = without CHD, 1 = with CHD.^c Only one male IW with CHD.

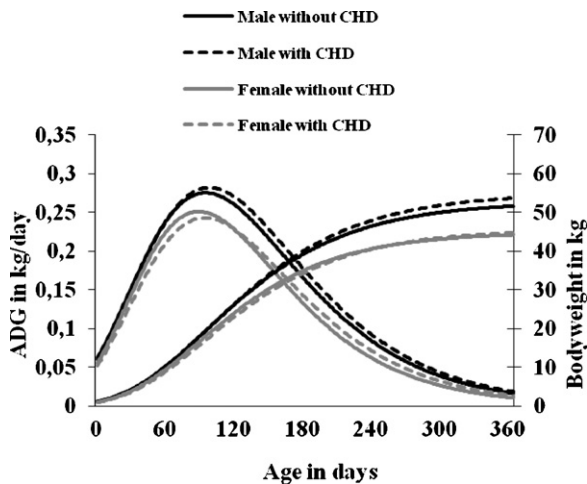


Fig. 3. Gompertz derivative (left axis) and average growth (ADG) curves (right axis) estimated with Gompertz function for male and female Leonberger in Norway with and without Canine Hip Dysplasia (CHD) (1998–2001).

ratio 3 months (OR 0.88), leucocytes 6 months (OR 0.83), and neutrophils 6 months (OR 0.77). When building this sub-model ($P < 0.05$), ALP change from 6 to 12 months and sodium/potassium ratio 3 months were retained, but only the change in ALP from 6 to 12 months was considered both significant and biologically plausible. No collinearity was detected among these variables.

Therefore the variables breed, sex, litter size, bodyweight at 14 days and 3 months, ADG from 4 to 6 months, and change in ALP from 6 to 12 months were variables considered for inclusion in the multilevel model. The unconditional OR, P -value, and 95% confidence interval (CI) for these variables are outlined in Table 4.

Breed and bodyweight at 3 months were the only significant variables in the final model. Litter size was forced in the model as a confounder. The following interactions

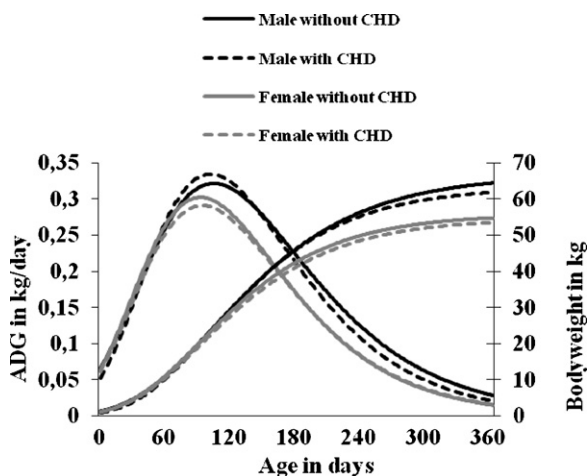


Fig. 4. Gompertz derivative (left axis) and average growth (ADG) curves (right axis) estimated with Gompertz function for male and female Irish wolfhound in Norway with and without Canine Hip Dysplasia (CHD) (1998–2001).

Table 4

Unconditional associations (with $P \leq 0.20$) from univariable mixed logistic regression models between risk factors related to signalment and weight/growth and Canine Hip Dysplasia (CHD) in four large breeds in Norway (1998–2001).

Variable	Odds ratio	P -value	95% confidence interval
Breed ^a			
NF	1.00	–	–
LR	0.38	0.03	0.15–0.91
LEO	0.44	0.05	0.20–1.00
IW	0.13	0.001	0.04–0.45
Sex			
Female	1.00	–	–
Male	0.72	0.173	0.44–1.16
Litter size	0.86	0.021	0.75–0.98
BW ^b			
Day 14	1.83	0.137	0.82–4.07
3 months	0.94	0.205	0.86–1.03
ADG ^c			
4–6 months	22.37	0.175	0.25–1998.93
ALP ^d			
6–12 months	1.74	0.049	1.00–3.01

^a Newfoundland (NF), Labrador retriever (LR), Leonberger (LEO), and Irish wolfhound (IW).

^b Bodyweight (BW).

^c Average daily gain (ADG) from 4 to 6 months.

^d Serum alkaline phosphatase (ALP), change from 6 to 12 months.

were tested: breed \times litter size, breed \times bodyweight at 3 months, and litter size \times bodyweight at 3 months. None of the tested interactions were significant. Manual backward elimination and forward selection procedures both resulted in the same model. Regression coefficients (β), OR, P -values, and 95% CI for the variables included in the final model and the ICC for the model are presented in Table 5. The OR for bodyweight at 3 months decreases by 0.10 for an increase across the interquartile range (IQR 13.6–18.7 kg). The OR for litter size decreases by 0.13 with an increase across the IQR (7–10 puppies). The multiple Wald test and LRT for comparing models with and without the categorical variable breed were both significant with $P = 0.0062$ and $P = 0.0063$, respectively. The differences between LR and LEO (OR 0.37, $P = 0.052$), LR and IW (OR 1.00, $P = 0.990$), and LEO and IW (OR 2.72, $P = 0.105$) were not significant.

3.4. Model evaluation

The litter level residuals from the random part of the final model showed no evidence of heteroscedasticity or lack of normality. No extreme values were found in the dog level residuals.

4. Discussion

The main findings in this cohort study of growth related risk factors for CHD were that the incidence risk varied by breed, that there appeared to be an inverse relationship between body weight at 3 months of age and odds of CHD, that CDRU and certain blood parameters were not associated with the odds of CHD, and that there was a strong clustering of the log odds of CHD within litters. Based on the findings we rejected our hypothesis that odds of CHD would be greater in heavy and fast growing dogs from large

Table 5

Results from the final multivariable random effects logistic regression model for weight/growth related risk factors for Canine Hip Dysplasia (CHD) in four large breeds in Norway (1998–2001).

Variable	β	Odds ratio	P-value	95% confidence interval
Breed ^a				
NF	–	1.00	–	–
LR	–1.498	0.22	0.005	0.08–0.63
LEO	–0.507	0.60	0.229	0.26–1.37
IW	–1.507	0.22	0.016	0.07–0.75
BW ^b				
3 months	–0.112	0.89	0.044	0.80–0.99
Litter size ^c	–0.131	0.88	0.068	0.76–1.01
Overall P (final model) ^d			0.002	
ICC ^e (estimate)	0.226		<0.001 ^f	

^a Newfoundland (NF), Labrador retriever (LR), Leonberger (LEO), and Irish wolfhound (IW).

^b Bodyweight (BW).

^c Included as confounder.

^d β_0 was 2.252 for the final model.

^e Intraclass correlation coefficient.

^f Likelihood ratio test of the random litter effect.

sized breeds. Each finding will be discussed in more detail in the following sections.

4.1. Breed and sex differences

Incidence risk of CHD differed between the four breeds and the effect of breed on the odds of CHD was statistically significant, as judged by the LRT of the breed variable in the random effects model. The largest breeds NF and LEO had the highest incidence of CHD, whereas the smaller LR had a lower incidence. The OR for categories of breed from the final multilevel model indicates that both LR and IW have decreased odds of CHD when compared to NF (baseline breed) (Table 5). Based upon the final model it appears that the odds of CHD among both LR and IW are about one-fifth (OR 0.22) of the odds for NF, while the odds for LEO (OR 0.60) are not significantly different from NF. The differences in the odds of CHD comparing LR and LEO, LR and IW, and LEO and IW were however not significant either. Interpretations of all coefficients in the model are conditional upon the random effect.

The findings regarding breed differences are in accordance with other studies showing differences between breeds (Martin et al., 1980; LaFond et al., 2002). In general, large and giant breeds seem more susceptible to CHD. Some exceptions are breeds like the Collie, Borzoi, and IW which are large breeds with low risk (Priester and Mulvihill, 1972; Corley and Hogan, 1985; LaFond et al., 2002). In our study, IW had a low incidence when compared to the other breeds, but after controlling for litter, weight at 3 months and litter size the odds of CHD in IW and LR were identical when compared to NF (Table 5). Small and miniature breeds are to a much lesser extent studied with regard to occurrence of CHD. However, the disease might be just as common in these breeds as in the large ones; Martin et al. (1980) found that 25% of radiographed miniature poodles had CHD. A recent Swedish study has found a marked increased hazard of having clinical signs related to CHD with deteriorating hip status and with breed differences; the largest breeds having the greatest hazard (Malm et al., 2010). Thus clinical signs could be more common and the

disease more detrimental in large dog breeds. The clinical signs and prognosis in dogs affected by CHD is to be studied further in our cohort.

The variable sex was considered a possible confounder in the way that sex affects bodyweight and growth and that other studies of large breeds have found a significant effect of sex on the risk of CHD (Hedhammar et al., 1979; Martin et al., 1980; Lingaas and Heim, 1987; Swenson et al., 1997; Wood et al., 2002). The difference between males and females was not significant in our study, and no evidence of confounding was found. Hence the variable sex was excluded from the final multivariable model.

4.2. Bodyweight and ADG

In the present study, dogs diagnosed with CHD had slightly higher mean birth weight compared to those not diagnosed with CHD, except for female NF and LR. During the growth period the differences in body weight and ADG were only modest between dogs with and without CHD, the difference being most obvious in female NF with CHD which were less heavy and had smaller ADG. Vanden Berg-Foels et al. (2006) found in LR that increased birth weight and increased early postnatal body weight increased the probability of degenerative changes in the hip joint later in life. In our study male LR with CHD seemed to have a peak in ADG although somewhat later in the growth period. In a previous study Trangerud et al. (2007a) modeled the growth pattern in dogs from the *main study* with the Gompertz function. In this model, as in ours, NF was the slowest growing breed and LR fastest growing breed. Interestingly, NF is the breed with the highest incidence of CHD.

The only weight variable in this study which was statistically significant ($P=0.044$) in the final model was body weight at 3 months of age. There was an apparent protective effect of greater body weight at 3 months of age on the odds of CHD. The upper limit of the 95% CI approached one and the effect seems modest (Table 5), but the change in OR for this variable over the IQR is quite large. The result is in conflict with some studies, but in line with others (Kasstrom, 1975; Kealy et al., 1992; Ohlerth et al., 1998;

Lopez et al., 2006). When growth is modeled with the Gompertz function, the point of inflection has been found to be at approximately 3 months of age (Trangerud et al., 2007a) and between 87 and 109 days in the present study (Figs. 1–4, Table 3). This may indicate that the body weight at, and growth rate around, 3 months of age might be important predictors of growth and possibly explain why body weight at 3 months was the only significant weight variable found in the present study.

Several studies have reported a correlation between early rapid growth and both frequency and severity of CHD. In these studies dogs fed *ad libitum* have been found to have a higher incidence of CHD than dogs on a restricted diet (Riser et al., 1964; Hedhammar et al., 1974; Kasstrom, 1975; Kealy et al., 1992). Lust et al. (1973) found that only abnormally slow growing and hand reared puppies seemed to a certain extent to be protected against development of CHD. Manipulating growth rate by restricted or *ad libitum* feeding might not cause CHD, but perhaps maximize the expression of the CHD phenotype (Todhunter and Lust, 2003). A recent study on a cohort of “mixed breed hounds” fed *ad libitum* revealed no significant effect of growth on hip distraction index. However, there was a trend for negative correlations between high distraction index and growth from 14 to 15 weeks of age (Lopez et al., 2006).

In a study of CHD in a colony of LR there was no significant association between weight measurements and risk for development of CHD (Ohlerth et al., 1998). Two recent cross-sectional studies have compared prevalence of CHD from official registries with the breed standards of weight, height, and body mass index (BMI). There seems to be a significant correlation between high prevalence of CHD and weight, BMI, and relative body length (Comhaire and Snaps, 2008; Roberts and McGreevy, 2010). Selection of body shapes that are longer than they are tall, in combination with high BMI can act together giving too much load on the coxofemoral joint thus exacerbating some characteristics of CHD such as subluxation and osteoarthritis (Roberts and McGreevy, 2010).

Most studies regarding rapid growth as risk factor for CHD have been done in dogs where either one or both parents have CHD, thus rendering the offspring more likely to be affected. Commonly, the studies include dogs pre-selected for certain purposes (e.g. guide dogs) and with housing and management controlled and standardized in a manner that will reduce the environmental variance (Lust et al., 1973; Kasstrom, 1975; Kealy et al., 1992; Ohlerth et al., 1998; Lopez et al., 2006). By reducing the environmental variance the effect of genetic variation will become relatively more important and estimates of heritability need to be interpreted with this in mind.

The present study differs from most other studies on CHD in several ways. In our study population of dogs, which are registered in the NKC, the occurrence of dysplastic parents is low as breeding restrictions exist on dogs with CHD in Norway. Furthermore, our study sample is heterogeneous consisting of dogs from 4 different breeds living in private homes. Hence they are under influence of maternal, genetic, and environmental factors which most probably influence growth simultaneously. Many studies regarding

growth on the risk of CHD were done 20–30 years ago and have provided the basis for recommendations on feeding of growing dogs, and especially the large breeds. There has been extensive research on dog feeds. The feeding of the dogs in our study is therefore likely to be different from what were common 20–30 years ago. Commonly puppies and young dogs of large breeds are fed diets designed for heavy fast-growing dogs and these diets intend to regulate growth thus reduce the risk of skeletal disorders. Size and body shape of the breeds might also have changed over this time period. These are all factors that might provide some explanation for the findings in the present study. Although weight and growth might be influenced by the diet, the incidence of CHD is high and genetic and other environmental factors are factors also influencing both weight and growth and the occurrence of CHD.

4.3. CDRU and blood parameters

The measure CDRU was originally included as a measure of skeletal growth and thought to be a potential predictor of skeletal diseases affecting the metaphyses. CDRU has been investigated previously in growing dogs (Trangerud et al., 2007a), and as a clinical measure to identify pathological metaphyses (Trangerud et al., 2007b). Disturbances in endochondral ossification in several joints have been found in dogs affected by CHD (Todhunter et al., 1997). In the present study it was investigated whether CDRU was different between dogs affected by CHD and those not affected. However, there was no statistically significant difference between the two groups of dogs.

Hip joint laxity and abnormalities in endochondral ossification are both proposed as important factors in the etiology of CHD, and the two most probably act together (Todhunter and Lust, 2003). Differences in collagen types in dysplastic hip joint capsules and delayed chondroepiphyseal ossification and growth plate closure in dysplastic hips are found. The disturbances in endochondral ossification are not confined to the hip joint (Madsen, 1997; Todhunter et al., 1997). These disturbances might be reflected in the blood, and factors related to modeling and remodeling of bone during growth were thought of as biologically plausible when analyzing the data from the blood samples; serum ALP, calcium, and phosphorus. Serum ALP has been found to be lower in a population of NF affected by metaphyseal irregularities (Trangerud et al., 2007b), but not found significantly different among German shepherds with and without CHD (Szilagyi and Sagi, 1976). In our study none of the mentioned blood parameters turned out significant in the final model. There could be other factors and hormones that are measurable in blood which might be more suitable biomarkers of CHD.

4.4. Clustering at litter level

In this study, a high and significant amount of clustering at the litter level was present; the ICC representing the proportion of variance at litter level was 22.6%. The variation in the log odds of CHD within a litter is smaller than between litters. Intraherd correlations for infectious diseases have been observed to range from 4% to 42%, but mostly below

20% (Otte and Gumm, 1997). In a study relating preweaning mortality in puppies to additive genetic, common-litter, and within-litter factors, the litter factors explained most of the variation (van der Beek et al., 1999).

The high level of clustering in the present study is most probably a result of common genetic background and common environment within a litter both before and after birth. This litter effect probably continues to have an influence after the puppies are delivered to their owners because the genetic background still is the same and many breeders have recommendations regarding management which the dog owners usually follow, at least to a certain extent. The environmental variance, i.e. all variation of non-genetic origin, is most probably greater in our study population than in dogs living in kennels under standardized conditions. Genotype by environment interactions have been described for several traits in several species (Lillehammer, 2008). Genotype–environment interaction is very important when individuals of a population are reared under different conditions (Falconer and Mackay, 1996) as the dogs in our cohort and might contribute to the observed litter effect. The high level of clustering at the litter level in this study makes estimation of how much the additive genetic variation contributes to the observed cluster effect important, and separation of additive genetic and litter variance would be desirable. Environmental influences on the CHD phenotype and development of clinical signs are to be further investigated in this cohort of large breed dogs.

4.5. Validity

In this cohort study all risk factors are measured prior to the outcome, which is necessary for claims of causation. Cohort studies generally have high relevance to real-world situations and a relatively high external validity (Dohoo et al., 2009). All kinds of dogs, from highly rewarded breeding dogs to privately owned pet dogs from the four breeds, were included in our cohort, which increases the external validity. The present study is a large scale prospective study of large sized breeds, and the results might be valid for other populations of large sized breeds, but perhaps not for small and miniature breeds. Some of the dogs eligible for inclusion in the present study were not officially screened for CHD and therefore not included a fact that could lead to selection bias. Reasons for not screening the dogs were, however, most commonly due to death of the dog and owner unwillingness to have the radiographs taken because of the cost. The vast majority of the CHD radiographs in the present study were scrutinized by a single radiologist, which reduces inter-observer variation.

A potential shortcoming of the study is the use of conventional hip radiography to diagnose CHD. False negative diagnoses occur more often when the conventional radiographic projection is used, but false positive results are more common with other methods like distraction index radiography (Zhu et al., 2009). Age of the dog at screening has been found affect the screening result. Older dogs tend get worse grades than younger because secondary changes in the hip joint are more common with increasing age (Swenson et al., 1997; Maki et al., 2000; Leppanen et al.,

2000; Wood and Lakhani, 2003) The fact that NF and LEO in our study were 6 months older than LR and IW at screening might be a source of differential misclassification. Reclassification of the hip status from five grades to two categories in the analyses in this study might reduce the variation and result in some loss of information. The fact that a very large number of predictors were investigated also warrants some caution in the interpretation of the final model. The effect of a predictor might appear significant by chance alone and strictly, a lower cut-off for statistical significance than the conventional $P < 0.05$ level should be applied to account for multiple comparisons. This is particularly relevant for the factor bodyweight at 3 months, which is only borderline significant ($P = 0.044$).

5. Conclusion

The aim of this study was to measure the effect of weight and growth related parameters on the risk of development of CHD in privately owned dogs followed from birth and throughout the growth period until the diagnosis of CHD was made. The findings failed to support the hypothesis that when comparing large sized breeds, large and fast growing dogs were at risk for development of CHD when compared to less heavy and slower growing dogs. On the contrary, it was found that higher body weight at 3 months of age was associated with lower odds of CHD, although the estimated effect was modest. A high level of clustering at the litter-level was observed and might indicate that environmental effects influence the development of the CHD phenotype, although the contribution of the genetic variance to the clustering needs to be further investigated.

Conflict of interest statement

Neither 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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